Add-On Cannabidiol Treatment for Drug-Resistant Seizures in Tuberous Sclerosis Complex:

Results of a Randomized, Placebo-Controlled Trial

This supplement contains the following items:

1. Original protocol (Version 1), final protocol (Version 8), summary of all amendments to the protocol, clinical protocol annex 1 for implementation at US sites only and the summary of amendments to annex 1, and clinical protocol annex 2 for implementation at Polish sites only and the summary of amendments to annex 2

2. Original statistical analysis plan (SAP), final SAP (Version 2), and SAP addendum
Study Title: A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled focal seizures

Study Code: GWEP1521

EudraCT Number: 2015-002154-12

CLINICAL PROTOCOL

GW Research Ltd
Sovereign House
Vision Park
Chivers Way
Histon
Cambridge CB24 9BZ
United Kingdom

Tel: PPD
Fax: PPD

Confidentiality Statement
This document contains confidential information of GW Research Ltd (GW) that must not be disclosed to anyone other than the recipient study staff and members of the Institutional Review Board or Ethics Committee. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW.
Investigator Agreement

I have read the attached protocol entitled ‘A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled focal seizures’, dated 16 June 2015 and agree to abide by all provisions set forth therein.

I agree to comply with applicable regulatory requirement(s); the U.S. Food and Drug Administration (FDA) regulations relating to good clinical practice (GCP) and clinical trials, the European Union (EU) Clinical Trials Directive (2001/20/EC), the EU Good Clinical Practice / GCP Directive (2005/28/EC) and subsequent applicable regulatory/statutory instruments, or the International Conference on Harmonization Tripartite Guidelines for GCP where the EU Clinical Trials and GCP Directives do not apply, and to complete Form FDA 1572, if required.

I am not aware that any conflicts of interest, financial or otherwise, exist for myself, my spouse [or legal partner] and dependent children and agree to confirm this in writing if required and update as necessary.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW.

Center No: __________________________

Print Name: __________________________ Date: __________________________

Principal Investigator (DD Month YYYY)

Signature: __________________________

GW Authorization

Print Name: __________________________ Date: __________________________

Clinical Manager (DD Month YYYY)

Signature: __________________________

Confidential
## 1 PROTOCOL SYNOPSIS

<table>
<thead>
<tr>
<th>Study Title</th>
<th>A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled focal seizures.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Study Type</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Indication</td>
<td>Focal seizures* in patients with tuberous sclerosis complex (TSC). Focal seizures include: focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures.</td>
</tr>
<tr>
<td>Primary Objective</td>
<td><strong>Blinded Phase:</strong> To evaluate the efficacy of GWP42003-P as add-on therapy in reducing the frequency of focal seizures when compared with placebo in patients with TSC. <strong>Open-Label Extension:</strong> To evaluate via the adverse events (AE) profile the long term safety and tolerability of GWP42003-P as add-on therapy in children and adults with TSC who experience inadequately-controlled focal seizures.</td>
</tr>
</tbody>
</table>
| Secondary Objectives | **Blinded Phase:**  
- To evaluate the effect of GWP42003-P compared with placebo on antiepileptic measures.  
- To evaluate the effect of GWP42003-P on cognitive and behavioral function compared with placebo.  
- To evaluate the effect of GWP42003-P on growth and development (in patients less than 18 years old) compared with placebo.  
- To evaluate the effect of GWP42003-P on autistic features compared with placebo.  
- To evaluate the effects of GWP42003-P on quality of life compared with placebo.  
- To evaluate the safety and tolerability of GWP42003-P compared with placebo.  
- To determine the pharmacokinetics (PK) of CBD, Δ⁹-Tetrahydrocannabinol (THC) and their major metabolites following single and multiple doses of GWP42003-P.  
- To evaluate the effects of GWP42003-P on plasma concentrations of concomitant antiepileptic drugs (AEDs), |
Open-label Extension:

- To evaluate the long term effects of GWP42003-P, as add-on therapy, on antiepileptic measures.
- To evaluate the long term effect of GWP42003-P on cognitive and behavioral function.
- To evaluate the long term effect of GWP42003-P on growth and development (in patients less than 18 years).
- To evaluate the long term effect of GWP42003-P on autistic features.
- To evaluate the long term effects of GWP42003-P on quality of life.
- To evaluate the long term safety and tolerability of GWP42003-P.

Study Design

This multicenter study consists of a randomized, placebo-controlled, double-blind phase followed by an open-label extension (OLE) phase.

Blinded Phase:
The blinded phase of the study is a 1:1:1 randomized, double-blind, parallel-group, 16-week comparison of two doses of GWP42003-P versus placebo. Patients will complete a 4-week baseline period before they are randomized to receive either 25 mg/kg/day GWP42003-P, 50 mg/kg/day GWP42003-P or placebo. Randomization will be stratified by age according to the following ranges: 2-6, 7-11, 12–17 years and 18+ years. Patients in the placebo group will be split into two equivalent cohorts; half receiving 25 mg/kg/day dosing volumes and half receiving 50 mg/kg/day dosing volumes. Patients will begin a 4-week dose escalation period, titrating up to their assigned dose, before continuing on a stable dose of blinded IMP for 12 weeks.

Dose escalation for each patient is subject to the Investigator’s assessment of safety and tolerability. If a dose becomes poorly tolerated, the Investigator may consider temporarily or permanently reducing the dose for the remainder of the study.

Clinic visits will occur for screening (Day -28), randomization (Day 1) and, on Days 15 and 29 during titration and on Days 43, 57, 71 (telephone) and 85 until the end of treatment (Day 113). Safety telephone calls will be completed every two days during titration, one week after the end of titration and, for patients not entering the OLE, weekly from Visit 9 to Visit 11.

Patients will be required to perform daily interactive voice response system (IVRS) telephone calls to record seizure information. They will also complete a paper diary daily with information about their IMP and concomitant AED.
Following completion of the blinded phase patients will be invited to continue to receive GWP42003-P in an OLE study.

Those patients opting not to enter the OLE will complete a 10 day taper period (down-titrating 10% per day for 10 days).

**Open-label Extension Transition:**

In order to maintain consistent exposure to IMP and maintain the integrity of the blind, patients will enter a 2-week blinded transition to the OLE. Doses will be titrated up or down, as appropriate, to ensure all patients enter the OLE taking 25 mg/kg/day GWP42003-P:

- Patients from the placebo group will titrate up to 25 mg/kg/day GWP42003-P.
- Patients from the 25 mg/kg/day GWP42003-P group will continue to take 25 mg/kg/day GWP42003-P.
- Patients from the 50 mg/kg/day GWP42003-P group will taper down (10% per day) to 25 mg/kg/day GWP42003-P.

Safety telephone calls will be completed every two days throughout the open label extension transition.

**Open-label Extension:**

The OLE consists of a 10-day titration period followed by a maintenance period and a 10-day taper period.

Following titration according to the titration schedule, patients will continue with their optimal GWP42003-P dose. However, investigators may decrease the dose if a patient experiences intolerance, or increase the dose to a maximum of 50 mg/kg/day if required for better seizure control, until the optimal dose is found. Dose increases above 25 mg/kg/day are recommended to be done slowly, with maximum increments of 2.5 mg every 5–7 days. Patients whose dose has been decreased can have their dose increased again provided there is adequate tolerance. Safety telephone calls will be completed every two days throughout the OLE titration and one week after the end of titration. If seizure freedom is achieved with use of GWP42003-P during the study, the Investigator should consider reducing the dose of concomitant AEDs after six months of seizure freedom.

If market authorization is granted for GWP42003-P in TSC, the patient will complete the study. Patients who do not immediately continue to use GWP42003-P will then commence a taper period (tapering 10% per day for 10 days).

**Primary Endpoint**

**Blinded Phase:**

The primary endpoint is the percentage change from baseline in number of focal seizures (average per 28 days) during the treatment period (maintenance and titration) in patients taking...
GWP42003-P compared with placebo.

**Open-label Extension:**
The safety of GWP42003-P will be evaluated by assessing the incidence, type and severity of AEs.

<table>
<thead>
<tr>
<th>Secondary Endpoints</th>
<th><strong>Blinded Phase:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The following endpoints will be compared between treatment groups over the 16-week, double-blind treatment period (all changes relative to baseline):</td>
</tr>
</tbody>
</table>

**Antiepileptic efficacy measures:**
- Number of patients considered treatment responders defined as those with a ≥25%, ≥50%, ≥75% or 100% reduction in focal seizure frequency.
- Number of patients experiencing a >25% worsening, −25 to +25% no change, 25–50% improvement, 50–75% improvement or >75% improvement in focal seizure frequency.
- Change in composite focal seizure score (frequency × severity).
- Change in number of focal seizure-free days.
- Change in number of seizures by subtype.
- Change in number of infantile/epileptic spasms.
- Change in use of rescue medication.
- Change in the number of episodes of status epilepticus (convulsive and non-convulsive).
- Changes in duration of seizure subtypes as assessed by the Subject Global Impression of Change in Seizure Duration (SGIC-SD) or the Caregiver Global Impression of Change in Seizure Duration (CGIC-SD)

**Cognitive and Behavioral Function:**
- Changes in Wechsler Scales (pre-school, primary, children, adult).
- Changes in Achenbach Child Behavior Checklist (CBCL) and Adult Behavior Checklist (ABCL).

**Growth and Development (in patients less than 18 years old):**
- Change in serum insulin-like growth factor-1 (IGF-1) levels.
- Change in Tanner Staging score (for patients aged 10–17 [inclusive]).

**Autistic Features:**
- Change in Social Communication Questionnaire (SCQ)
Quality of Life:
- Changes in the Quality of Life in Childhood Epilepsy (QOLCE; patients 2–18 years) or Quality of Life in Epilepsy (QOLIE-31-P; patients 19+ years) score.
- Change in Caregiver Global Impression of Change (CGIC) or Subject Global Impression of Change (SGIC) score.
- Change in Physician Global Impression of Change (PGIC) score.

Safety and Tolerability:
- AEs.
- Clinical laboratory parameters.
- 12-lead electrocardiogram (ECG).
- Physical examination parameters (including height and weight).
- Vital signs.
- Columbia Suicide Severity Rating Scale (C-SSRS; 19+ years) or C-SSRS Children’s (6–18 years) score, where applicable.
- Number of inpatient hospitalizations due to epilepsy.
- Abuse liability.
- Effects on menstruation cycles (in females).

PK:
- The plasma concentration/time curve of CBD, THC and their major metabolites will be described following single and multiple doses of GWP42003-P, with the aim being to estimate:
  - Peak plasma concentration (C_max).
  - Time to peak concentration (t_max).
  - Area under the plasma concentration curve from time zero to infinity (AUC(0–∞)).
  - Terminal half-life (t½).
- Plasma concentrations of concomitant AEDs before and after treatment with GWP42003-P, where available.

Open-label Extension:
The following endpoints will be assessed relative to the pre-randomization baseline of the blinded phase:

Antiepileptic efficacy measures:
- Percentage change in number of focal seizures (average per 28 days).
- Number of patients considered treatment responders.
defined as those with a ≥25%, ≥50%, ≥75% or 100% reduction in focal seizure frequency.

- Number of patients experiencing a >25% worsening, −25 to +25% no change, 25–50% improvement, 50–75% improvement or >75% improvement in focal seizure frequency.
- Change in composite focal seizure score (frequency × severity).
- Change in number of focal seizure-free days.
- Change in number of seizure subtypes.
- Change in number of infantile/epileptic spasms.
- Change in use of rescue medication.
- Change in the number of episodes of status epilepticus (convulsive and non-convulsive).
- Changes in duration of seizure subtypes as assessed by the SGIC-SD or the CGIC-SD.

Cognitive and Behavioral Function:
- Changes in Vineland-II.
- Changes in Wechsler Scales (pre-school, primary, children, adult).
- Changes in CBCL or ABCL.

Growth and Development (patients less than 18 years):
- Change in serum IGF-1 levels.
- Change in Tanner Staging score (for patients aged 10–17 [inclusive]).

Autistic Features:
- Changes in SCQ score.

Quality of Life:
- Changes from baseline in the QOLCE (patients 2–18 years) or QOLIE-31-P (patients 19+ years) score.
- Change in CGIC or SGIC score.
- Change in PGIC score.

Safety and Tolerability:
- Clinical laboratory parameters.
- ECG.
- Physical examination parameters (including height and weight).
- Vital signs.
- C-SSRS (19+ years) or C-SSRS Children’s (6–18 years) score, where applicable.
- Number of inpatient hospitalizations due to epilepsy.
- Abuse liability.
- Effects on menstruation cycles (in females).

**Sample Size**

**Blinded Phase:**

A total of 144 patients will be targeted to be enrolled. The 144 patients will be randomly allocated on a 1:1:1 basis (25 mg/kg/day GWP42003-P, 50 mg/kg/day and placebo, 48 patients per group). Patients in the placebo group will be split into two cohorts (24 patients receiving 25 mg/kg/day dosing volumes and 24 patients receiving 50 mg/kg/day dosing volumes), but it is assumed that these two cohorts can be pooled for the analyses of efficacy. If it is assumed that patients in the placebo group will experience a mean reduction in focal seizure frequency of 15% (from baseline), this sample size of 48 patients per group will be sufficient to detect a difference of 35% between treatments (i.e., patients receiving GWP42003-P will experience at least a 50% reduction in focal seizures). This is based on a standard deviation of 60%, using a two-sided 5% significance level and 80% power.

**Open-label Extension:**

All patients who wish to continue on IMP following the blinded phase.

**Summary of Patient Eligibility Criteria**

Inclusion: Patients meeting the following criteria will be considered eligible for this study:

- Patient is male or female aged between two and 65 years inclusive.
- Patient and/or parent(s)/legal representative is willing and able to give informed consent/assent for participation in the study.
- Patient and their caregiver are willing and able (in the Investigator’s opinion) to comply with all study requirements (including accurate diary and IVRS completion).
- Well-documented history of focal epilepsy, with focal seizures as the primary seizure type, compatible electroencephalogram (EEG) and clinical history.
- Clinical diagnosis of TSC according to criteria agreed by the 2012 International Tuberous Sclerosis Complex Consensus Conference.
- All medications or interventions for epilepsy (including ketogenic diet and any neurostimulation devices for epilepsy) must have been stable for one month prior to screening and the patient is willing to maintain a stable regimen throughout the study.
- Patient is willing to keep any factors expected to affect seizures stable (such as the level of alcohol consumption and...
smoking).

- Patient and/or parent(s)/legal representative is willing to allow the responsible authorities to be notified of participation in the study, if mandated by local law.
- Patient and/or parent(s)/legal representative is willing to allow his or her primary care practitioner and consultant (if they have one) to be notified of participation in the study, if mandated by local law.

**At the end of the baseline period patients must also meet the following criterion:**

- Experienced at least eight focal seizures during the first 28 days of the baseline period with at least one seizure occurring in at least three of the four weeks.
- Completed at least 90% of calls to IVRS during the first 28 days of the baseline period.

Exclusion: The patient may not enter the study if ANY of the following apply:

- Patient has a history of pseudo-seizures.
- Patient has clinically significant unstable medical conditions other than epilepsy.
- Patient has an illness in the four weeks prior to screening or randomization, other than epilepsy, which in the opinion of the Investigator could affect seizure frequency.
- Patient has undergone general anesthetic in the four weeks prior to screening or randomization.
- Patient has undergone surgery for epilepsy in the six months prior to screening.
- Patient is being considered for epilepsy surgery or any procedure involving general anesthesia.
- Patient is taking felbamate, and they have been taking it for less than one year prior to screening.
- Patient is taking an oral mammalian target of rapamycin (mTOR) inhibitor.
- Patient has, in the investigator’s opinion, clinically significantly abnormal laboratory values.
- Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the Investigational Medicinal Product (IMP), such as sesame oil.
- Active suicidal plan/intent in the past six months, or a history of suicide attempt in the last two years, or more than one lifetime suicide attempt.
- C-SSRS grade 4 or 5 at screening.
• Patient is currently using or has in the past used recreational or medicinal cannabis, or cannabinoid-based medications, within the three months prior to screening and is unwilling to abstain for the duration of the study.

• Patient has tumor growth which, in the opinion of the Investigator, could affect the primary endpoint.

• In the opinion of the Investigator the patient has clinically significant abnormalities in the ECG measured at screening or randomization or any concurrent cardiovascular conditions, which will interfere with the ability to read their ECGs.

• Patient has significantly impaired hepatic function at the screening visit (Visit 1) or the randomization visit (Visit 2), defined as any of the following:
  - Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 × upper limit of normal (ULN).
  - Serum ALT or AST ≥ 3 × ULN and (TBL [serum total bilirubin] ≥ 2 × ULN or international normalized ratio [INR] > 1.5).
  - Serum ALT or AST ≥ 3 × ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

  This criterion can only be confirmed once the laboratory results are available.

• Patient is female and of child bearing potential, or is male whose partner is of child bearing potential, unless willing to ensure that they or their partner use a highly effective method of birth control (e.g., hormonal contraceptives, intrauterine devices/hormone-releasing systems, bilateral tubal occlusion, vasectomized partner, sexual abstinence) during the study and for three months thereafter.

• Female patient who is pregnant (positive pregnancy test), lactating or planning pregnancy during the course of the study and for three months thereafter.

• Patient has received an IMP within the 12 weeks prior to the screening visit.

• Patient has any other significant disease or disorder which, in the opinion of the Investigator, may either put the patient at risk because of participation in the study, may influence the result of the study, or may affect the patient’s ability to take part in the study.

• Any abnormalities identified following a physical examination of the patient that, in the opinion of the Investigator, would jeopardize the safety of the patient if they take part in the
<table>
<thead>
<tr>
<th>Criteria for Withdrawal</th>
<th>The patient must be withdrawn from the study if any of the following apply:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Administrative decision by the Investigator, GW or Regulatory Authority.</td>
</tr>
<tr>
<td></td>
<td>• Did not meet eligibility criteria.</td>
</tr>
<tr>
<td></td>
<td>• Pregnancy.</td>
</tr>
<tr>
<td></td>
<td>• Protocol deviation that is considered to potentially compromise the safety of the patient.</td>
</tr>
<tr>
<td></td>
<td>• Withdrawal of patient consent/assent.</td>
</tr>
<tr>
<td></td>
<td>• Withdrawal of parent(s)/legal representative consent.</td>
</tr>
<tr>
<td></td>
<td>• ALT or AST $&gt;3 \times$ ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($&gt;5%$).</td>
</tr>
<tr>
<td></td>
<td>• ALT or AST $&gt;8 \times$ ULN.</td>
</tr>
<tr>
<td></td>
<td>• ALT or AST $&gt;5 \times$ ULN for more than two weeks.</td>
</tr>
<tr>
<td></td>
<td>• ALT or AST $&gt;3 \times$ ULN and (TBL $&gt;2 \times$ ULN or INR $&gt;1.5$).</td>
</tr>
<tr>
<td></td>
<td>• Lost to follow-up.</td>
</tr>
</tbody>
</table>

The patient may also be withdrawn from the study for any of the following:

• Patient non-compliance.
• AE (including clinically significant laboratory result) which, in the opinion of the Investigator, would compromise the continued safe participation of the patient in the study.
• Suicidal ideation or behavior of type 4 or 5 during the treatment period, as evaluated with the C-SSRS.
• Any evidence of drug abuse or diversion.
• General anesthesia (Blinded Phase only).

<table>
<thead>
<tr>
<th>Investigational Medicinal Product: Formulation, Mode of Administration,</th>
<th>GWP42003-P oral solution (100 mg/mL cannabidiol in sesame oil with anhydrous ethanol, sweetener [sucralose] and strawberry flavoring).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo oral solution (sesame oil) containing the excipients anhydrous ethanol, sweetener (sucralose) and strawberry flavoring.</td>
<td></td>
</tr>
</tbody>
</table>
## Dose and Regimen

| Dose and Regimen | **Blinded Phase:**
|------------------|--------------------------------------------------
|                  | Patients will titrate the IMP up to the required dose over four weeks as per randomization. Patients will then remain at this maintenance dose for 12 weeks. |
|                  | Dose escalation for each patient is subject to the Investigator’s assessment of safety and tolerability. If a dose becomes poorly tolerated, the Investigator may consider temporarily or permanently reducing the dose for the remainder of the study. Patients will be on treatment for a total of 15 weeks. |
|                  | Patients not entering the OLE or who withdraw early will down-titrate over a period of 10 days. Patients who decide to enter the open label extension will enter the Open-label Extension Transition. |
|                  | Titration from 0 - 25 mg/kg/day will begin at 5 mg/kg/day and will be increased in increments of 5 mg/kg/day every two days (patients will remain on each dose level for two days before they progress on to the next dose). |
|                  | Titration from 25 - 50 mg/kg/day will continue at smaller increments of 2.5 mg/kg/day every two days. |
|                  | IMP will be taken twice daily (morning and evening). |
|                  | **Open-label Extension Transition:**
|                  | This double-blind transition phase will take two weeks to complete. Doses will be titrated up or down, as appropriate to ensure all patients enter the OLE taking 25 mg/kg/day: |
|                  | - Patients from the placebo group will titrate up to 25 mg/kg/day. |
|                  | - Patients from the 25 mg/kg/day group will continue to take 25 mg/kg/day. |
|                  | - Patients from the 50 mg/kg/day will taper down (10% per day for 5 days) to 25 mg/kg/day. |
|                  | **Open-label Extension:**
|                  | Patients may titrate the IMP up to the target dose of 50 mg/kg/day. Patients will then remain at this dose until the ‘End of Treatment’ visit, with the option for doses to be increased or decreased if deemed necessary by the investigator, to a maximum of 50 mg/kg/day. Following the ‘End of Treatment’ visit or decision to withdraw, doses of the IMP will be tapered down (10% per day for 10 days) at home until the ‘End of Taper’ visit. IMP will be taken twice daily (morning and evening). |
| **Control Group** | The control group will receive equal volumes of matching placebo. |
Procedures

Screening Assessments (Blinded Phase) Will Include:

- Informed consent
- Demographic assessment
- Full medical history (including seizure information since diagnosis and all prior AEDs taken)
- Concomitant medication review (including AEDs)
- Physical examination
- Vital signs assessment
- Postural blood pressure
- Clinical laboratory samples (blood and urine) will be taken for:
  - Hematology
  - Biochemistry
  - Urinalysis
  - Urine THC screen
  - Serum pregnancy test (if applicable)
  - TSC1 and TSC2 mutation status (if not known previously)
- ECG
- C-SSRS or Children’s C-SSRS, where applicable
- IVRS training
- Patient diary issue and training

The Diagnostic Review Form (DRF) will be completed for review and verification by the Epilepsy Study Consortium (ESC).

Patients who satisfy all inclusion and none of the exclusion criteria will be assigned a unique patient number and then begin the 28-day baseline observation period. The investigator will review and train the patient or their caregiver to identify the patient’s expected seizure types. Patients will make a daily IVRS call to record daily seizure information including focal seizures and episodes of status epilepticus. Patients or their caregivers will be given a paper diary to record daily seizure information, usage of IMP, rescue medication, concomitant AEDs, and AEs and will be instructed on how to do so.

Randomization Visit Assessments

Following the 28-day baseline observation period the investigator will assess the patient’s daily number of seizures from IVRS data and confirm ESC verification of diagnosis. Patients who continue
to satisfy all inclusion and none of the exclusion criteria will be randomized. Patients will then receive sufficient IMP, as assigned by IVRS, every 14 to 28 days for the 15-week treatment period. Before taking their first dose of IMP in clinic the following assessments will be completed:

- Concomitant medication review (including AEDs)
- AE review
- Epilepsy-related hospitalizations review
- Physical examination
- Tanner Staging (where appropriate)
- ECG (including baseline and +4 hours after first dose)
- Vital signs
- Postural blood pressure
- C-SSRS or Children’s C-SSRS, where applicable
- SGIC-SD or CGIC-SD
- Vineland II
- Wechsler Tests
- CBCL or ABCL
- SCQ
- QOLCE or QOLIE-31-P
- CGIC or SGIC
- PGIC
- Clinical Laboratory samples (blood and urine) will be taken for:
  - Hematology
  - Biochemistry
  - Urinalysis
  - Urine THC screen
  - Serum pregnancy test (if applicable)
  - Serum IGF-1
  - PK
  - AED concentrations
- Review of paper diary
- IMP dispensing

**Post Randomization Assessments**

Clinic visits will occur on Day 15, Day 29, Day 43, Day 57, Day 85 and Day 113 with a telephone visit occurring on Day 71. Additional safety telephone calls will be completed every two
days during titration and one week after the end of titration.

The following assessments will be completed at every clinic visit except where indicated:

- Concomitant medication review (including AEDs)
- AE review
- Epilepsy-related hospitalizations review
- Physical examination
- Tanner Staging, where appropriate (Visits 2 and 9)
- ECG
- Vital signs
- C-SSRS or Children’s C-SSRS, where applicable
- SGIC-SD or CGIC-SD (Visit 9)
- Vineland II
- Wechsler Tests (Visits 2 and 9)
- CBCL or ABCL (Visits 2 and 9)
- SCQ (Visits 2 and 9)
- QOLCE or QOLIE-31-P (Visits 2 and 9)
- CGIC or SGIC (Visits 2 and 9)
- PGIC (Visits 2 and 9)
- Clinical Laboratory samples (blood and urine) will be taken for:
  - Hematology
  - Biochemistry
  - Urinalysis
  - Urine THC screen
  - Serum pregnancy test (if applicable)
  - Serum IGF-1
  - PK (Visits 2 and 9)
  - AED concentrations
- Review of patient diary
- IMP dispensing, collection and compliance review

PK:
Blood sample collection for PK analysis of CBD, THC and their major metabolites will be taken at the at the following time points:

- Visit 2 (Randomization) - Pre-IMP-dose and 2 hours and 4 hours after IMP dose.
• Visit 9 (End of Treatment) - Pre-IMP-dose and 2 hours and 4 hours after IMP dose.

Blood samples will be collected for analysis of plasma concentrations of concomitant AEDs (if possible) ideally at the following time points:

• Visit 2 - Pre-IMP-dose.
• Visit 4 - Pre-IMP-dose.
• Visit 6 - Pre-IMP-dose.
• Visit 8 - Pre-IMP-dose.
• Visit 9 - Pre-IMP-dose.

Additional blood samples may be taken for AED monitoring if there is a suspicion of changes in AED levels, with the aim to keep the AED plasma levels within the patient’s therapeutic level.

Open-label Extension Transition and Open-label Extension:

Following completion of the blinded phase of the study, patients will enter a 2-week blinded transition followed by a 2-week titration. Safety telephone calls will be conducted every two days during this 4-week period and one week after the end of titration. OLE visits will occur on Day 15, Day 29, Day 85 and then every three months up to one year, then every six months thereafter until the end of treatment. Additional IMP Re-Supply Visits will be scheduled between Assessment Visits.

The following assessments will be completed at all visits during the OLE:

• Concomitant medication review (including AEDs)
• AE review
• Physical examination
• Tanner Staging, where appropriate (Visits B2, B5 and subsequent Assessment Visits)
• ECG
• Vital signs
• C-SSRS or Children’s C-SSRS, where applicable
• SGIC-SD or CGIC-SD
• Vineland II
• Wechsler Tests
• CBCL or ABCL
• SCQ
• QOLCE or QOLIE-31-P
• CGIC or SGIC
• PGIC
• Clinical Laboratory samples (blood and urine) will be taken for:
  o Hematology
  o Biochemistry
  o Urinalysis
  o Serum pregnancy test (if applicable)
  o Serum IGF-1
  o AED concentrations
• Review of patient diary
• IMP dispensing, collection and compliance review

**Monitoring of Drug Abuse Liability (for Patients 12 Years of Age and Older):**

During the routine collection of AEs in this study, if AEs are reported which can illuminate an abuse potential signal, then the Investigator or study coordinator is required to complete an additional Supplemental Adverse Event Form and Site Classification Form (Investigator only) following further discussion of the event(s) with the patient/caregiver.

The second trigger that will require the Investigator or study coordinator to discuss abuse potential signals with the patient/caregiver is drug accountability issues regarding overuse of the IMP or missing bottles.

Irrespective of the above, all patients/caregivers will be interviewed at their final dosing visit (Visit 9 or the Withdrawal visit) of the blinded phase and again at their final dosing visit of the OLE). A Study Medication Use and Behavior Survey will be completed by the Investigator or study coordinator.

A formal Adjudication Committee will be appointed and assigned to this initiative to classify triggered cases. The Adjudication Committee will meet on a periodic basis to review and assess all of the information collected on triggered cases.

<table>
<thead>
<tr>
<th>Statistical Considerations</th>
<th><strong>Blinded Phase:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Each of the primary and secondary endpoints will be described and compared between treatment groups, using appropriate statistical methods, over the 15- week, double-blind maintenance and titration period.</td>
<td></td>
</tr>
<tr>
<td>The primary comparison of interest is 50 mg/kg/day GWP42003-</td>
<td></td>
</tr>
</tbody>
</table>
P vs. placebo, but the dose-response relationship between the 25 mg/kg/day and 50-mg/kg/day doses of GWP42003-P and placebo will also be explored.

All statistical tests will be two-tailed and carried out at the 5% level of significance.

All safety data will be summarized using appropriate statistical methods.

**Open-label Extension:**

All data collected during this study will be summarized across time, using appropriate statistical methods. Where baseline data are available from the Core study, changes from baseline will also be presented.

Descriptive statistical methods will be used throughout. There will be no formal hypothesis testing.

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>GW Research Ltd</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sovereign House</td>
</tr>
<tr>
<td></td>
<td>Vision Park</td>
</tr>
<tr>
<td></td>
<td>Chivers Way</td>
</tr>
<tr>
<td></td>
<td>Histon</td>
</tr>
<tr>
<td></td>
<td>Cambridge CB24 9BZ</td>
</tr>
<tr>
<td></td>
<td>United Kingdom</td>
</tr>
</tbody>
</table>
**For patients not entering the open label extension at Visit 9. Patients who opt not to enter the open label extension study must have weekly (±3 days) safety telephone calls until Visit 11.**

**For patients not entering the open label extension; can be conducted by telephone.**

# Safety telephone calls must be completed every two days during titration and one week after the end of titration.
To avoid double-dosing of IMP at Visit 1, patients will be instructed to begin titration of IMP the following day, which will be regarded as Day 1. As such, Visit 1 will occur on Day −1 with no clinic visit on Day 1.

§ Between visits, safety telephone calls must be made every four weeks to assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.

¶ ‘End of Treatment’ visit will occur once market authorization is granted for GWP42003-P (in TSC).

# Following the ‘End of Taper Period’ visit, a safety telephone call must be made two weeks later to collect seizure information, and to assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.

** Can be conducted by telephone.

B5, B7, B9, B11, B12, B14 and B15 – Resupply visits.

^Visits continue sequentially after B16 with assessment visits every 6 months (±14 days) and resupply visits every 8-10 weeks between assessment visits.

†† Safety telephone calls must be completed every two days during blinded transition, titration and one week after the end of titration.
Table of Contents

Title Page ................................................................. 1

1 PROTOCOL SYNOPSIS......................................................... 3
   Table of Contents .............................................................. 22
   List of Appendices ............................................................... 28
   List of In-text Tables ........................................................... 29
   List of In-text Figures .......................................................... 30
   List of Abbreviations ........................................................... 31
   Definition of Terms ............................................................ 33

2 OBJECTIVES ................................................................. 34
   2.1 Primary ............................................................................. 34
   2.2 Secondary ........................................................................... 34

3 BACKGROUND AND RATIONALE ....................................... 36
   3.1 Disease .............................................................................. 36
   3.2 GWP42003-P Background ...................................................... 39
   3.3 Rationale ............................................................................ 40
       3.3.1 Selection of Study Dose ...................................................... 40
   3.4 Clinical Hypothesis ............................................................ 41

4 EXPERIMENTAL PLAN ....................................................... 42
   4.1 Study Design ..................................................................... 42
       4.1.1 Primary Endpoint ............................................................. 43
       4.1.2 Secondary Endpoint(s) ....................................................... 44
   4.2 Number of Centers ............................................................ 47
   4.3 Number of Patients ............................................................. 47

5 INVESTIGATIONAL MEDICINAL PRODUCT ....................... 48
   5.1 GWP42003-P Oral Solution ..................................................... 48
   5.2 Placebo Oral Solution ........................................................... 48
   5.3 Packaging, Storage and Drug Accountability ................................. 48
       5.3.1 Packaging and Labeling ..................................................... 48
       5.3.2 Storage ......................................................................... 49
       5.3.3 Supply and Return of Investigational Medicinal Product .......... 50
       5.3.4 Investigational Medicinal Product Accountability .................... 50
5.3.5 Post-trial Provision ................................................................. 51

6  PATIENT ELIGIBILITY .......................................................... 52
   6.1 Inclusion Criteria ............................................................... 52
   6.2 Exclusion Criteria ............................................................. 53

7  PATIENT ENROLMENT ......................................................... 55
   7.1 Treatment Assignment ..................................................... 55
   7.2 Randomization ............................................................... 55

8  TREATMENT PROCEDURES ............................................... 56
   8.1 Investigational Medicinal Product Dosage, Administration and Schedule ........................................................................ 56
   8.1.1 Dose Administration ...................................................... 56
   8.1.2 Dose Escalation and Dose Adjustments ......................... 56
   8.2 Concomitant Therapy ....................................................... 58
   8.3 Prohibited Therapy During Study Period ......................... 58
   8.4 Compliance in Investigational Medicinal Product Administration ................................................................. 58
   8.5 Access to Blinded Treatment Assignment (Blinded Phase and OLE Transition only) ........................................................................................................ 59

9  STUDY PROCEDURES ......................................................... 60
   9.1 Study Procedures by Visit ................................................. 60
   9.1.1 Blinded Phase .............................................................. 60
   9.1.1.1 Visit 1 (Day -28, Screening) ........................................ 60
   9.1.1.2 Visit 2 (Day 1, Randomization) ................................. 61
   9.1.1.3 Visit 3 (Day 15) .......................................................... 62
   9.1.1.4 Visit 4 (Day 29) .......................................................... 63
   9.1.1.5 Visit 5 (Day 43) .......................................................... 64
   9.1.1.6 Visit 6 (Day 57) .......................................................... 64
   9.1.1.7 Visit 7 (Day 71) .......................................................... 65
   9.1.1.8 Visit 8 (Day 85) .......................................................... 65
   9.1.1.9 Visit 9 (Day 113, End of Treatment/Withdrawal Visit) ................. 65
   9.1.1.10 Visit 10 (Day 123, End of Taper) ............................. 67
   9.1.1.11 Visit 11 (Day 151, Safety Follow-Up) ....................... 67
   9.1.2 Open Label Extension ................................................... 67
   9.1.2.1 Visit B1 (Day 1) ......................................................... 68
   9.1.2.2 Visit B2 (Day 15) ....................................................... 69
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.1.2.3 Visit B3 (Day 29)</td>
<td>70</td>
</tr>
<tr>
<td>9.1.2.4 Visit B4 (Day 85)</td>
<td>70</td>
</tr>
<tr>
<td>9.1.2.5 Visit B5 to End of Treatment</td>
<td>71</td>
</tr>
<tr>
<td>9.1.2.5.1 Assessment Visits</td>
<td>72</td>
</tr>
<tr>
<td>9.1.2.5.2 Re-supply Visits</td>
<td>72</td>
</tr>
<tr>
<td>9.1.2.6 End of Treatment/Withdrawal Visit</td>
<td>73</td>
</tr>
<tr>
<td>9.1.2.7 End of Taper Period Visit</td>
<td>74</td>
</tr>
<tr>
<td>9.1.2.8 Post-Taper Safety Telephone Call</td>
<td>74</td>
</tr>
<tr>
<td>9.1.2.9 Follow-up Visit</td>
<td>75</td>
</tr>
<tr>
<td>9.1.2.10 Safety Telephone Calls</td>
<td>75</td>
</tr>
<tr>
<td>9.2 Study Procedure Listing</td>
<td>75</td>
</tr>
<tr>
<td>9.2.1 Informed Consent/Assent</td>
<td>75</td>
</tr>
<tr>
<td>9.2.2 Contraception Requirements</td>
<td>76</td>
</tr>
<tr>
<td>9.2.3 Demographics</td>
<td>76</td>
</tr>
<tr>
<td>9.2.4 Medical History</td>
<td>77</td>
</tr>
<tr>
<td>9.2.5 Concomitant Medication</td>
<td>77</td>
</tr>
<tr>
<td>9.2.6 Physical Examination</td>
<td>77</td>
</tr>
<tr>
<td>9.2.7 Vital Signs</td>
<td>77</td>
</tr>
<tr>
<td>9.2.8 12-Lead Electrocardiogram</td>
<td>77</td>
</tr>
<tr>
<td>9.2.9 Clinical Laboratory Sampling</td>
<td>78</td>
</tr>
<tr>
<td>9.2.9.1 Pharmacokinetic Blood Sampling</td>
<td>79</td>
</tr>
<tr>
<td>9.2.9.2 Determination of Plasma Concentrations of Concomitant Antiepileptic Drugs</td>
<td>80</td>
</tr>
<tr>
<td>9.2.10 Interactive Voice Response System</td>
<td>80</td>
</tr>
<tr>
<td>9.2.11 Patient Diary</td>
<td>81</td>
</tr>
<tr>
<td>9.2.12 Questionnaires and Assessments Completed at Scheduled Visits</td>
<td>81</td>
</tr>
<tr>
<td>9.2.12.1 Subject/Caregiver Global Impression of Change</td>
<td>82</td>
</tr>
<tr>
<td>9.2.12.2 Subject/Caregiver Global Impression of Change in Seizure Duration</td>
<td>82</td>
</tr>
<tr>
<td>9.2.12.3 Quality of Life in Childhood Epilepsy (18 Years of Age and Younger) or Quality of Life in Epilepsy (19 Years of Age and Older)</td>
<td>82</td>
</tr>
<tr>
<td>9.2.12.5 Child/Adult Behavior Checklist</td>
<td>83</td>
</tr>
<tr>
<td>9.2.12.6 Social Communication Questionnaire</td>
<td>83</td>
</tr>
</tbody>
</table>
9.2.12.7 Children's/Columbia Suicide Severity Rating Scale ..................... 84
9.2.12.8 Wechsler Tests ................................................................................. 84
9.2.13 Menstruation ......................................................................................... 85
9.2.14 Tanner Staging ....................................................................................... 85
9.2.15 Investigational Medicinal Product Accountability ......................... 85
9.2.16 Adverse Events ....................................................................................... 85
9.2.17 Monitoring of Abuse Liability (for Patients 12 Years of Age and Older) ......................................................................................... 86
  9.2.17.1 Monitoring of Adverse Events ................................................................. 86
  9.2.17.1.1 List of ‘Triggering Adverse Events of Interest’ ................................. 86
  9.2.17.1.2 Supplemental Adverse Event Form ................................................. 87
  9.2.17.1.3 Monitoring Drug Accountability Discrepancies ................................ 87
  9.2.17.1.4 List of ‘Triggering Drug Accountability Discrepancies’ ................ 87
  9.2.17.1.5 Supplemental Drug Accountability Form ....................................... 88
9.2.17.2 Site Classification Form ........................................................................ 88
9.2.17.3 Study Medication Use and Behavior Survey ........................................ 88
9.2.17.4 Adjudication Committee: Assessment of Abuse Potential of GWP42003-P ......................................................................................... 89

10 WITHDRAWAL ................................................................................................. 91

11 URGENT SAFETY MEASURES ................................................................. 93

12 ADVERSE EVENT REPORTING ................................................................. 94
  12.1 Definitions ................................................................................................. 94
  12.1.1 Adverse Event ......................................................................................... 94
  12.1.2 Investigator ............................................................................................... 94
  12.2 Serious Adverse Events ............................................................................ 94
  12.3 Reporting Procedures for Serious Adverse Events .................................... 95
  12.4 Pregnancy .................................................................................................... 96
  12.5 Causality Assessment ............................................................................... 96
  12.6 Reporting Procedures for All Adverse Events .......................................... 97
  12.7 Follow-up Procedures for Adverse Events .............................................. 98
  12.8 Potential Cases of Drug-Induced Liver Injury ........................................... 99
  12.9 Notification of Safety Information to Investigators, Regulatory Authorities and Ethics Committees ................................................................. 100

13 STATISTICAL CONSIDERATIONS ......................................................... 102
13.1 Sample Size, Power and Significance Levels ........................................... 102
13.2 Interim Analysis ........................................................................................ 102
13.3 Analysis Sets ............................................................................................. 102
13.3.1 Protocol Deviations ................................................................................ 103
13.4 General Considerations ............................................................................. 103
13.5 Accountability and Background Characteristics ....................................... 104
13.5.1 Enrollment and Disposition .................................................................... 104
13.5.2 Baseline and Demographic Characteristics ............................................ 104
13.5.3 Medical History ...................................................................................... 104
13.5.4 Concomitant Medication ........................................................................ 104
13.6 Endpoints and Statistical Methods ............................................................ 104
13.6.1 Evaluable Period ..................................................................................... 105
13.6.2 Primary Endpoint(s) ................................................................................ 105
13.6.2.1 Sensitivity Analysis for the Primary Endpoint.................................... 106
13.6.3 Secondary Endpoint(s) ............................................................................ 108
13.6.4 Pharmacokinetics .................................................................................... 110
13.6.5 Safety ...................................................................................................... 110
13.6.5.1 Treatment Compliance and Extent of Treatment Exposure.............. 110
13.6.5.2 Adverse Events ................................................................................ 110
13.6.5.3 Clinical Laboratory Data ..................................................................... 110
13.6.5.4 Vital Signs, 12-Lead Electrocardiogram, Physical Examination and Other Safety Data ................................................................. 111

14 SAFETY MONITORING COMMITTEE................................. 112

15 REGULATORY AND ETHICAL OBLIGATIONS............... 113
15.1 Declaration of Helsinki ............................................................................. 113
15.2 Informed Consent/Assent .......................................................................... 113
15.3 Ethics Committee/Institutional Review Board .......................................... 113
15.4 Pre-Study Documentation Requirements .................................................. 114
15.5 Patient Confidentiality ............................................................................... 114

16 ADMINISTRATIVE AND LEGAL OBLIGATIONS.............. 116
16.1 Protocol Amendments and End of Study or Termination ......................... 116
16.2 Study Documentation and Storage ............................................................ 116
16.3 Study Monitoring and Data Collection ..................................................... 117
16.4 Electronic Data collected by Interactive Voice Response System............. 118
16.5 Quality Assurance ................................................................. 118
16.6 Compensation ...................................................................... 119
16.7 Publication Policy............................................................... 119
16.8 Intellectual Property Rights ............................................... 119
16.9 Confidential Information .................................................. 120

17 REFERENCES ........................................................................ 121
List of Appendices

APPENDIX 1  SCHEDULE OF ASSESSMENTS.................................126
APPENDIX 2  TANNER STAGING......................................................129
APPENDIX 3  STUDY PERSONNEL.............................................132
Appendix 3.1  Investigator Details........................................132
Appendix 3.2  Sponsor Contact Details.................................132
List of In-text Tables

Table 5.1-1  Formulation of GWP42003-P Oral Solution ......................... 48
Table 5.2-1  Formulation of Placebo Oral Solution .............................. 48
Table 8.1.2-1 Dose Titration Regimen* .............................................. 56
Table 9.1.2-1 OLE Visit Schedule .................................................... 71
Table 9.2-1  Biochemistry, Hematology, Urinalysis and THC Screen ....... 78
List of In-text Figures

Figure 1-1  Study Design and Treatment Schema: Blinded Phase .......... 20
Figure 1-2  Study Design and Treatment Schema: Open-label
              Extension ............................................................................. 21
Figure 9-1  Flow Diagram for Identifying and Evaluating Clinical
              Trial Adverse Event Data Through Systematic
              Categorization, Tabulation and Analysis which can
              Illuminate an Abuse Potential Signal (for Patients 12
              Years of Age and Older) ..................................................... 90
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCL</td>
<td>Adult Behavior Checklist</td>
</tr>
<tr>
<td>ACTH</td>
<td>Adrenocorticotropic hormone</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>AED</td>
<td>Antiepileptic Drug(s)s</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine Aminotransferase</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate Aminotransferase</td>
</tr>
<tr>
<td>CBCL</td>
<td>Child Behavior Checklist</td>
</tr>
<tr>
<td>CBD</td>
<td>Cannabidiol</td>
</tr>
<tr>
<td>CGIC</td>
<td>Caregiver Global Impression of Change</td>
</tr>
<tr>
<td>CGIC-SD</td>
<td>Caregiver Global Impression of Change in Seizure Duration</td>
</tr>
<tr>
<td>CIOMS</td>
<td>Council for International Organizations of Medical Sciences</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CRO</td>
<td>Contract Research Organization</td>
</tr>
<tr>
<td>C-SSRS</td>
<td>Columbia Suicide Severity Rating Scale</td>
</tr>
<tr>
<td>DRF</td>
<td>Diagnostic Review Form for Epilepsy Study Consortium</td>
</tr>
<tr>
<td>EC</td>
<td>Ethics Committee</td>
</tr>
<tr>
<td>ECG</td>
<td>12-Lead Electrocardiogram</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
</tr>
<tr>
<td>ESC</td>
<td>Epilepsy Study Consortium</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FDA</td>
<td>U.S. Food and Drug Administration</td>
</tr>
<tr>
<td>GABA</td>
<td>$\gamma$-aminobutyric acid</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GW</td>
<td>GW Research Ltd</td>
</tr>
<tr>
<td>IB</td>
<td>Investigator Brochure</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>IGF-1</td>
<td>Insulin-like growth factor-1</td>
</tr>
<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug</td>
</tr>
<tr>
<td>INR</td>
<td>International Normalized Ratio</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>IVRS</td>
<td>Interactive Voice Response System</td>
</tr>
<tr>
<td>mTOR</td>
<td>Mammalian target of rapamycin</td>
</tr>
<tr>
<td>OLE</td>
<td>Open-label Extension</td>
</tr>
<tr>
<td>PGIC</td>
<td>Physician Global Impression of Change</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>PRN</td>
<td>Packaging Reference Number</td>
</tr>
<tr>
<td>PVD</td>
<td>Pharmacovigilance Department</td>
</tr>
<tr>
<td>QOLCE</td>
<td>Quality of Life in Childhood Epilepsy</td>
</tr>
<tr>
<td>QOLIE-31-P</td>
<td>Quality of Life in Epilepsy</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SCQ</td>
<td>Subject Communication Questionnaire</td>
</tr>
<tr>
<td>SGIC</td>
<td>Subject Global Impression of Change</td>
</tr>
<tr>
<td>SGIC-SD</td>
<td>Subject Global Impression of Change in Seizure Duration</td>
</tr>
<tr>
<td>SEGAs</td>
<td>Subependymal giant-cell astrocytomas</td>
</tr>
<tr>
<td>SENS</td>
<td>Subependymal nodules</td>
</tr>
<tr>
<td>SMC</td>
<td>Safety Monitoring Committee</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>TBL</td>
<td>Total Bilirubin</td>
</tr>
<tr>
<td>THC</td>
<td>$\Delta^9$-Tetrahydrocannabinol</td>
</tr>
<tr>
<td>TSC</td>
<td>Tuberous sclerosis complex</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper Limit of Normal</td>
</tr>
<tr>
<td>VFDs</td>
<td>Visual field defects</td>
</tr>
<tr>
<td>VGB</td>
<td>Vigabatrin</td>
</tr>
</tbody>
</table>
### Definition of Terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>The 28-day (±3 days) period from screening to randomization</td>
</tr>
<tr>
<td>Day 1</td>
<td>The day a patient first receives investigational medicinal product in this study.</td>
</tr>
<tr>
<td>End of study</td>
<td>Last patient last visit or last contact, whichever occurs last.</td>
</tr>
<tr>
<td>Enrolled patient</td>
<td>Patient is considered enrolled in the study from the time of providing written informed consent</td>
</tr>
<tr>
<td>IMP</td>
<td>Investigational Medicinal Product (Study Medication)</td>
</tr>
<tr>
<td>International Normalized Ratio</td>
<td>A calculation made to standardize prothrombin time.</td>
</tr>
<tr>
<td>Investigator</td>
<td>Study Principal Investigator or a formally delegated study physician.</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>Any seizure lasting 30 minutes or longer</td>
</tr>
</tbody>
</table>
2 OBJECTIVES

2.1 Primary

Blinded Phase:
To evaluate the efficacy of GWP42003-P as add-on therapy in reducing the frequency of focal seizures when compared with placebo in patients with tuberous sclerosis complex (TSC).

Open Label Extension:
To evaluate via the adverse events (AE) profile the long term safety and tolerability of GWP42003-P as add-on therapy in children and adults with TSC who experience inadequately-controlled focal seizures.

2.2 Secondary

Blinded Phase:
- To evaluate the effect of GWP42003-P compared with placebo on antiepileptic measures.
- To evaluate the effect of GWP42003-P on cognitive and behavioral function compared with placebo.
- To evaluate the effect of GWP42003-P on growth and development (in patients less than 18 years old) compared with placebo.
- To evaluate the effect of GWP42003-P on autistic features compared with placebo.
- To evaluate the effects of GWP42003-P on quality of life compared with placebo.
- To evaluate the safety and tolerability of GWP42003-P compared with placebo.
- To determine the pharmacokinetics (PK) of cannabidiol (CBD), Δ⁹-Tetrahydrocannabinol (THC) and their major metabolites following single and multiple doses of GWP42003-P.
- To evaluate the effects of GWP42003-P on plasma concentrations of concomitant antiepileptic drugs (AEDs), if applicable.

Open-label Extension:
- To evaluate the long term effects of GWP42003-P, as add-on therapy, on antiepileptic measures.
• To evaluate the long term effect of GWP42003-P on cognitive and behavioral function.
• To evaluate the long term effect of GWP42003-P on growth and development (in patients less than 18 years old).
• To evaluate the long term effect of GWP42003-P on autistic features.
• To evaluate the long term effects of GWP42003-P on quality of life.
• To evaluate the long term safety and tolerability of GWP42003-P.
3 BACKGROUND AND RATIONALE

3.1 Disease

Tuberous sclerosis complex (TSC) is a genetic disorder characterized by the formation of nonmalignant tumors (tubers) in multiple organ systems. The clinical signs of TSC arise as a result of inactivating mutations in either of two tumor suppressor genes: \textit{TSC1} (located on chromosome 9q34.13\textsuperscript{1}) or \textit{TSC2} (located on chromosome 16p13.32\textsuperscript{2}). \textit{TSC1} encodes the 130-kDa protein TSC1 (hamartin)\textsuperscript{1} while \textit{TSC2} encodes the 200-kDa protein TSC2 (tuberin)\textsuperscript{2}. TSC1 and TSC2 share no homology yet bind to each other with high affinity to form a functional heterodimer\textsuperscript{3} which suppresses the mammalian target of rapamycin (mTOR), a key regulator of cell growth and proliferation\textsuperscript{4}. Thus, inactivating mutations in \textit{TSC1} and \textit{TSC2} lead to inadequate suppression of mTOR signaling, resulting in abnormal cellular growth and tumorigenesis\textsuperscript{5,6}. TSC is transmitted in an autosomal dominant pattern of inheritance, although two-thirds of all cases are caused by \textit{de novo} mutations\textsuperscript{2,7,8}. Mutations in \textit{TSC1} account for approximately 15% of all cases of TSC while approximately 70% of all cases are due to mutations in \textit{TSC2}; ~15% of TSC patients have no identifiable mutation in the coding regions of either gene\textsuperscript{8,9}. Generally, \textit{TSC2} mutations result in a more severe disease phenotype compared with \textit{TSC1} mutations\textsuperscript{8,9}. The birth incidence of TSC is estimated to be 1 in 6,000 with approximately 50,000 individuals in the United States and 1 million individuals worldwide affected\textsuperscript{10,11}.

Tumors in TSC patients can occur in any major organ yet develop primarily in the brain, eyes, heart, kidney, skin and lungs\textsuperscript{12}. The random location, number, size and distribution of tumors result in a great variety of clinical manifestations, yet most patients exhibit dermatological, renal and/or neurological abnormalities, which appear at distinct developmental points\textsuperscript{13}. Dermatological abnormalities generally first appear in infancy or early childhood and include hypomelanotic macules, which are present in more than 90% of TSC patients, and facial angiofibromas, found in approximately 75% of TSC patients\textsuperscript{7,14,15}. In contrast, renal abnormalities tend not to develop until late childhood/adolescence and include angiomyolipomas (found in 50–70% of TSC patients), renal cysts (found in 25–35% of TSC patients) and, very rarely, renal-cell carcinomas (found in 2–3% of TSC patients)\textsuperscript{16,17,18}. Neurological abnormalities first appear during embryogenesis and include cerebral cortical tubers and subependymal nodules (SENs), each of which are found in 80–90% of TSC patients, as well as subependymal giant-cell astrocytomas (SEGAs), which are presumed to derive from SENs and are found in 5–15% of TSC patients\textsuperscript{19}. Whereas
SENs and SEGAs are usually asymptomatic, the presence of cortical tubers is widely believed to underlie the neurologic manifestations of TSC, which include epilepsy, cognitive disability and autism\textsuperscript{12,13,19}.

Epileptic seizures are the most common clinical manifestation of TSC, affecting more than 70\% of patients\textsuperscript{9,20,21,22}. Seizure onset occurs within the first year of life in approximately two-thirds of TSC patients and occurs within the first 3 years of life in 80\% of TSC patients\textsuperscript{13,20}. The onset of epilepsy in TSC commonly manifests as partial motor seizures, which in approximately one-third of TSC patients coexist with infantile spasms\textsuperscript{20}. Interictal electroencephalogram (EEG) recordings at onset typically show hypsarrhythmia, characterized by focal or multifocal spike discharges and irregular slow-wave activity\textsuperscript{23}. Virtually all TSC patients with infantile spasms and approximately half of all epileptic TSC patients without them develop multiple seizure types, including complex partial seizures (with or without secondary generalization), generalized tonic–clonic seizures, atonic seizures, and atypical absences\textsuperscript{20}. Although infantile spasms resolve with time, the frequency and severity of other seizures tend to increase throughout early childhood and nearly two-thirds of TSC patients develop medically intractable epilepsy, including Lennox–Gastaut syndrome\textsuperscript{20}. Cognitive impairment (intelligence/developmental quotient < 70) is observed in around 60\% of all TSC patients with a history of seizures and in approximately three-quarters of all TSC patients with a history of refractory epilepsy\textsuperscript{20}. Early management of seizures is therefore important in preventing subsequent epileptic encephalopathy and in reducing the associated cognitive and neuropsychiatric consequences\textsuperscript{22,24}.

In both the European Union and the United States, the drug of first choice for the treatment of infantile spasms secondary to TSC is vigabatrin (VGB), which was approved by the U.S. Food and Drug Administration (FDA) in 2009 (as Sabril\textsuperscript{®}) to treat infantile spasms in children aged 1 month to 2 years\textsuperscript{25}. VGB is a structural analog of \(\gamma\)-aminobutyric acid (GABA; the major inhibitory neurotransmitter in the central nervous system) that irreversibly inhibits GABA-transaminase and thereby increases brain levels of GABA\textsuperscript{26}. The initial prospective clinical study compared VGB (100–150 mg/kg/day) with adrenocorticotropic hormone (ACTH; 10 IU/day) in 42 patients with infantile spasms, only 4 of whom were diagnosed with TSC (3 received VGB; 1 received ACTH)\textsuperscript{27}. Although all 4 TSC patients became spasm-free after 20 days’ treatment (irrespective of which therapy was received), VGB was considered more effective than ACTH for the treatment of infantile spasms due to
TSC. In a separate randomized trial which compared VGB (150 mg/kg/day, \( n = 11 \)) with the oral steroid hydrocortisone (15 mg/kg/day, \( n = 11 \)) for the treatment of infantile spasms due to TSC, 100% of patients taking VGB were spasm-free after 1 month’s treatment compared with 45% taking hydrocortisone. Furthermore, of the non-responders who received hydrocortisone, all became spasm-free on switching to VGB therapy. A larger study compared 2 doses of VGB in treatment-naïve patients with infantile spasms. Of the patients with TSC, 52% were spasm-free after 2 weeks’ treatment compared with 16% of patients with other etiologies. Furthermore, 92% of TSC patients who began VGB therapy were spasm-free after 71 days’ treatment, although whether these patients received additional treatments during this time is unclear. Following recruitment of more patients into the trial and use of intent-to-treat analysis, however, only 21% of TSC patients could be classed as primary responders after 2 weeks’ treatment compared with 9% of patients with other etiologies. Although VGB is generally well tolerated, long-term treatment with VGB is associated with irreversible peripheral visual field defects (VFDs), the risk of which increases with increasing dose and cumulative exposure. The prevalence of VGB-associated VFDs in children with refractory complex partial seizures is approximately 15%; however, a very recent study found that 60% of TSC patients who received VGB treatment for infantile spasms subsequently developed VFDs. Furthermore, there is evidence that spasms may relapse and become refractory to VGB following discontinuation of treatment in children with focal cortical dysplasia/TSC.

ACTH (corticotropin) is a long-established therapy for infantile spasms and was approved by the FDA in 2010 (as Acthar Gel) as monotherapy in infants and children younger than 2 years. Although a number randomized controlled trials have demonstrated efficacy for ACTH in the treatment of infantile spasms and resolution of hypsarrhythmia, many of these studies do not provide TSC-specific data. Side effects are common with ACTH treatment and long-term exposure is associated with serious adverse events (SAEs), including fulminant infections secondary to immunosuppression, hypertension, glucosuria and metabolic abnormalities. Furthermore, there is evidence that ACTH may contribute to the enlargement of cardiac rhabdomyoma in TSC patients. ACTH treatment is therefore generally short-term (~2 weeks followed by taper) and close monitoring is required in TSC patients with cardiac rhabdomyoma. Relapse rates following effective ACTH treatment range from 15–60%. Oral corticosteroids (prednisone/prednisolone) have
also been used to treat infantile spasms, although randomized controlled trials demonstrate that even at very high doses only ~30–60% of patients achieve freedom from spasms\cite{37,38,39,40}.

The mTOR inhibitor everolimus (the 40-O-[2-hydroxyethyl] derivative of sirolimus/rapamycin) has demonstrated efficacy in reducing seizure frequency in TSC patients with SEGA\cite{41}. In an open-label study of add-on everolimus (3 mg/m\(^2\)/day; \(n=16\)), 56% of patients had a clinically-relevant reduction in total seizure frequency at 6 months\cite{42}. In a randomized controlled trial comparing everolimus (4.5 mg/m\(^2\)/day; \(n=78\)) with placebo (\(n=39\)), analysis of change in seizure frequency was inconclusive because most patients had no seizures at baseline or at 24 weeks’ follow-up\cite{43}. As both studies demonstrated significant reductions in SEGA volume, the FDA approved everolimus in 2010 (as Afinitor\textsuperscript{\textregistered}) and in 2012 (as Afinitor Disperz\textsuperscript{\textregistered\textsuperscript{TM}}) for the treatment of TSC patients with SEGA who are not eligible for curative surgical resection. In addition to resective surgery, other non-pharmacological treatments of TSC-associated epilepsy include vagus nerve stimulation and the introduction of a ketogenic diet\cite{22}.

### 3.2 GWP42003-P Background

The Investigational Medicinal Product (IMP), GWP42003-P, is formulated from extracts prepared from Cannabis sativa L. plants that have a defined chemical profile and contain consistent levels of CBD as the principal phytocannabinoid. Extracts from these plants are processed to yield purified (>95%) CBD that typically contains less than 0.5% (w/w) THC. The purified CBD is subsequently dissolved in excipients with added sweetener and flavoring.

The pharmacological effects of phytocannabinoids are thought to be mediated primarily via their interaction with the endocannabinoid system, which consists of cannabinoid receptors, endogenous ligands (endocannabinoids) and enzymes for endocannabinoid synthesis and degradation. To date, 2 G-protein-coupled receptors for cannabinoids have been identified, designated CB\(_1\) receptor and CB\(_2\) receptor. CBD does not bind to either of these receptors with any great affinity but does modulate the metabolizing enzymes of the endocannabinoid system. CBD also affects conduction of ion channels and acts on other G-protein-coupled receptors such as the transient receptor potential channel TRPV1\textsuperscript{44} and the orphan receptor GPR55\textsuperscript{45}. Importantly, CBD lacks the psychoactivity associated with THC. Further to this, CBD has demonstrated anticonvulsant, antipsychotic, anxiolytic, neuroprotective, antioxidant and anti-inflammatory activity\cite{46}. Very little data concerning AEs of CBD...
in humans currently exist; however, in the small number of placebo-controlled trials published to date investigating the anticonvulsant effects of CBD, few side effects have been reported after 4–12 months of 200–300 mg/day CBD46.

3.3 Rationale

The pharmacological therapies currently available for TSC-associated epilepsy often produce serious adverse effects, and a significant proportion of patients (37–63%) become resistant to treatment20,21. Consequently, there is a clear need for new, efficacious pharmaceutical treatments for refractory epilepsy. Given the limitations of current synthetic AEDs, it has been suggested that CBD should be tested for anticonvulsive efficacy in randomized controlled clinical trials, especially in infantile epileptic syndromes46. Although there are no published reports to date investigating the efficacy of CBD for seizures in TSC patients, a recent parent survey has reported that 84% of children with treatment-resistant epilepsy experienced a reduction in seizures while taking CBD-enriched cannabis, with over half of those reporting >80% reduction in seizure frequency47. The CBD-enriched cannabis was behaviorally well-tolerated and children often experienced improved sleep, increased alertness, and better mood.

3.3.1 Selection of Study Dose

Doses up to 800 mg CBD per day for up to 8 weeks have been well tolerated in adults in the GW Research Ltd (GW) clinical study GWMD0911248, which — assuming an average weight of 70 kg — equates to 11.4 mg/kg. In the literature, doses of CBD have been given up to 1500 mg CBD per day for 4 weeks in adults49, which, in a 70 kg human, equates to a daily dose of 21.4 mg/kg CBD.

GWP42003-P is currently being used by physicians for treatment of patients with intractable epilepsy resulting from a variety of etiologies in two open Individual Expanded Access Investigational New Drug (IND) studies and five open Intermediate Expanded Access IND studies. In the ongoing Individual Expanded Access IND studies, the initial dosing has been cautious (100 mg [morning] + 150 mg [afternoon/evening]), progressively increasing to 400 mg/day CBD; doses up to 22 mg/kg/day have been well tolerated in an individual pediatric patient. The Sponsor reviews all safety information on an ongoing basis from the patients in the Individual Expanded Access IND studies and is not aware of any safety issues arising from the dosing used to date.
The maximum dose patients can receive during the maintenance period of the blinded phase will be 50 mg/kg/day. During the open-label phase, the maximum dose patients can receive will be 50 mg/kg/day although all patients will initially titrate to 25 mg/kg/day. The maximum dose is based on emerging data from the Intermediate Expanded Access IND program. There are currently 10 open centers in this program, from which the physicians have shared data from 65 patients. Of these patients, the Sponsor has dosing data for 59. The maximum dose safely used to date is 51 mg/kg/day, with a mean dose of 24 mg/kg/day and 64% of doses falling within the 20–30 mg/kg/day range. Based on the available safety data, no dose-related changes in benefit-risk have been established.

3.4 Clinical Hypothesis

The primary clinical hypothesis is that there will be a difference between 50 mg/kg/day GWP42003-P and placebo in their effect on mean focal seizure frequency as measured by ANCOVA. The mean treatment difference would need to be at least 35% in order to achieve a clinically-relevant decrease in focal seizure frequency\(^5\). This study will also evaluate the effect of GWP42003-P compared with placebo on further measures of antiepileptic efficacy (responder analysis, focal seizure score, number of focal seizure-free days, number of seizures by subtype, number of infantile/epileptic spasms, usage of rescue medication, number of episodes of status epilepticus, duration of seizure subtypes), cognitive and behavioral function, autistic features, and quality of life. These endpoints are among those recommended by the European Medicines Agency guideline on clinical investigation of medicinal products in the treatment of epileptic disorders\(^5\).

The dose response relationship between two GWP42003-P Dose Levels (25 mg/kg/day and 50 mg/kg/day) and placebo will also be explored.
4 EXPERIMENTAL PLAN

4.1 Study Design

This multicenter study consists of a randomized, placebo-controlled, double-blind phase followed by an open-label extension (OLE) phase.

Blinded Phase:
The blinded phase of the study is a 1:1:1 randomized, double-blind, parallel-group, 16-week comparison of two doses of GWP42003-P versus placebo. Patients will complete a 4-week baseline period before they are randomized to receive either 25 mg/kg/day GWP42003-P, 50 mg/kg/day GWP42003-P or placebo. Randomization will be stratified by age according to the following ranges: 2–6, 7–11, 12–17 years and 18+ years. Patients in the placebo group will be split into two equivalent cohorts; half receiving 25 mg/kg/day dosing volumes and half receiving 50 mg/kg/day dosing volumes. Patients will begin a 4-week dose escalation period, titrating up to their assigned dose, before continuing on a stable dose of blinded IMP for 12 weeks.

Dose escalation for each patient is subject to the Investigator’s assessment of safety and tolerability. If a dose becomes poorly tolerated, the Investigator may consider temporarily or permanently reducing the dose for the remainder of the study.

Clinic visits will occur for screening (Day -28), randomization (Day 1) and, on Days 15 and 29 during titration and on Days 43, 57 and 85 until the end of treatment (Day 113). Safety telephone calls will be completed every two days during titration, one week after the end of titration and, for patients not entering the OLE, weekly from Visit 9 to Visit 11.

Patients will be required to perform daily interactive voice response system (IVRS) telephone calls to record seizure information. They will also complete a daily paper diary with information about their IMP and concomitant AED administration.

Following completion of the blinded phase, patients will be invited to continue to receive GWP42003-P in an OLE study.

Those patients opting not to enter the OLE will complete a 10 day taper period (down-titrating 10% per day for 10 days).

Open-label Extension Transition:
In order to maintain consistent exposure to IMP and maintain the integrity of the blind, patients will enter a 2-week blinded transition to the OLE. Doses will be titrated up or down, as appropriate, to ensure all patients enter the OLE taking 25 mg/kg/day GWP42003-P:
• Patients from the placebo group will titrate up to 25 mg/kg/day GWP42003-P.
• Patients from the 25 mg/kg/day GWP42003-P group will continue to take 25 mg/kg/day GWP42003-P.
• Patients from the 50 mg/kg/day GWP42003-P group will taper down (10% per day) to 25 mg/kg/day GWP42003-P.

Safety telephone calls will be completed every two days throughout the OLE transition.

**Open-label Extension:**
The OLE consists of a 10-day titration period followed by a maintenance period and a 10-day taper period.

Following titration according to the titration schedule, patients will continue with their optimal GWP42003-P dose. However, investigators may decrease the dose if a patient experiences intolerance, or increase the dose to a maximum of 50 mg/kg/day if required for better seizure control, until the optimal dose is found. Dose increases above 25 mg/kg/day are recommended to be done slowly, with maximum increments of 2.5 mg every 5–7 days. Safety telephone calls will be completed every two days throughout titration and one week after the end of titration. Patients whose dose has been decreased can have their dose increased again, provided there is adequate tolerance. If seizure freedom is achieved with use of GWP42003-P during the study, the Investigator should consider reducing the dose of concomitant AEDs after six months of seizure freedom.

If market authorization is granted for GWP42003-P in TSC, the patient will complete the study. Patients who do not immediately continue to use GWP42003-P will then commence a taper period (tapering 10% per day for 10 days).

A study schema (Figure 1-1), presented at the end of Section 1, depicts the overall study design. More detailed information on treatment and study procedures is provided in Section 8 and Section 9, respectively.

### 4.1.1 Primary Endpoint

**Blinded Phase:**
The primary endpoint is the percentage change from baseline in number of focal seizures (average per 28 days) during the treatment period (maintenance and titration) in patients taking GWP42003-P compared with placebo.

Focal seizures include: focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures. All seizures will have
focal onset in TSC but may not be discernable by patient or caregiver. All definite and probable seizures will be counted and assumed to be focal in origin.

**Open-label Extension:**
The safety of GWP42003-P will be evaluated by assessing the incidence, type and severity of AEs.

### 4.1.2 Secondary Endpoint(s)

#### Blinded Phase:
The following endpoints will be compared between treatment groups over the 16-week, double-blind treatment period (all changes relative to baseline):

**Antiepileptic efficacy measures:**

- Number of patients considered treatment responders defined as those with a ≥25%, ≥50%, ≥75% or 100% reduction in focal seizure frequency.
- Number of patients experiencing a >25% worsening, −25 to +25% no change, 25–50% improvement, 50–75% improvement or >75% improvement in focal seizure frequency.
- Change in composite focal seizure score (frequency × severity).
- Change in number of focal seizure-free days.
- Change in number of seizures by subtype.
- Change in number of infantile/epileptic spasms.
- Change in use of rescue medication.
- Change in the number of episodes of *status epilepticus* (convulsive and non-convulsive).
- Changes in duration of seizure subtypes as assessed by the Subject Global Impression of Change in Seizure Duration (SGIC-SD) or the Caregiver Global Impression of Change in Seizure Duration (CGIC-SD).

**Cognitive and Behavioral Function:**

- Changes in Wechsler Scales (pre-school, primary, children, adult).
- Changes in Achenbach Child Behavior Checklist (CBCL) and Adult Behavior Checklist (ABCL).

**Growth and Development (patients less than 18 years):**

- Change in serum insulin-like growth factor-1 (IGF-1) levels.
- Change in Tanner Staging score (for patients aged 10–17 [inclusive]).
Autistic Features:

- Change in Social Communication Questionnaire (SCQ) score.

Quality of Life:

- Changes in the Quality of Life in Childhood Epilepsy (QOLCE; patients 2–18 years) or Quality of Life in Epilepsy (QOLIE-31-P; patients 19+ years) score.
- Change in Caregiver Global Impression of Change (CGIC) or Subject Global Impression of Change (SGIC) score.
- Change in Physician Global Impression of Change (PGIC) score.

Safety and Tolerability:

- AEs.
- Clinical laboratory parameters.
- 12-lead electrocardiogram (ECG).
- Physical examination parameters (including height and weight).
- Vital signs.
- Columbia Suicide Severity Rating Scale (C-SSRS; 19+ years) or C-SSRS Children’s (6–18 years) score, where applicable.
- Number of inpatient hospitalizations due to epilepsy.
- Abuse liability.
- Effects on menstruation cycles (in females).

Pharmacokinetics:

- The plasma concentration/time curve of CBD, THC and their major metabolites will be described following single and multiple doses of GWP42003-P, with the aim being to estimate:
  - Peak plasma concentration ($C_{\text{max}}$).
  - Time to peak concentration ($t_{\text{max}}$).
  - Area under the plasma concentration curve from time zero to infinity ($\text{AUC}_{(0-\infty)}$).
  - Terminal half-life ($t_{\frac{1}{2}}$).
- Plasma concentrations of concomitant AEDs before and after treatment with GWP42003-P, where available.

Open-label Extension:

The following endpoints will be assessed relative to the pre-randomization baseline of the blinded phase:

Antiepileptic Efficacy Measures:

- Percentage change in number of focal seizures (average per 28 days).
• Number of patients considered treatment responders, defined as those with a ≥25%, ≥50%, ≥75% or 100% reduction in focal seizure frequency.
• Number of patients experiencing a >25% worsening, −25 to +25% no change, 25–50% improvement, 50–75% improvement or >75% improvement in focal seizure frequency.
• Change in composite focal seizure score (frequency × severity).
• Change in number of focal seizure-free days.
• Change in number of seizure subtypes.
• Change in number of infantile/epileptic spasms.
• Change in use of rescue medication.
• Change in the number of episodes of status epilepticus (convulsive and non-convulsive).
• Changes in duration of seizure subtypes as assessed by the SGIC-SD or the CGIC-SD.

Cognitive and Behavioral Function:
• Changes in Vineland-II.
• Changes in Wechsler Scales (pre-school, primary, children, adult).
• Changes in CBCL or ABCL.

Growth and Development (patients less than 18 years):
• Change in serum IGF-1 levels.
• Change in Tanner Staging score (for patients aged 10–17 [inclusive]).

Autistic Features:
• Changes in SCQ score.

Quality of Life:
• Changes from baseline in the QOLCE (patients 2–18 years) or QOLIE-31-P (patients 19+ years) score.
• Change in CGIC or SGIC score.
• Change in PGIC score.

Safety and Tolerability:
• Clinical laboratory parameters.
• ECG.
• Physical examination parameters (including height and weight).
• Vital signs.
• C-SSRS (19+ years) or C-SSRS Children’s (6–18 years) score, where applicable.
• Number of inpatient hospitalizations due to epilepsy.
• Abuse liability.
• Effects on menstruation cycles (in females).

4.2 Number of Centers

Approximately 20 centers are expected to participate in this study.

4.3 Number of Patients

Blinded Phase:
A total of 144 patients will be targeted to be enrolled. The 144 patients will be randomly allocated on a 1:1:1 basis (25 mg/kg/day GWP42003-P, 50 mg/kg/day and placebo, 48 patients per group). Patients in the placebo group will be split into two cohorts (24 patients receiving 25 mg/kg/day dosing volumes and 24 patients receiving 50 mg/kg/day dosing volumes), but it is assumed that these two cohorts can be pooled for the analyses of efficacy. If it is assumed that patients in the placebo group will experience a mean reduction in focal seizure frequency of 15% (from baseline), this sample size of 48 patients per group will be sufficient to detect a difference of 35% between treatments (i.e., patients receiving GWP42003-P will experience at least a 50% reduction in focal seizures). This is based on a standard deviation of 60%, using a two-sided 5% significance level and 80% power.

Open-label Extension:
All patients who wish to continue on IMP following the blinded phase.

The sample size calculation is explained fully in Section 13.1.
5 INVESTIGATIONAL MEDICINAL PRODUCT

Please refer to the separate Pharmacy Manual for more detailed information on the Investigational Medicinal Product (IMP).

5.1 GWP42003-P Oral Solution

GWP42003-P oral solution is presented as a yellow oily solution containing 100 mg/mL CBD dissolved in the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring (Table 5.1-1).

<table>
<thead>
<tr>
<th>Material</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBD</td>
<td>100 mg/mL</td>
</tr>
<tr>
<td>Anhydrous ethanol</td>
<td>79 mg/mL</td>
</tr>
<tr>
<td>Sucralose</td>
<td>0.5 mg/mL</td>
</tr>
<tr>
<td>Strawberry flavoring</td>
<td>0.2 mg/mL</td>
</tr>
<tr>
<td>Sesame oil</td>
<td>make up to 1 mL</td>
</tr>
</tbody>
</table>

Table 5.1-1 Formulation of GWP42003-P Oral Solution

5.2 Placebo Oral Solution

Placebo oral solution is presented as a yellow oily solution containing the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring (Table 5.2-1).

<table>
<thead>
<tr>
<th>Material</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anhydrous ethanol</td>
<td>79 mg/mL</td>
</tr>
<tr>
<td>Sucralose</td>
<td>0.5 mg/mL</td>
</tr>
<tr>
<td>Strawberry flavoring</td>
<td>0.2 mg/mL</td>
</tr>
<tr>
<td>Sesame oil</td>
<td>make up to 1 mL</td>
</tr>
</tbody>
</table>

Table 5.2-1 Formulation of Placebo Oral Solution

5.3 Packaging, Storage and Drug Accountability

5.3.1 Packaging and Labeling

The IMP will be manufactured, packaged, labeled and/or distributed by G-Pharm or delegated contractors. The IMP will be presented in 100 mL amber glass bottles with child-resistant caps and packed in cartons. Sufficient IMP will be dispensed at each relevant visit considering the dose group and weight of each patient. A unique identification number will be used to identify each box and the IMP it contains. The unique identification number together with the packaging reference number (PRN) will permit full traceability of manufacture, pack and label activities conducted at or on behalf of G-Pharm and the IMP information held on the Interactive Voice Response System (IVRS). G-Pharm will ensure that all IMP provided is fully labeled and packaged. Label text will include the following information, as a minimum:
• Sponsor’s name.
• Product identification (e.g., “GWP42003-P/placebo”).
• Dose and/or Potency.
• Expiry date.
• Storage conditions.
• Instruction: “For clinical trial use only”.
• Instruction: “Keep out of the sight and reach of children”.

In addition, any local country requirements in accordance with local Drug Law or Regulatory Requirement will be included in the final label text.

Directions of use, name, address and the telephone number of the Investigator (or main contact for information about the product or the clinical trial) will be provided separately to the patient. Patients will be instructed to retain and carry this information with them at all times.

5.3.2 Storage

The IMP must be stored upright at room temperature (<30°C) and must not be refrigerated or frozen. It must also be kept away from heat and direct sunlight.

The IMP must be stored in compliance with the local regulations for a controlled drug (if applicable to country). The sponsor must approve storage location and facilities. Temperature records of the clinical site storage location must be maintained (recording a minimum of Monday–Friday, excluding public holidays) from date of receipt of first shipment until end of study dispensing period at each center. These records must contain at least the minimum and maximum daily temperatures and should be made available to the appropriate GW personnel for review throughout the study. Temperature records taken during transit of IMP to center must be checked on receipt.

Should storage conditions deviate from these specified requirements, the GW study monitor must be contacted immediately to confirm if the IMP remains suitable for use. IMP should be placed under quarantine until written confirmation is received that IMP is suitable for use.

IMP will be transported to country depots and clinical sites in compliance with Good Distribution Practice guidelines.
5.3.3 Supply and Return of Investigational Medicinal Product

All IMP will be shipped to approved Depot facilities and clinical sites with a Product Release Certificate that includes a physical description of the product for confirmation of identity on receipt.

Once a center has been activated via the IVRS at study initiation, IMP will be shipped to the identified responsible person, such as the pharmacist, at the Investigator’s center, who will check the amount received (against the IVRS Shipment Request) and condition of the drug (i.e., integrity, physical appearance, temperature during transit).

Details of IMP received will be recorded in the IMP accountability record (see Section 5.3.4). The center will acknowledge IMP receipt via the IVRS and will complete any receipt forms required. IMP will be dispensed and returned as detailed in Section 8.4 with further IMP shipments to be initiated by IVRS. As directed, all supplies, including unused, partially used, or empty containers, will be returned to G-Pharm / depot or destroyed at a G-Pharm-approved site if agreed in writing by the study monitor.

5.3.4 Investigational Medicinal Product Accountability

The Investigator has overall responsibility for the accountability of all used and unused IMP. A drug accountability record for the IMPs must be kept current and should contain:

- Study Code
- PRN, Treatment number, date of receipt and quantity of IMP received.
- Patient’s trial identification and /or Treatment number.
- Date and quantity of IMP dispensed.
- The initials of the dispensing / dosing party.
- Date and quantity of IMP returned to the Investigator.
- IMP expiry dates.

IMP will be dispensed at Visits 2, 3, 4, 6 and 8 during the blinded phase and Visits B1, B2, B3 and B4 and every three months thereafter during the OLE. Patients will be asked to return all IMP (used and unused) to each subsequent visit. The center will check the returned IMP against the usage recorded in the IVRS. Any discrepancies will be discussed with the patient or their caregiver at the time of the visit and documented accordingly within the patient’s source documents.

The Investigator must inform GW promptly of all missing or unaccountable IMP.
A record of returned IMP must be completed and included in the shipment of used and unused IMP to GW or the relevant Drug Distribution Depot. At the end of the study, a record/statement of reconciliation must be completed and provided to GW. These inventories must be made available for inspection by an authorized GW representative and local officials or regulatory agency inspectors.

Please refer to the separate Pharmacy Manual for more detailed information on the IMP.

5.3.5 Post-trial Provision

Following completion of the blinded phase patients will be invited to continue to receive GWP42003-P in an open-label extension study. The open-label extension will continue until market authorization is granted for GWP42003-P in TSC.
6 PATIENT ELIGIBILITY

Investigators are responsible for confirming patient eligibility and will be required to maintain a log that includes limited information about all screened patients (initials, age, sex; as allowed per local regulations) and outcome of screening. After the screening visit, investigators will submit the patient’s documented history of TSC directly to the Epilepsy Study Consortium (ESC) for confirmation of diagnosis by the ESC. The ESC may ask the investigator for additional information to assist in their decision. The decision will be made within 14 days of receipt of all required information and the ESC will provide written confirmation directly to the investigator.

6.1 Inclusion Criteria

For inclusion in the study, patients must fulfil ALL of the following criteria:

6.1.1 Patient is male or female aged between two and 65 years inclusive.
6.1.2 Patient and/or parent(s)/legal representative is willing and able to give informed consent/assent for participation in the study (see Section 15.2).
6.1.3 Patient and their caregiver are willing and able (in the Investigator’s opinion) to comply with all study requirements (including accurate diary and IVRS completion).
6.1.4 Well-documented history of focal epilepsy, with focal seizures as the primary seizure type, compatible electroencephalogram (EEG) and clinical history.
6.1.5 Clinical diagnosis of TSC according to the criteria agreed by the 2012 International Tuberous Sclerosis Complex Consensus Conference19.
6.1.6 All medications or interventions for epilepsy (including ketogenic diet and any neurostimulation devices for epilepsy) must have been stable for one month prior to screening and the patient is willing to maintain a stable regimen throughout the study.
6.1.7 Patient is willing to keep any factors expected to affect seizures stable (such as the level of alcohol consumption and smoking).
6.1.8 Patient and/or parent(s)/legal representative is willing to allow the responsible authorities to be notified of participation in the study, if mandated by local law.
6.1.9 Patient and/or parent(s)/legal representative is willing to allow his or her primary care practitioner and consultant (if they have one) to be notified of participation in the study, if mandated by local law.

At the end of the baseline period, patients must also meet the following criterion:

6.1.10 Experienced at least eight focal seizures during the first 28 days of the baseline period, with at least one seizure occurring in at least three of the four weeks.
6.1.11 Completed at least 90% of calls to IVRS during the first 28 days of the baseline period.
6.2 Exclusion Criteria

The patient may not enter the study if ANY of the following apply:

6.2.1 Patient has a history of pseudo-seizures.
6.2.2 Patient has clinically significant unstable medical conditions other than epilepsy.
6.2.3 Patient has an illness in the four weeks prior to screening or randomization, other than epilepsy, which in the opinion of the Investigator could affect seizure frequency.
6.2.4 Patient has undergone general anesthetic in the four weeks prior to screening or randomization.
6.2.5 Patient has undergone surgery for epilepsy in the six months prior to screening.
6.2.6 Patient is being considered for epilepsy surgery or any procedure involving general anesthesia.
6.2.7 Patient is taking felbamate, and they have been taking it for less than one year prior to screening.
6.2.8 Patient is taking an oral mTOR inhibitor.
6.2.9 Patient has, in the investigator’s opinion, clinically significantly abnormal laboratory values.
6.2.10 Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the Investigational Medicinal Product (IMP), such as sesame oil.
6.2.11 Active suicidal plan/intent in the past six months, or a history of suicide attempt in the last two years, or more than one lifetime suicide attempt.
6.2.12 C-SSRS grade 4 or 5 at screening.
6.2.13 Patient is currently using or has in the past used recreational or medicinal cannabis, or cannabinoid-based medications, within the three months prior to screening and is unwilling to abstain for the duration for the study.
6.2.14 Patient has tumor growth which, in the opinion of the Investigator, could affect the primary endpoint.
6.2.15 In the opinion of the Investigator the patient has clinically significant abnormalities in the ECG measured at screening or randomization or any concurrent cardiovascular conditions, which will interfere with the ability to read their ECGs.
6.2.16 Patient has significantly impaired hepatic function at the screening visit (Visit 1) or the randomization visit (Visit 2), defined as any of the following:
   i) Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 × upper limit of normal (ULN).
   ii) Serum ALT or AST ≥ 3 × ULN and (TBL [serum total bilirubin] ≥ 2 × ULN or international normalized ratio [INR] > 1.5).
iii) Serum ALT or AST $\geq 3 \times$ ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

This criterion can only be confirmed once the laboratory results are available.

6.2.17 Patient is female and of child bearing potential, or is male whose partner is of child bearing potential, unless willing to ensure that they or their partner use a highly effective method of birth control (e.g., hormonal contraceptives, intrauterine devices/hormone-releasing systems, bilateral tubal occlusion, vasectomized partner, sexual abstinence) during the study and for three months thereafter.

6.2.18 Female patient who is pregnant (positive pregnancy test), lactating or planning pregnancy during the course of the study and for three months thereafter.

6.2.19 Patient has received an IMP within the 12 weeks prior to the screening visit.

6.2.20 Patient has any other significant disease or disorder which, in the opinion of the Investigator, may either put the patient at risk because of participation in the study, may influence the result of the study, or may affect the patient’s ability to take part in the study.

6.2.21 Any abnormalities identified following a physical examination of the patient that, in the opinion of the Investigator, would jeopardize the safety of the patient if they take part in the study.

6.2.22 Patient has donated blood during the past 12 weeks and is unwilling to abstain from donation of blood during the study.

6.2.23 Patient has been previously randomized into this study.

6.2.24 Patient has any known or suspected history of alcohol or substance abuse.

6.2.25 Patient has travel outside the country of residence planned during the study.
7 PATIENT ENROLMENT

Before patients may be entered into the study, GW requires a copy of the relevant center’s Ethics Committee (EC) or Institutional Review Board (IRB) written approval of the protocol, informed consent/assent forms (ICF) and other patient information material. Patients will be considered enrolled in the study from the time of providing written informed consent/assent. All patients and/or parent(s)/legal representatives, where appropriate, must personally sign and date the consent and, if allowed per local regulations, assent forms prior to any procedures being performed (refer to Section 9.2.1 and Section 15.2).

7.1 Treatment Assignment

At the start of Visit1, enrolled patients will be allocated a unique patient number using an IVRS. After confirmation of eligibility at Visit 2, patients will be randomly allocated to 25 mg/kg/day, 50 mg/kg/day or placebo using the IVRS. G-Pharm will provide all IMP in a packed and labelled state and the IVRS will identify the pack number to be dispensed to the patient at each relevant visit, according to the treatment assigned in the randomization schedule.

7.2 Randomization

The allocation of IMP to treatment number will be done according to a randomization schedule produced by an independent statistician. The randomization schedule will be held centrally and not divulged to any other person involved in the study until the database has been locked and unblinding authorized by the relevant GW personnel. For access to blinded treatment assignment, see Section 8.5.

The randomization will be stratified by age group (2–6 years, 7–11 years, 12–17 years and 18–65 years).
8 TREATMENT PROCEDURES

8.1 Investigational Medicinal Product Dosage, Administration and Schedule

The use of placebo in the current study was deemed necessary to determine the efficacy and safety of the current intervention, since the best proven intervention had already been tried or may be given as an adjuvant treatment, failing to fully alleviate the patient’s symptoms. For details regarding IMP formulations, see Section 5.

Patients will be assigned one of two Dose Levels of active IMP or placebo on a 1:1:1 basis (48 patients per treatment group). Patients in the placebo group will be split into two cohorts (24 receiving Low Dose Level dosing volumes and 24 receiving High Dose Level dosing volumes), but it is assumed that these two cohorts can be pooled for the analyses of efficacy.

8.1.1 Dose Administration

The IMP will be administered orally by the patient or their caregiver twice each day (morning and evening) using the syringe(s) provided. The IMP will be swallowed and may be taken with other concomitant medications, as directed by the investigator.

8.1.2 Dose Escalation and Dose Adjustments

All patients will be weighed during Visit 2 and the daily volumes of IMP solution to be taken during the four-week titration period and for the remainder of the blinded phase maintenance period will be calculated via the IVRS and the dosing regimen provided to the patient and/or caregiver. Doses may be altered during the OLE according to changes in patient weight. Further information on dispensing procedures will be provided in a separate Pharmacy Manual.

Titration from 0 - 25 mg/kg/day will begin at 5 mg/kg/day and will be increased in increments of 5 mg/kg/day every two days (patients will remain on each dose level for two days before they progress on to the next dose). Titration from 25 - 50 mg/kg/day will continue at smaller increments of 2.5 mg/kg/day every two days.

<table>
<thead>
<tr>
<th>Table 8.1.2-1</th>
<th>Dose Titration Regimen*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>Dose Level 1 (25 mg/kg/day)</td>
</tr>
<tr>
<td>1</td>
<td>5.0 mg/kg</td>
</tr>
<tr>
<td>2</td>
<td>5.0 mg/kg</td>
</tr>
<tr>
<td>3</td>
<td>10.0 mg/kg</td>
</tr>
<tr>
<td>4</td>
<td>10.0 mg/kg</td>
</tr>
</tbody>
</table>
Table 8.1.2-1  Dose Titration Regimen*

<table>
<thead>
<tr>
<th>Day</th>
<th>Dose Level 1 (25 mg/kg/day)</th>
<th>Dose Level 2 (50 mg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>15.0 mg/kg</td>
<td>15.0 mg/kg</td>
</tr>
<tr>
<td>6</td>
<td>15.0 mg/kg</td>
<td>15.0 mg/kg</td>
</tr>
<tr>
<td>7</td>
<td>20.0 mg/kg</td>
<td>20.0 mg/kg</td>
</tr>
<tr>
<td>8</td>
<td>20.0 mg/kg</td>
<td>20.0 mg/kg</td>
</tr>
<tr>
<td>9</td>
<td>25.0 mg/kg</td>
<td>25.0 mg/kg</td>
</tr>
<tr>
<td>10</td>
<td>25.0 mg/kg</td>
<td>25.0 mg/kg</td>
</tr>
<tr>
<td>11</td>
<td>25.0 mg/kg</td>
<td>27.5 mg/kg</td>
</tr>
<tr>
<td>12</td>
<td>25.0 mg/kg</td>
<td>27.5 mg/kg</td>
</tr>
<tr>
<td>13</td>
<td>25.0 mg/kg</td>
<td>30.0 mg/kg</td>
</tr>
<tr>
<td>14</td>
<td>25.0 mg/kg</td>
<td>30.0 mg/kg</td>
</tr>
<tr>
<td>15</td>
<td>25.0 mg/kg</td>
<td>32.5 mg/kg</td>
</tr>
<tr>
<td>16</td>
<td>25.0 mg/kg</td>
<td>32.5 mg/kg</td>
</tr>
<tr>
<td>17</td>
<td>25.0 mg/kg</td>
<td>35.0 mg/kg</td>
</tr>
<tr>
<td>18</td>
<td>25.0 mg/kg</td>
<td>35.0 mg/kg</td>
</tr>
<tr>
<td>19</td>
<td>25.0 mg/kg</td>
<td>37.5 mg/kg</td>
</tr>
<tr>
<td>20</td>
<td>25.0 mg/kg</td>
<td>37.5 mg/kg</td>
</tr>
<tr>
<td>21</td>
<td>25.0 mg/kg</td>
<td>40.0 mg/kg</td>
</tr>
<tr>
<td>22</td>
<td>25.0 mg/kg</td>
<td>40.0 mg/kg</td>
</tr>
<tr>
<td>23</td>
<td>25.0 mg/kg</td>
<td>42.5 mg/kg</td>
</tr>
<tr>
<td>24</td>
<td>25.0 mg/kg</td>
<td>42.5 mg/kg</td>
</tr>
<tr>
<td>25</td>
<td>25.0 mg/kg</td>
<td>45.0 mg/kg</td>
</tr>
<tr>
<td>26</td>
<td>25.0 mg/kg</td>
<td>45.0 mg/kg</td>
</tr>
<tr>
<td>27</td>
<td>25.0 mg/kg</td>
<td>47.5 mg/kg</td>
</tr>
<tr>
<td>28</td>
<td>25.0 mg/kg</td>
<td>47.5 mg/kg</td>
</tr>
<tr>
<td>29</td>
<td>25.0 mg/kg</td>
<td>50.0 mg/kg</td>
</tr>
</tbody>
</table>

* IMP is to be taken twice daily. Total daily doses are shown.

Each patient will take their first dose of IMP at Visit 2 (Day 1) and their final maintenance dose of IMP at Visit 9 (Day 113). If an unacceptable AE develops at any time during the titration period, dosing should initially be suspended or amended, at the investigator’s discretion, until the event has resolved. During the maintenance period, patients should continue on a stable dosing regimen at the target Dose Level. If that dose becomes poorly tolerated, the investigator may consider temporarily or permanently reducing the dosage for the remainder of the maintenance period. However, where possible, the patient should be encouraged to return to the target Dose Level.

Patients entering the OLE will first complete a two-week open label extension transition. This double blind transition phase will take two weeks to complete. Doses will be titrated up or down, as appropriate, to ensure all patients enter the open label extension taking 25 mg/kg/day. Patients from the placebo group will titrate up to 25 mg/kg/day, patients from the 25 mg/kg/day group will continue to take 25 mg/kg/day and patients from the 50 mg/kg/day will taper down (10% per day) to 25 mg/kg/day.
Patients who do not enter the OLE study at Visit 9 or withdraw early will have their dose of IMP tapered gradually (10% each day) over a period of 10 days unless continued dosing is not possible due to an AE. Patients not entering the OLE will return used and unused IMP to the clinic at Visit 10.

8.2 Concomitant Therapy

It is theoretically possible that GWP42003-P may modify the metabolism of other drugs (including AEDs) administered concurrently and there remains the possibility of pharmacological interactions between GWP42003-P and other concurrently administered drugs. Doses of any concomitant AEDs must have been stable for at least four weeks prior to screening and must remain stable throughout the study period. If plasma concentrations of concomitant AEDs are found to be altered following administration of IMP then the dosage of concomitant AEDs may be modified, depending on the clinical need, following discussion with the GW medical advisor. Further information on drug interactions can be found in the Investigator Brochure (IB)\(^5\).

The use of rescue medication is allowed when necessary. Any medication, other than the IMP, taken during the study must be recorded on the Case Report Form (CRF). Any non-pharmacological therapies (e.g., ketogenic diet, VNS) must also be stable up to four weeks prior to screening and throughout the duration of the study.

8.3 Prohibited Therapy During Study Period

The following medications are prohibited for the duration of the study beginning from acquisition of patient consent/assent. However, any patients taking these medications after randomization should not be withdrawn from the study unless there are safety concerns. If applicable, the possible effects of these medications on the primary endpoint will be considered during the assessment of the evaluable period (see Section 13.6.1).

- Any new medications or interventions for epilepsy (including ketogenic diet and VNS) or changes in dosage.
- Recreational or medicinal cannabis or synthetic cannabinoid based medications (including Sativex) within three months prior to or during the study.
- Any other IMP taken as part of a clinical trial within six months or during the study.

8.4 Compliance in Investigational Medicinal Product Administration

The IMP is dispensed to the patient at each of the following visits:
• Visit 2 (Day 1)
• Visit 3 (Day 15)
• Visit 4 (Day 29)
• Visit 5 (Day 43)
• Visit 6 (Day 57)
• Visit 8 (Day 85)
• All OLE visits until the end of treatment

The patient or their caregiver will record the volume of solution taken on each treatment day in the diary.

Patients should return all IMP (used and unused) at each of visits 3, 4, 6, 8 and 9 during the blinded phase and at all OLE visits. The usage recorded in the diary and the usage projected in the IVRS system will be checked and any discrepancies discussed with the patient or their caregiver at the time of the visit and documented accordingly within the patient’s source documents.

Records of IMP accountability will be maintained according to Section 5.3.4.

8.5 Access to Blinded Treatment Assignment (Blinded Phase and OLE Transition only)

The identity of IMP assigned to patients will be held by the IVRS. The Principal Investigator (PI) at each center, or his/her designee, is responsible for ensuring that information on how to access the IVRS for an individual patient is available to the relevant staff in case of an emergency and unblinding is required. A patient’s treatment assignment should only be unblinded when knowledge of the treatment is essential to make a decision on the medical management of the patient. Unblinding for any other reason will be considered a protocol deviation.

The Investigator is encouraged to contact GW to discuss the rationale for unblinding prior to doing so. However, to prevent delays to the Investigator or medical personnel responding to a potentially emergent situation, unblinding of study medication will not be dependent upon the Investigator receiving approval from GW (i.e., the Investigator will be able to obtain the code break information independent of contacting GW).

If the Investigator does unblind, they must contact GW within one working day of the event and must document the time, date and reason(s) for unblinding on the patient’s CRF.
9 STUDY PROCEDURES

A list of the required study procedures is provided in the subsections that follow; refer also to the Schedule of Assessments (APPENDIX 1). Assessments or tests that are not done and examinations that are not conducted must be reported as such in the CRFs.

The location of the source data for the following procedures will be documented, per center, in a signed ‘Source Data Verification’ plan; for further details see Section 16.2.

9.1 Study Procedures by Visit

Patients and their parent(s)/legal representative will be invited to take part in the study and will be issued with the patient information and informed consent/assent or the patient/parent(s)/legal representative information and informed consent. Following adequate time to discuss the study with the Investigator, nurse, relatives or caregiver, as wished, patients/parent(s)/legal representatives who provide written informed consent/assent will be screened for entry into the study.

9.1.1 Blinded Phase

9.1.1.1 Visit 1 (Day -28, Screening)

The following observations will be made at Visit 1: demographics, medical history (including seizure information since diagnosis, history of epilepsy-specific genetic testing and all prior AEDs taken), concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, postural blood pressure and visit procedure-related AEs. A blood test to determine the mutation status of TSC1 and TSC2 will be carried out if it is unknown.

The Diagnostic Review Form (DRF) will be sent to the ESC to confirm the diagnosis of TSC.

Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry, urinalysis, a urine THC screen and a pregnancy test (using a serum sample, if appropriate). Suicidality will be assessed using the C-SSRS/Children’s C-SSRS (Baseline) or, in patients with profound cognitive impairment, by interview and clinical judgement.

Patients who satisfy all inclusion and none of the exclusion criteria specified in Section 6 will be assigned a unique patient number and then begin the 28 (+3)-day baseline period. The investigator will review and train the caregiver to identify the patient’s expected seizure types. Patients or their caregivers will be issued with IVRS details and will be instructed on how to use it to record daily seizure information.
Patients or their caregivers will also be given a paper diary to record usage of IMP, rescue medication, concomitant AEDs and AEs and will be instructed on how to do so.

The investigator must record the patient’s attendance at the visit and confirm the outcome of screening on the CRF. The laboratory results will be available within 3-5 working days after Visit 1. If the results show a patient is ineligible, the patient will be withdrawn from the study.

9.1.1.2 Visit 2 (Day 1, Randomization)

This visit will occur 28 days after Visit 1. A visit window of +3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

The following observations will be made at Visit 2: concomitant medications, (including AEDs), physical examination (including height and body weight), details of menstruation (for females), Tanner Staging (for patients aged 10-17 years [inclusive], or earlier if clinically indicated by onset of menarche or other signs of precocious puberty), ECG, vital signs, postural blood pressure, epilepsy-related hospitalizations, AEs and paper diary review. The ECG will be repeated four hours after the first dose of IMP. The investigator will verify that the Epilepsy Study Consortium has confirmed the diagnosis of TSC.

Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry, urinalysis, a urine THC screen, determination of serum IGF-1 levels (for patients less than 18 years of age) a pregnancy test and if appropriate (using both a serum sample and a urine dipstick). Provided that the risk/benefit outcome is favorable in the investigator’s opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs. PK samples (patients >20 kg in weight only) will be taken following randomization and at two hours and four hours after first dose of IMP. An additional PK sample will be taken six hours after the first dose for patients aged 18 years or above.

The investigator must assess the patient’s daily number of focal seizures from the patient’s IVRS data, record the patient’s attendance at the visit, and confirm the outcome of the visit prior to randomization. Patients who have experienced at least eight focal seizures during the first 28 days of the baseline period, and who meet all of the other inclusion and none of the exclusion criteria, will be eligible to continue in the study.
At Visit 2 eligible patients will be randomized to receive either 25 mg/kg/day GWP42003-P, 50 mg/kg/day GWP42003-P or placebo on a 1:1:1 basis.

Following randomization at Visit 2, patients will remain at the clinic where the following baseline assessments will be performed prior to the administration of study medication: QOLCE/QOLIE-31-P, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II. Suicidality will be assessed using the C-SSRS/ Children’s C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgement.

Patients/caregivers will be asked to write a brief description of their/the patient’s overall condition and assess the average duration of seizure subtypes as a memory aid for the SGIC/CGIC and SGIC-SD/CGIC-SD; these will be referred to at relevant, subsequent visits or withdrawal.

IMP will be dispensed for the following three weeks and patients or their caregivers will be provided with individual dosing schedules as described in Section 8.1. Each patient will then receive a titration regime. The first dose of IMP will be administered in clinic.

Patients or their caregivers will be instructed how to record the diary information, including both the paper and IVRS diaries. Provided that the risk/benefit outcome is favorable in the investigator’s opinion, a blood sample will be collected prior to administration of IMP to determine plasma concentrations of concomitant AEDs.

Following Visit 2, during titration, safety telephone calls must be made every two days. A further call must be completed one week after the end of titration. During these calls, caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.

9.1.1.3 Visit 3 (Day 15)

This visit will occur 14 days after Visit 2 (randomization). A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

The following observations will be made at Visit 3: concomitant medications, (including AEDs), physical examination (including height and body weight), ECG, vital signs, epilepsy-related hospitalizations and AEs.

Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry and urinalysis. Provided that the risk/benefit outcome is favorable in the investigator’s opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs.
The PGIC, SGIC/CGIC and Vineland-II will also be performed. Suicidality will be assessed using the C-SSRS/Children’s C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgement.

The investigator must assess adherence to the titration regimen by reviewing the patient’s diary and IVRS data and record the patient’s attendance at the visit.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients will then receive a new treatment pack of the IMP.

Following Visit 3, during titration, safety telephone calls must be made every two days. During these calls, caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.

### 9.1.1.4 Visit 4 (Day 29)

This visit will occur 28 days after Visit 2. A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

The following observations will be made at Visit 4: concomitant medications, (including AEDs), physical examination (including height and body weight), ECG, vital signs, epilepsy-related hospitalizations and AEs.

Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry and urinalysis. Provided that the risk/benefit outcome is favorable in the investigator’s opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs.

The PGIC, SGIC/CGIC and the Vineland-II will also be performed. Suicidality will be assessed using the C-SSRS/Children’s C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgement.

The investigator must assess adherence to the titration regimen by reviewing the patient’s diary and IVRS data and record the patient’s attendance at the visit.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients will then receive a new treatment pack of the IMP.

A safety telephone call must be made one week after the end of titration (Visit 4). During this call, caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.
9.1.1.5 Visit 5 (Day 43)

This visit will occur 42 days after Visit 2 (randomization). A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

The following observations will be made at Visit 5: concomitant medications, (including AEDs), physical examination (including height and body weight), ECG, vital signs, epilepsy-related hospitalizations and AEs.

Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry and urinalysis. The PGIC, SGIC/CGIC and Vineland-II will also be performed. Suicidality will be assessed using the C-SSRS/ Children’s C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgement.

The investigator must assess adherence to the dosing regimen by reviewing the patient’s diary and IVRS data and record the patient’s attendance at the visit.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients will then receive new IMP.

9.1.1.6 Visit 6 (Day 57)

This visit will occur 56 days after Visit 2 (randomization). A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

The following observations will be made at Visit 6: concomitant medications, (including AEDs), physical examination (including height and body weight), ECG, vital signs, epilepsy-related hospitalizations and AEs.

Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry and urinalysis. Provided that the risk/benefit outcome is favorable in the investigator’s opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs.

The PGIC, SGIC/CGIC and Vineland-II will also be performed. Suicidality will be assessed using the C-SSRS/ Children’s C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgement.

The investigator must assess adherence to the dosing regimen by reviewing the patient’s diary and IVRS data and record the patient’s attendance at the visit.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients will then receive new IMP.
9.1.1.7 Visit 7 (Day 71)

This visit will occur 70 days after Visit 2 (randomization). A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

Visit 7 will be completed by telephone and will comprise a review of concomitant medications (including AEDs), epilepsy-related hospitalizations and AEs.

9.1.1.8 Visit 8 (Day 85)

This visit will occur 84 days after Visit 2 (randomization). A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

The following observations will be made at Visit 8: concomitant medications, (including AEDs), physical examination (including height and body weight), ECG, vital signs, epilepsy-related hospitalizations and AEs.

Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry and urinalysis. Provided that the risk/benefit outcome is favorable in the investigator’s opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs.

The PGIC, SGIC/CGIC and Vineland-II will also be performed. Suicidality will be assessed using the C-SSRS/Children’s C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgement.

The investigator must assess adherence to the dosing regimen by reviewing the patient’s diary and IVRS data and record the patient’s attendance at the visit.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients will then receive new IMP.

9.1.1.9 Visit 9 (Day 113, End of Treatment/Withdrawal Visit)

This visit will occur 112 days after Visit 2 (randomization) or earlier if the subject withdraws from the study. A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible. Patients will be instructed to record the dosing time of their concomitant AEDs in the diary.

The following observations will be made at Visit 9 / the Withdrawal visit: concomitant medications, (including AEDs), physical examination (including height and body weight), Tanner Staging (for patients aged 10-17 years [inclusive], or earlier
if clinically indicated by onset of menarche or other signs of precocious puberty),
details of menstruation (for females), ECG, vital signs, epilepsy-related
hospitalizations and AEs.

Clinical laboratory samples (blood and urine [where possible]) will be taken for
hematology, biochemistry, urinalysis, a urine THC screen, determination of serum
IGF-1 levels (for patients less than 18 years of age) and a pregnancy test (using a
serum sample, if appropriate), to be performed by the central laboratory. Provided that
the risk/benefit outcome is favorable in the investigator’s opinion, prior to the first
daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations
of concomitant AEDs. PK samples (patients >20 kg in weight only) will be taken at
baseline and at 2-hours and 4-hours after the last dose of IMP (taken in clinic). An
additional PK sample will be taken six hours after the first dose for patients aged 18
years or above.

The following assessments will also be performed: QOLCE/QOLIE-31-P,
SGIC/CGIC, SGIC-SD/CGIC-SD, Wechsler Tests, CBCL/ABCL, SCQ and the
Vineland-II. Suicidality will be assessed using the C-SSRS/Children’s C-SSRS (Since
Last Visit) or, in patients with profound cognitive impairment, by interview and
clinical judgement.

The investigator must assess adherence to the dosing regimen by reviewing the
patient’s diary and IVRS data, record the patient’s attendance at the visit and confirm
the outcome of the visit.

All IMP (used and unused) will be collected and a check of the returned IMP against
usage should be made.

For patients 12 years of age and older, the trained investigator or study coordinator
will complete the Study Medication Use and Behavior Survey as an interview with
the patient/caregiver.

For patients who withdraw early, the IVRS will be contacted to confirm withdrawal
from the study. Patients who withdraw should have their dose of IMP tapered
gradually (10% each day) over a period of 10 days, beginning at the time the decision
is made to discontinue. In some cases, tapering the dose of IMP may be inadvisable
(e.g., continued dosing is not possible due to an AE). The decision on whether or not
to taper IMP will be left to the investigator’s clinical judgment. If tapering is
undertaken, a 10-day supply of IMP (if required) and instructions for tapering the
dose will be provided. Patients should continue to complete the IVRS and paper diary
and should return for Visit 10 (the ‘End of Taper Period’ visit), if possible.
Patients who have completed all of the scheduled study visits will be offered the option of entering an OLE study. Entry is to be on the same day as Visit 9 (Day 113). Patients not entering the OLE study at this visit will be given a 10-day supply of IMP (if required) and instructions for tapering the dose, during which time IVRS and paper diary information will continue to be recorded.

9.1.1.10 Visit 10 (Day 123, End of Taper)

This visit is required only for those patients who do not enter the OLE study on the day of Visit 9 or for those who withdraw early and taper IMP. For patients who complete the study but opt not to enter the OLE study, Visit 10 should occur 10 (+3) days after Visit 9 (i.e., on Day 123 [+3]). For patients who withdraw early and taper IMP, this visit should occur 10 (+3) days after the Withdrawal visit. For patients who begin to taper IMP but subsequently withdraw/do not complete the full taper period, this visit should occur on the final day of dosing or as soon as possible after this date.

The following observations will be made at Visit 10: seizure information, concomitant medications (including AEDs), epilepsy-related hospitalizations and AEs, physical examination (including height and body weight), vital signs, ECG and clinical laboratory samples (blood and urine for hematology, biochemistry and urinalysis). Suicidality will be assessed using the C-SSRS/Children’s C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgement.

For patients 12 years of age and older, the trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. The patient diaries will be collected.

9.1.1.11 Visit 11 (Day 151, Safety Follow-Up)

This visit is required for patients who do not enter the OLE study or who withdraw from the study early. This visit should occur four weeks after Visit 10 (+3 days), or date of final dosing, and can be conducted over the telephone. The following observations will be made at Visit 11: concomitant medications (including AEDs), epilepsy-related hospitalizations and AEs.

9.1.2 Open Label Extension

Patients and their parent(s)/legal representative will be invited to participate in the OLE when they reach the End of Treatment visit (Visit 9) of the Blinded Phase. They
will be issued with the OLE patient information and informed assent or the patient/parent(s)/legal representative information and informed consent (as applicable). Following adequate time to discuss the study with the investigator, nurse, relatives or caregiver, patients/parent(s)/legal representatives who provide written informed consent/assent at Visit 1 will be enrolled into the OLE.

9.1.2.1 Visit B1 (Day 1)

Day 1 is regarded as the first day of IMP dosing. The following data collected at the ‘End of Treatment’ visit of the Core Study will also be considered as Visit B1 data: vital signs, physical examination (including height and body weight), details of menstruation (for females), Tanner Staging (patients aged 10–17 [inclusive]), ECG, clinical laboratory samples (including THC screen, serum IGF-1 levels (patients less than 18 years of age) and pregnancy test (if appropriate), IVRS and paper diary information from the blinded phase (including information regarding seizures, AEs, usage of rescue medication, concomitant AEDs, IMP dosing), epilepsy-related hospitalizations, concomitant medications and/or changes to medication, suicidality, QOLCE/QOLIE-31-P, SGIC/CGIC, SGIC-SD/CGIC-SD, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II. A pregnancy test (if appropriate) must be conducted.

Patients will take their final dose of Core Study IMP in the morning of Visit 1, followed by collection of the Blinded Phase ‘End of Treatment’ assessments. Patients will be instructed to begin the Blinded Open-label transition, taking their first dose of Blinded Transition OLE IMP in the evening of Visit B1 (Day 1).

Eligibility will be assessed according to the entry criteria, as specified in Section 6. Eligible patients or their caregivers will receive sufficient IMP for two weeks’ home dosing together with a blinded transition phase provided via the IVRS. If an unacceptable AE develops at any time during transition, dosing should initially be suspended or amended, at the investigator’s discretion, until the event has resolved or is well tolerated.

Patients or their caregivers will be given a paper diary to record information regarding AEs, IMP, usage of rescue medication, concomitant AEDs and IMP dosing. In addition, patients/caregivers will be instructed to complete a weekly seizure reporting diary until the ‘End of Treatment’/withdrawal visit using the IVRS.

The investigator should review the laboratory results as soon as these become available. If the results raise any safety concerns, the investigator should consider whether it will be appropriate for the patient to continue to participate in the extension study, or if the patient should be withdrawn.
In order to complete the SGIC/CGIC, the patient/caregiver is to compare to the memory aid from the Baseline of the blinded phase. If the memory aid is not available from the Baseline of the blinded phase then the patient/caregiver should do this from memory, if possible, and complete a memory aid at Visit B1.

In order to complete the SGIC-SD/CGIC-SD, the patient/caregiver would have been asked to assess and note the average duration of the patient’s seizures at the Baseline of the blinded phase as a memory aid for subsequent visits. If the memory aid is not available from the Baseline of the blinded phase then the patient/caregiver should do this from memory, if possible, and complete a memory aid at Visit B1.

Following Visit B1, during the blinded transition, safety telephone calls must be made every two days. During these calls, caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.

9.1.2.2 Visit B2 (Day 15)

Visit B2 will take place 14 days after Visit B1. A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

The following assessments will be made at Visit B2: vital signs, physical examination (including height and body weight) and ECG. Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry and urinalysis. Provided that the risk/benefit outcome is favorable in the investigator’s opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs. Suicidality will be assessed using the C-SSRS/Children’s C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgement.

The patient’s IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, IMP, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The investigator must assess adherence to the titration regimen.

Upon completion of the two-week blinded transition at Visit B2 all patients will be taking 25 mg/kg/day. All blinded IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients/caregivers will then receive sufficient open-label IMP for two weeks’ home dosing together with a titration schedule provided via the IVRS. Patients will titrate up to the target dose of
50 mg/kg/day according to the defined titration schedule. If an unacceptable AE develops at any time during titration, dosing should initially be suspended or amended, at the investigator’s discretion, until the event has resolved or is well tolerated.

Following Visit B2, during titration, safety telephone calls must be made every two days. An additional call should be complete one week after the end of titration. During these calls, caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.

9.1.2.3 Visit B3 (Day 29)

Visit B3 will take place 28 days after Visit B1. A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

The following assessments will be made at Visit B3: vital signs, physical examination (including height and body weight), ECG, suicidality, PGIC, SGIC/CGIC and Vineland-II. Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry and urinalysis. Provided that the risk/benefit outcome is favorable in the investigator’s opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs.

The patient’s IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, IMP usage, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The investigator must assess adherence to the titration regimen.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients/caregivers will then receive sufficient open label IMP for eight weeks’ home dosing.

9.1.2.4 Visit B4 (Day 85)

This visit will occur 84 days after Visit B1. A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

The following observations will be made at Visit B4: concomitant medications, (including AEDs), physical examination (including height and body weight), Tanner Staging (for patients aged 10-17 years [inclusive], or earlier if clinically indicated by onset of menarche or other signs of precocious puberty), details of menstruation (for females), ECG, vital signs, epilepsy-related hospitalizations and AEs.
Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry, urinalysis and determination of serum IGF-1 levels (for patients less than 18 years of age) to be performed by the central laboratory. Provided that the risk/benefit outcome is favorable in the investigator’s opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs.

The following assessments will also be performed: QOLCE/QOLIE-31-P, SGIC/CGIC, SGIC-SD/CGIC-SD, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II. Suicidality will be assessed using the C-SSRS/Children’s C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgement.

The investigator must assess adherence to the dosing regimen by reviewing the patient’s diary and IVRS data, record the patient’s attendance at the visit and confirm the outcome of the visit.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made.

9.1.2.5 Visit B5 to End of Treatment

From Visit B5, visits will be defined as either Assessment Visits or Re-supply Visits.

Assessment Visits will be scheduled every three months beginning at Visit B5 (Week 26) until patients have been enrolled in the OLE for one year. From one year to the End of Treatment, Assessment Visits will be scheduled every six months.

Re-supply Visits will be scheduled to occur between Assessment Visits to ensure re-supply volumes of IMP are manageable for both patients and dispensing staff. Re-supply Visit dates will be calculated from the previous Assessment Visit. At each Re-supply Visit patients will be dispensed with sufficient IMP for a maximum of 10 weeks’ treatment.

A full visit schedule, from Visit B5 to the End of Treatment, is detailed below:

<table>
<thead>
<tr>
<th>Table 9.1.2-1</th>
<th>OLE Visit Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit Number</td>
<td>Visit Type</td>
</tr>
<tr>
<td>B5</td>
<td>Re-supply</td>
</tr>
<tr>
<td>B6</td>
<td>Assessment</td>
</tr>
<tr>
<td>B7</td>
<td>Re-supply</td>
</tr>
<tr>
<td>B8</td>
<td>Assessment</td>
</tr>
<tr>
<td>B9</td>
<td>Re-supply</td>
</tr>
<tr>
<td>B10</td>
<td>Assessment</td>
</tr>
</tbody>
</table>
### 9.1.2.5.1 Assessment Visits

The following observations will be made at Assessment Visits: concomitant medications, (including AEDs), physical examination (including height and body weight), Tanner Staging (for patients aged 10-17 years [inclusive], or earlier if clinically indicated by onset of menarche or other signs of precocious puberty), details of menstruation (for females), ECG, vital signs, epilepsy-related hospitalizations and AEs.

Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry, urinalysis, determination of serum IGF-1 levels (for patients less than 18 years of age), to be performed by the central laboratory. Provided that the risk/benefit outcome is favorable in the investigator’s opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs.

The following assessments will also be performed: QOLCE/QOLIE-31-P, SGIC/CGIC, SGIC-SD/CGIC-SD, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II. Suicidality will be assessed using the C-SSRS/Children’s C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgement.

The investigator must assess adherence to the dosing regimen by reviewing the patient’s diary and IVRS data, record the patient’s attendance at the visit and confirm the outcome of the visit.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients/caregivers will then receive a three-month supply of IMP.

### 9.1.2.5.2 Re-supply Visits

Re-supply Visits will comprise a review of concomitant medications (including AEDs), epilepsy-related hospitalizations and AEs.
The investigator must assess adherence to the dosing regimen by reviewing the patient’s diary and IVRS data, record the patient’s attendance at the visit and confirm the outcome of the visit.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients/caregivers will then receive sufficient IMP until the next scheduled visit.

9.1.2.6 End of Treatment/Withdrawal Visit

This visit will take place once market authorization is granted for GWP42003-P in TSC or following early withdrawal from the study.

The following assessments will be made at the ‘End of Treatment’/Withdrawal visit: vital signs, physical examination (including height and body weight), details of menstruation (for females), Tanner Staging (patients aged 10–17 [inclusive]), ECG, clinical laboratory samples (including THC screen), serum IGF-1 levels (patients less than 18 years of age) and pregnancy test (if appropriate), IVRS and paper diary information (including information regarding seizures, AEs, usage of rescue medication, concomitant AEDs, IMP dosing), epilepsy-related hospitalizations, concomitant medications and/or changes to medication, AEs, suicidality, QOLCE/QOLIE-31-P, SGIC/CGIC, PGIC, SGIC-SD/CGIC-SD, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II. Provided that the risk/benefit outcome is favorable in the investigator’s opinion, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs. The investigator must assess adherence to the dosing regimen.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. For patients who withdraw early, the IVRS will be contacted to confirm withdrawal from the study. For patients who immediately continue to use GWP42003-P following the ‘End of Treatment’ visit, the IVRS will be contacted to confirm the patient’s completion of this study and the paper diaries will be collected.

For patients who do not immediately continue to use GWP42003-P following the ‘End of Treatment’ visit, IMP will be down-titrated at home (10% per day for 10 days). Additional IMP will be dispensed, if required. Patients who withdraw early should also begin the taper period following the Withdrawal visit (unless continued dosing is not possible due to an AE). The IVRS will generate the patient’s daily IMP dosing volumes for the 10-day taper period, during which time diary information will continue to be recorded in the paper diary.
For patients 12 years of age and older, the trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.

Following the ‘End of Treatment’/Withdrawal visit, the IVRS seizure reporting diary should only be completed on the day before the ‘End of Taper Period’ visit and on the day before the Follow-up visit.

9.1.2.7 End of Taper Period Visit

This visit will take place 10 (+3) days after the ‘End of Treatment’ visit or Withdrawal visit for patients who withdraw early and taper IMP. For patients who begin to taper IMP but subsequently withdraw/do not complete the full taper period, this visit should occur on the final day of dosing or as soon as possible after this date.

The following assessments will be made: vital signs and physical examination (including height and body weight). Suicidality will be assessed using the C-SSRS/Children’s C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgement. In addition, the following assessments will be made for patients who withdraw early and taper IMP (including withdrawal during the taper period): ECG and clinical laboratory samples (blood and urine for hematology, biochemistry and urinalysis). The patient’s IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, IMP usage, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The investigator must assess adherence to the dosing regimen.

For patients 12 years of age and older, the trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made.

Following the ‘End of Taper Period’ visit (or date of final dosing), the IVRS seizure reporting diary should only be completed on the day before the Follow-up visit.

9.1.2.8 Post-Taper Safety Telephone Call

A safety telephone call must be made two weeks (±3 days) after the ‘End of Taper Period’ visit or date of final dosing. Patients or their caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.
Following this call, the IVRS seizure reporting diary should only be completed on the day before the Follow-up visit.

### 9.1.2.9 Follow-up Visit

This visit is required for patients who withdraw from the study or complete treatment but do not wish to continue to use GWP42003-P. The Follow-up visit will be performed four weeks (+3 days) after the patient’s last dose of GWP42003-P (including final taper period dose) and can be conducted over the telephone. During this visit/call, caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.

### 9.1.2.10 Safety Telephone Calls

Safety Telephone calls must be made every two days during the two-week blinded transition and the two-week OLE titration period and one week after the end of titration to assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.

### 9.2 Study Procedure Listing

#### 9.2.1 Informed Consent/Assent

Adult patients with an adequate level of understanding must personally sign and date the EC/IRB-approved / ICF before any study-specific procedures are performed or any patient-related data are recorded for the study. For adult patients with an insufficient level of understanding of what is proposed, only parent(s)/legal representative consent will be sought. If an adult patient is unable to read (illiterate or visually impaired), or is physically unable to speak or write, an impartial witness should be present during the entire informed consent discussion. After the ICF is read and explained to the patient and after the patient has orally consented to participation in the trial and has signed and dated the ICF (if capable of doing so), the witness should also sign and personally date the ICF. By signing the ICF, the witness attests that the information in the ICF was accurately explained to and apparently understood by the patient and that informed consent was freely given by the patient (as outlined in the International Conference on Harmonization [ICH] Tripartite Guideline for GCP Topic E6(R1)\textsuperscript{52}, Section 4.8.9)

The parent(s)/legal representative of minor patients must personally sign and date the EC/IRB-approved ICF before any study-specific procedures are performed or any patient-related data is recorded for the study. In addition, in cases where the patient possesses adequate understanding, assent will be taken (if allowed per local
regulations) along with parent(s)/legal representative consent, using EC/IRB-approved assent forms. Assent is defined as the minor’s permission or affirmative agreement to participate in the study. The explicit wish of a minor, who is capable of forming an opinion and assessing the information provided, to refuse participation in or to be withdrawn from the clinical trial at any time must be considered by the Investigator.

For patients who go from being a minor to an adult (as per the country or state’s age-of-majority regulation) during the course of the study, a new ICF will be signed if the patient possesses adequate understanding to do so.

If the patient cannot write, they can give consent/assent by “making their mark” on the consent/assent form (e.g., writing an “X”).

GW requires a physician to be present for consent and assent and to sign the consent and assent forms also. Patients/parent(s)/legal representatives will be given the option of being informed about the summary outcome and results of the trial as part of the ICF. For further details, see Section 15.2.

**9.2.2 Contraception Requirements**

To be eligible for the study, the patient must have agreed that if they or their partner are of child bearing potential they are willing to use highly effective contraception for the duration of the study and for three months thereafter. Highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. Such methods include hormonal contraceptives, intrauterine devices/hormone-releasing systems, bilateral tubal occlusion, vasectomized partner (provided that partner is the sole sexual partner of the trial patient and that the vasectomized partner has received medical assessment of the surgical success), or sexual abstinence. Abstinence, as referenced above, is only acceptable as true abstinence: when this is in line with the preferred and usual lifestyle of the patient; periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

**9.2.3 Demographics**

Patient demographics will be recorded at Visit 1. The following information will be obtained for each patient: date of birth, sex and ethnic origin (if allowed per local regulations).
9.2.4 Medical History

Relevant, significant medical history (including seizure information since diagnosis, history of epilepsy-specific genetic testing and all prior AEDs taken) will be obtained during Visit 1 and is defined as any condition or disease that:

- May affect the condition under study.
- Is ongoing on entry into the study.
- Has occurred within one year prior to screening (Visit 1).

The mutation status of the TSC1 and TSC2 genes, if known, will be obtained through the patient’s medical records. If the mutation status of TSC1 and TSC2 is unknown, genetic analysis will be carried out during the study analysis (a blood sample will be taken during Visit 1).

9.2.5 Concomitant Medication

Details of all current and recent medication (i.e., taken within the previous 14 days) including AEDs will be recorded at the screening visit (Visit 1) and reviewed at each subsequent visit. AEDs used during the study should be maintained at a stable dose.

Any changes in concomitant medication during the study must be recorded in the CRF at study visits. Patients should stop taking any prohibited therapy prior to enrollment, as defined in Section 8.2.

9.2.6 Physical Examination

A physical examination will be performed at the screening visit (Visit 1) to ensure that the patient is eligible to enter the study. To ensure patient safety, further physical examinations will be performed during subsequent visits. Physical examinations will include height and body weight measurements.

9.2.7 Vital Signs

Vital sign measurements, taken in a sitting position at rest for five minutes, will be completed alongside the physical examination. Postural blood pressure should be measured after five minutes in supine position followed by two minutes in standing position, if possible. Blood pressure must be recorded using the same arm throughout the study, where possible.

9.2.8 12-Lead Electrocardiogram

A 12-lead ECG will be performed after five minutes in a supine position. A physician must review the ECG and any abnormal findings considered to indicate significant
medical history or AEs must be recorded appropriately in the CRF. Additional ECG measurements can be taken at any time during the study, if clinically indicated.

9.2.9 Clinical Laboratory Sampling

Laboratory tests will include hematology, biochemistry, urinalysis (provided urine can be obtained), urine THC screening and a serum pregnancy test (if appropriate). At screening, a urine dipstick pregnancy test will also be performed (if appropriate) at the study center to assess eligibility. Analysis of all clinical blood samples, pregnancy tests (using serum) and tests to detect the presence of THC will be conducted at a central clinical laboratory.

Urine samples for biochemistry will be analyzed at the study center by use of a dipstick with any relevant findings being sent for further urinalysis at the central laboratory (urinalysis, microscopy, culture and sensitivity, as applicable). In cases where urine samples cannot be analyzed at center due to local regulations, a full set of urine samples should be sent to the central laboratory for analysis. Sample volume requirements and processing procedures will be detailed in a separate laboratory manual.

The Investigator and study monitor will be provided with a list of the normal ranges used by the testing laboratory for all variables assayed during the study and a statement of accreditation (or similar) for the laboratory. Clinical laboratory sample parameters are detailed in Table 9.2-1.

<table>
<thead>
<tr>
<th>Table 9.2-1</th>
<th>Biochemistry, Hematology, Urinalysis and THC Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>**Biochemistry (Serum)**¹</td>
<td>**Hematology (Whole Blood)**¹</td>
</tr>
<tr>
<td>Alanine aminotransferase (ALT)</td>
<td>Hematocrit</td>
</tr>
<tr>
<td>Albumin</td>
<td>Hemoglobin</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>Mean cell volume</td>
</tr>
<tr>
<td>Aspartate aminotransferase (AST)</td>
<td>Mean corpuscular hemoglobin</td>
</tr>
<tr>
<td>Calcium</td>
<td>Platelets</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Red blood cell count</td>
</tr>
<tr>
<td>Estimates of glomerular filtration rate</td>
<td>White blood cell count with automated differential</td>
</tr>
<tr>
<td>Gamma-glutamyl transferase</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td></td>
</tr>
<tr>
<td>Insulin-like growth factor-1 (IGF-1)</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td></td>
</tr>
</tbody>
</table>
Investigators at study centers will be notified of safety laboratory test results. All laboratory results will be reviewed and the reports signed by an Investigator. Any results considered to be of clinical significance must be addressed and followed up as clinically appropriate. The results of THC screening will be reported back to the study site to permit confirmation of eligibility and to be used as a measure of study compliance (i.e., to confirm that the patient did not use cannabis during the course of the study). Any samples reported to be THC-positive at screening must be sent for analysis by gas chromatography–mass spectrometry at the central laboratory. All laboratory results considered to represent an AE must be documented in the CRF. See Section 12.8 for guidance on evaluation of potential drug induced liver injury. All laboratory results considered to represent an AE must be documented on the CRF. Repeat samples will be taken, if required, for clinical follow up or if the sample is lost or damaged. Any abnormal end of treatment clinical laboratory result of clinical significance must be repeated at regular intervals until it returns to normal, or until an Investigator is satisfied that the abnormality is not related to the IMP and needs no further investigation.

Sample volume requirements and processing procedures will be detailed in a separate laboratory manual. The patient/caregiver must be advised that it may not be safe for them to undertake further blood tests within one month of any study-related blood draws and to inform the Investigator if they suffered any blood loss.

### 9.2.9.1 Pharmacokinetic Blood Sampling

The plasma concentration/time curves of CBD, THC and their major metabolites will be assessed at Visits 2 and 9. Blood samples will be taken as follows:

- One sample pre-dose (i.e., prior to administration of IMP).
• One sample between two and three hours post-dose.
• One sample between four and five hours post-dose.
• One sample between six and seven hours post-dose (patients 18 years and above only).

There must be a minimum period of at least two hours between each of the three blood sampling time points. In the event of an AE that, in the opinion of the investigator, is related to a concomitant AED, additional blood samples may be collected.

Analysis of all pharmacokinetic samples will be conducted at a central clinical laboratory. Sample volume requirements and processing procedures will also be detailed in a separate laboratory manual.

The patient/caregiver must be advised that it may not be safe for them to undertake further blood tests within one month of any study-related blood draws and to inform the Investigator if they suffered any blood loss during the one-month period leading up to a planned blood draw.

9.2.9.2 Determination of Plasma Concentrations of Concomitant Antiepileptic Drugs

Plasma concentrations of concomitant AEDs will be assessed at Visits 2, 4, 6, 8 and 9/ the Withdrawal visit (if possible) during the blinded phase and at Visits B2, B3, B4 and all subsequent Assessment Visits during the OLE. Samples will be collected for all patients provided that the risk/benefit outcome is favorable in the investigator’s opinion. At each visit, blood samples will be taken prior to administration of IMP. Patients will be instructed to record the dosing time of their concomitant AEDs in the diary.

Additional bloods may be taken for AED monitoring if there is a suspicion of changes in AED levels, with the aim to keep the AED plasma levels within the patient’s therapeutic level. AED doses should be adjusted, as appropriate, following discussion with the GW Medical Monitor in order to maintain stable AED plasma concentrations.

9.2.10 Interactive Voice Response System

The IVRS will be used to collect patient reported diary data (refer to Section 9.2.11), to assign patients to treatment groups and to provide treatment allocation information in the event of patient unblinding. The IVRS will also be used to manage IMP supply.

A member of the study team must contact the IVRS at each clinic visit in order to:
• Obtain a patient’s screening number (Visit 1).
• Randomize a patient and obtain their patient number (Visit 2).
• Obtain dispensing information (Visits 2, 3, 4, 5, 6, 8, and during OLE).
• Provide completion/taper/premature termination information (Visit 9).

Training will be given to all centers prior to the start of the study.

9.2.11 Patient Diary

A diary will be completed daily throughout the study. Patients or their caregivers will be instructed on how to complete the diary and will be asked to record information daily. The number and type and severity of seizures as well as information on AEs, concomitant AEDs and rescue medication will be collected each day from screening (Visit 1) until completion of dosing (Visit 9/Withdrawal visit). Information on IMP intake will also be recorded each day from randomization (Visit 2) until completion of dosing or withdrawal (Visit 9/Withdrawal visit).

Seizure information, including the number, type and severity of focal seizures and the number of infantile/epileptic spasms and episodes of status epilepticus will be collected through an IVRS telephone diary completed daily throughout the blinded phase of the study by the patient or their caregiver. This IVRS telephone diary will be completed on a weekly basis during the OLE. The patient or their caregiver will also complete a paper diary daily to record AEs, concomitant AEDs, IMP intake and rescue medication throughout the study.

The severity of seizures will be assessed according to the following criteria:

• Type 1 - Focal motor seizures without impairment of consciousness or awareness.
• Type 2 - Focal seizures with impairment of consciousness or awareness.
• Type 3 - Focal seizures evolving to bilateral convulsive seizures.

9.2.12 Questionnaires and Assessments Completed at Scheduled Visits

Questionnaires should be completed by the caregiver. The same person should complete/answer the questionnaires/assessments in order to maintain consistency. The C-SSRS (where applicable) will be administered by a trained rater.

Questionnaires should be completed by the patient or the caregiver, as appropriate. The same person should answer/complete the questionnaires/assessments in order to maintain consistency. The C-SSRS/Children’s C-SSRS (where applicable) will be administered by a trained rater.
9.2.12.1 Subject/Caregiver Global Impression of Change

The SGIC/CGIC, as appropriate, will be performed for all patients. At Visit 1 the patient or patient’s caregiver will be asked to write a brief description of the patient’s overall condition as a memory aid for the SGIC/CGIC at subsequent visits. It is preferred that the same person performs this assessment at each visit.

The CGIC comprises the following question to be rated on a seven-point scale:

- Since your child started treatment, please assess the status of your child’s overall condition (comparing their condition now to their condition before treatment) using the scale below.

The SGIC comprises the following question to be rated on a seven-point scale:

- Since you started treatment, please assess the status of your overall condition (comparing your condition now to your condition before treatment) using the scale below.

The markers are: Very Much Improved; Much Improved; Slightly Improved; No Change; Slightly Worse; Much Worse; Very Much Worse.

If the main caregiver is not available at the appropriate visit then this information can be captured over the telephone, ideally on the day of the visit or otherwise within three days.

9.2.12.2 Subject/Caregiver Global Impression of Change in Seizure Duration

The caregiver will be asked to assess the average duration of the patient’s seizures at Visit 1 (i.e., prior to commencement of IMP) as a memory aid for subsequent visits.

The SGIC-SD/CGIC-SD comprises a question to be rated on a three-point scale for each seizure subtype:

The markers are: Average duration of seizures has decreased; Average duration of seizures has stayed the same; Average duration of seizures has increased.

If the main caregiver is not available at the appropriate visit then this information can be captured over the telephone, ideally on the day of the visit or otherwise within three days.

CGIC-SD:

- Since the patient started treatment, please assess the average duration of the patient’s seizures (comparing their condition now to their condition before treatment) using the scale below.
SGIC-SD:

- Since you started treatment, please assess the average duration of your seizures (comparing their condition now to their condition before treatment) using the scale below.

### 9.2.12.3 Quality of Life in Childhood Epilepsy (18 Years of Age and Younger) or Quality of Life in Epilepsy (19 Years of Age and Older)

The QOLCE and the QOLIE-31-P are composed of 16 and 31 subscales, respectively, assessing seven domains of Health Related Quality of Life (physical function, social function, emotional well-being, cognition, behavior, general health and general quality of life). The QOLCE (and QOLIE-31-P, if completed by the caregiver) must be completed by a person who interacts with the patient on a consistent, daily basis. Quality of life assessments will be performed for all patients. The questionnaires should take 20–30 minutes to complete.


The Vineland-II is an individually administered instrument for assessing adaptive behaviors. Communication, Daily Living Skills, Socialization, and Motor Skills will be assessed by the caregiver using a rating scale. Vineland-II assessments will be performed for all patients.

### 9.2.12.5 Child/Adult Behavior Checklist

Achenbach CBCL and ABCL, for ages 1½–5, 6–18 and 18–59 examine internalizing behaviors (such as depression and anxiety), externalizing behaviors (such as aggression), stress, obsessive-compulsive behaviors and ‘sluggish cognitive tempo’ (SCT). Statements about the patient’s behavior are recorded on a Likert scale: 0 = Not True, 1 = Somewhat or Sometimes True, 2 = Very True or Often True.

The age appropriate checklist will be used for all patients.

### 9.2.12.6 Social Communication Questionnaire

The current version of the SCQ will be completed by the caregiver for all patients above the age of 4 years with a mental age of at least 2 years. The scale provides sub-scores to assess the domains Reciprocal Social Interaction, Communication and Restricted, Repetitive and Stereotyped Patterns of Behavior. The scale assesses behavior over the most recent three month period using 40 questions, each to be answered ‘yes’ or ‘no’.
9.2.12.7 Children’s/Columbia Suicide Severity Rating Scale

Suicidality will be assessed using the C-SSRS/Children’s C-SSRS or, in patients with profound cognitive impairment, by interview and clinical judgement. Where the C-SSRS/Children’s C-SSRS is not considered appropriate and clinical interview is used instead, the reason must be clearly documented by the Investigator.

The definitions of behavioral suicidal events used in this scale are based on those used in the Columbia-Suicide History Form. Questions are asked on suicidal behavior, suicidal ideation and intensity of ideation. During the screening visit (Visit 1) questions will be in relation to lifetime experiences and all subsequent questioning will be in relation to the last assessment (Since Last Visit).

The C-SSRS is to be completed by the investigator or his/her qualified designee at every visit as indicated in the Schedule of Assessments (see APPENDIX 1); “qualified designee” is defined as a physician, osteopath, nurse practitioner, clinical psychologist or physician’s assistant, who is licensed and has completed the C-SSRS training within the past two years. The survey should be completed by the same assessor, where possible, throughout the study. The Children’s C-SSRS will be used for patients aged 6–18 (inclusive) while the C-SSRS will be used for patients aged 19 and older.

9.2.12.8 Wechsler Tests

The Wechsler Tests are age specific and will only be administered at a sub-group of centers that have the expertise to conduct the assessments (ideally before any other study procedures but can be completed on a separate day, if necessary, within three days of the visit). Each assessment will need to be conducted by an experienced psychometrician. The age of the patient at entry will be the age used when choosing the items to be administered. Children and adults are to complete the tests as able. The following Wechsler Subtests will be used:

Age 2 - 6:
- WPPSI-4 - Vocabulary and Matrix Reasoning

Age 6 - Adult:
- WASI-2 - Vocabulary and Matrix Reasoning
- WISC-4 and WAIS-4 Digit Span and Coding
9.2.13 Menstruation

Caregivers will be asked if the female patient is menstruating and details will be recorded as part of their baseline (Visit 2); any changes in normal cycles will be captured at Visit 9 / the Withdrawal visit and subsequent OLE visits.

9.2.14 Tanner Staging

The pubic hair growth (both sexes), genital (males only) and breast (females only) development of all adolescent patients (i.e., 10 to 17 years of age at the time of signing the informed consent form, or earlier if clinically indicated by onset of menarche or other signs of precocious puberty) will be assessed using Tanner Staging\(^55\) (see APPENDIX 2). The patients will undergo a discreet physical examination and be assigned a value under each category of Pubic Hair Growth (both sexes), Genitals (male patients only), and Breasts (female patients only).

Once a patient reaches a score of V (i.e., 5) the examination need not be performed again.

9.2.15 Investigational Medicinal Product Accountability

Records of IMP accountability will be maintained according to Section 5.3.4.

9.2.16 Adverse Events

Any adverse changes in the patient’s medical condition, following completion of the consent form by the patient, will be recorded on the CRF as AEs, questioning the patient further if necessary. All AEs* occurring during the study, whether or not attributed to the IMP, observed by the investigator or reported by the patient will be recorded in the CRF.

*For the patient’s expected seizure types, these do not routinely require documentation as AEs. However, any worsening, including change in the pattern or severity of seizures, must be documented as an AE. As part of the ongoing safety review, the SMC will monitor any worsening of seizures, including change in the pattern or severity. Any AE which meets Serious Adverse Event (SAE) criteria should still be reported as a SAE.

SAEs must be reported to GW Pharmacovigilance Department (PVD) within 24 hours of discovery or notification of the event, and recorded in the CRF.

Refer to Section 12 for definitions, procedures and further information.
The number of inpatient hospitalizations that are, in the investigator’s opinion, due to epilepsy will be recorded in the patient’s CRF and through the SAE reporting process.

9.2.17 Monitoring of Abuse Liability (for Patients 12 Years of Age and Older)

There are two triggers that will require the investigator or study coordinator to discuss abuse potential signals with the patient or their caregiver. These are either AEs of interest that may be reported by the patient/caregiver, or drug accountability issues regarding overuse of the IMP or missing bottles. Different questionnaires will be completed by the site depending upon which trigger occurs (see Figure 9-1, Section 9.2.17.4). Irrespective of the above, all patients/caregivers will be interviewed at their final dosing visit (‘End of Treatment’/Withdrawal visit or ‘End of Taper Period’ visit, as applicable) and a Study Medication Use and Behavior Survey will be completed by the investigator or study coordinator. Investigators and study coordinators will be provided with training on how to complete and perform the processes outlined in this section. This training must be completed and documented by the relevant site staff prior to implementation at site.

9.2.17.1 Monitoring of Adverse Events

AE information will be collected according to Section 9.2.16.

9.2.17.1.1 List of ‘Triggering Adverse Events of Interest’

During the collection of AEs, if the patient reports an AE consistent with any of the following categories, then the investigator or study coordinator is required to complete an additional Supplemental Adverse Event Form and a Site Classification Form (investigator only) following further discussion of the event(s) with the patient or their caregiver. The categories are:

- Euphoria or inappropriate elation.
- Inappropriate laughter or exhilaration.
- Mood changes.
- Drunk, high or intoxicated.
- Hallucinations (visual or auditory), dissociations, disorientation, agitation.
- Disturbance in cognition, memory, or attention.
- Drug abuse.
- Drug withdrawal or drug withdrawal syndrome.
- Addiction.
- Overdose.
- Misuse of IMP.
• Thoughts of suicide, attempted suicide or suicide. An AE that is consistent with the above categories will be known as a ‘triggering AE of interest’ for the purposes of this study.

9.2.17.1.2 Supplemental Adverse Event Form

This form consists of 15 questions regarding the AE and use of IMP. It is completed as part of an interview with the patient/caregiver when a triggering AE of interest is reported. It is important that this is completed by a trained investigator or study coordinator with the patient/caregiver present. The answers on the Supplemental Adverse Event Form will then be transcribed into the patient’s CRF for the study. If the Supplemental Adverse Event Form cannot be completed at the time the triggering AE of interest is reported, then the site should contact the patient/caregiver to obtain the required answers as soon as possible.

9.2.17.1.3 Monitoring Drug Accountability Discrepancies

Any time after enrollment until final collection of study data, drug accountability discrepancies are monitored as follows:

• At routine Drug Accountability collection times:
  the site personnel will collect the IMP clinical supplies and make sure the usage is in line with the expectations reported within the IVRS report and paper diary.

• At any time that the site is informed by either the IVRS or by the patient/caregiver about any overuse of IMP, suspected misuse, abuse, or diversion.

9.2.17.1.4 List of ‘Triggering Drug Accountability Discrepancies’

If there are any discrepancies in drug accountability as outlined by the criteria below, known as ‘triggering drug accountability discrepancies’, then the trained investigator or study coordinator will complete a Supplemental Drug Accountability Form and Site Classification Form (investigator only) following further discussion of the event(s) with the patient/caregiver. The triggering drug accountability discrepancies are as follows:

• Missing bottle(s).

• Compliance issues where one or more bottles are used compared to what was the expected use, according to the IVRS report and paper diary.

• Returned IMP supply with evidence of tampering.

• Greater than the target daily dose as recorded in the IVRS report and paper diary.
9.2.17.1.5 Supplemental Drug Accountability Form

This form consists of eight questions regarding various aspects of drug accountability and patient usage. It is completed as part of an interview with the patient/caregiver when a triggering drug accountability discrepancy is identified. It is important that this is completed by a trained investigator or study coordinator with the patient/caregiver present. The answers on the Supplemental Drug Accountability Form will then be transcribed into the patient’s CRF for the study. The accountability reporting procedures will still occur. If the Supplemental Drug Accountability Form cannot be completed at the time the triggering drug accountability discrepancy is identified, then the site should contact the patient/caregiver by telephone to obtain the required answers as soon as possible. (Note: IMP refers to GWP42003-P, not other concomitant medications).

9.2.17.2 Site Classification Form

The investigator should review the applicable Supplemental Adverse Event Form or Supplemental Drug Accountability Form, and then complete the Site Classification Form. For each Supplemental Adverse Event Form or Supplemental Drug Accountability Form completed, there should be an associated Site Classification Form.

The Site Classification Form requires the investigator to assign the finding to an appropriate classification and then to also assign the possible relationship to the IMP. The investigator is also required to indicate the level of the certainty of the classification. The answers from the Site Classification Form will then be transcribed into the patient’s CRF for the study.

9.2.17.3 Study Medication Use and Behavior Survey

This form consists of 18 questions regarding the use of the IMP. The trained investigator or study coordinator will complete this survey as an interview with the patient/caregiver at the final dosing visit (‘End of Treatment’/Withdrawal visit or ‘End of Taper Period’ visit, as applicable). The answers on the Study Medication Use and Behavior Survey will then be transcribed into the patient’s CRF for the study.

The Study Medication Use and Behavior Survey will be completed for all patients 12 years of age and older in the study and not only those that have reported a triggering AE or drug accountability discrepancy.
9.2.17.4 Adjudication Committee: Assessment of Abuse Potential of GWP42003-P

A formal Adjudication Committee will be appointed and assigned to this initiative to classify triggered cases. The Adjudication Committee will meet on a periodic basis to review and assess all of the information collected on triggered cases.

A detailed charter will be agreed, which will describe the roles, responsibilities and duties of the members of Adjudication Committee. The Committee will review all of the information collected in the process and in the assessment of the abuse potential of GWP42003-P, such as:

- All triggering AE information.
- Supplemental Adverse Event Form (if applicable).
- All triggering drug accountability discrepancies.
- Supplemental Drug Accountability Form (if applicable).
- Site Classification Form.
- Study Medication Use and Behavioral Survey.
- Additional information from site(s) as requested by the Committee.

The Adjudication Committee will assess all of the information. It will form a position on the classification of each event and will write a study-related report, detailing the conclusions and recommendations.

The overall process is summarized in Figure 9-1.
**Flow Diagram for Identifying and Evaluating Clinical Trial Adverse Event Data Through Systematic Categorization, Tabulation and Analysis which can Illuminate an Abuse Potential Signal (for Patients 12 Years of Age and Older)**

**Stage 1**
- Patients with ‘Triggering Adverse Events of Interest’
- Patients with ‘Triggering Drug Accountability Discrepancy’
- All patients

**Stage 2**
- When a Triggering Adverse Event of Interest is identified, a patient interview is conducted with the **Supplemental Adverse Event Form** and, if applicable, the **Supplemental Drug Accountability Form**.
- When a Triggering Drug Accountability discrepancy is identified, a patient interview is conducted with the **Supplemental Drug Accountability Form** and, if applicable, the **Supplemental Adverse Event Form**.

**Stage 3**
Investigator completes a **Site Classification Form** after supplemental information is collected, drug accountability evaluated, and the patient evaluated. One Site Classification Form is completed per Supplemental Adverse Event Form or Drug Accountability Form.

**Stage 4**
Site completes **Study Medication Use and Behavior Survey** at end of dosing.

**Stage 5**
- **Adjudication Committee**
  - Evaluates all of the information collected (as detailed above in stages 1–4) in the assessment of the abuse potential of GWP42003-P and completes a report.
  - Committee submits a report to GW.
10 WITHDRAWAL

In accordance with the Declaration of Helsinki, the ICH Tripartite Guideline for GCP Topic E6(R1), the U.S. Food and Drug Administration (FDA) regulations relating to good clinical practice and clinical trials, the European Union (EU) Clinical Trials Directive, the EU Good Clinical Practice (GCP) Directive and/or other applicable regulations, a patient has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

The patient must be withdrawn from the study if any of the following apply:

- Administrative decision by the Investigator, GW, or a Regulatory Authority.
- Did not meet eligibility criteria.
- Pregnancy.
- Protocol deviation that is considered to compromise potentially the safety of the patient.
- Withdrawal of patient consent/assent.
- Withdrawal of parent(s)/legal representative consent.
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).
- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for more than two weeks.
- ALT or AST > 3 × ULN and (TBL > 2 × ULN or INR > 1.5).
- Lost to follow-up.

Patients may also be withdrawn from the study for any of the following:

- Patient non-compliance.
- AE (including clinically significant laboratory result) which, in the opinion of the Investigator, would compromise the continued safe participation of the patient in the study.
- Suicidal ideation or behavior of type 4 or 5 during the treatment period, as evaluated with the C-SSRS.
- Any evidence of drug abuse or diversion.
- General anesthesia (Blinded Phase only).

Should a patient request or decide to withdraw from the study, all efforts must be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. Patients withdrawing due to an AE should be followed up according to Section 12.7. All information should be reported in the applicable CRF pages (refer to
Section 9.2). Wherever possible, a post-study follow-up visit should take place 28-
days after last dose of IMP (refer to Section 9.1.1.11 and 9.1.2.9). If withdrawing
patients decline to give a reason for withdrawal of consent, the Investigator must
respect the patient’s wishes.
11 URGENT SAFETY MEASURES

The sponsor and Investigator may take appropriate urgent safety measures in order to protect the patients of a clinical trial against any immediate hazard to their health or safety. If such measures are taken by the Investigator they must notify GW immediately or at least within 24 hours of awareness. GW will report urgent safety measures to Regulatory Authorities by telephone within 24 hours of awareness, wherever possible, and will provide a written report to the Regulatory Authorities and EC/IRB within three days.
12 ADVERSE EVENT REPORTING

12.1 Definitions

12.1.1 Adverse Event

For the purposes of this study an AE is defined as:

Any new unfavorable/unintended signs/symptoms (including abnormal laboratory findings when relevant), or diagnosis or worsening of a pre-existing condition, which occurs following screening (Visit 1) and at any point up to the post-treatment, safety follow-up visit (Visit 11 and Visit OLE Follow-up), which may or may not be considered to be related to the IMP. Any event that is the result of a study procedure must be recorded as an AE.

Surgical/Investigational procedures are not AEs. The medical reason for the procedure is the AE. Elective hospitalizations for pre-study existing conditions or elective procedures are not AEs. The exception may be if the patient has an AE during hospitalization which prolongs their scheduled hospital stay in which case it would be considered a SAE (refer to Section 12.2).

If reporting a fatal event, the SAE term should be the underlying cause of the death (e.g., disease or medical condition leading to death).

12.1.2 Investigator

The term Investigator refers to the study Principal Investigator (PI) or a formally delegated study physician.

12.2 Serious Adverse Events

During clinical investigations, AEs may occur which, if suspected to be IMP-related, might be significant enough to lead to important changes in the way the IMP is developed (e.g., change in dose, population, monitoring need, consent/assent forms). This is particularly true for events that threaten life or function. Such SAEs will be reported promptly to Regulatory Authorities, applicable ECs/IRBs and Investigators (expedited reporting) by GW.

An AE must only be classed as serious, i.e., a SAE, when the event falls into one of the following criteria:

- Results in death.
- Is life-threatening*.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
• Is a congenital anomaly/birth defect.
• Is medically significant**.

* The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which, hypothetically, might have caused death if it were more severe.

** Medical and scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. Important medical events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

12.3 Reporting Procedures for Serious Adverse Events

All SAEs occurring during the study must be reported to GW with any other supporting information and recorded in the AE section of the CRF. Any on-going SAEs should be followed up until resolution wherever possible. For all deaths, the working diagnosis or cause of death as stated on a death certificate, available autopsy reports and relevant medical reports should be sent to GW promptly.

**All SAEs must be reported directly to the GW PVD within 24 hours of discovery or notification of the event.** All SAE information must be recorded in the SAE Report forms provided in the center files and faxed to the GW PVD. Additional information received for a case (follow-up or corrections to the original case) need to be detailed on a new SAE Report form, signed/dated and faxed to the GW PVD and the AE section of the CRF must be updated.

The Investigator is not obliged to actively monitor for any new SAEs which occurred after the last formal follow-up observational period (Visit 11 or OLE Follow-up). However, if the Investigator becomes aware of any deaths or a new IMP-related SAE occurring within 28 days of the final dose of IMP, these should be reported to the GW PVD.

Any other problem discovered outside these time limits (Visit 11 or OLE Follow-up) which is deemed to be an unexpected safety issue and is likely to have an impact on patients who have taken part in the study must be treated as an SAE and reported to the GW PVD. Such post-study SAEs do not need to be recorded in the patient’s CRF if editing rights to the CRF have been removed due to final study data lock. GW PVD
may request safety follow-up information after the final study visit in order to investigate a potential safety issue.

Contact details for the GW PVD are provided at the front of the center files for all study centers, and upon the GW SAE Report form.

**12.4 Pregnancy**

Any patient, or patient’s partner, who has become pregnant whilst receiving IMP, or within 90 days of last dose of IMP, must be reported to the GW PVD, using the GW Pregnancy Monitoring forms provided. Where possible the Investigator should provide the outcome of the pregnancy.

Pregnancy reports must be sent to the GW PVD using the fax number for SAE reporting (see Appendix 3.2) within 24 hours of becoming aware.

The Investigator is not obliged to actively monitor for any pregnancies that commence more than 90 days after the final dose of IMP. However, if the Investigator becomes aware of a new pregnancy outside this time limit then they should report it as above. The GW PVD will follow up for all pregnancy outcomes.

**12.5 Causality Assessment**

Causality assessment is required for all AEs and SAEs. Causality assessment must only be assigned by the Investigator. All cases judged as having a reasonable suspected causal relationship to the IMP must be reported as such. The expression “reasonable causal relationship” is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

The following question which must be answered by the Investigator for all AEs is used to capture the reasonable causal relationship of an event to the IMP:

“In your opinion is there a plausible relationship to the IMP?” The answer is either “yes” or “no”.

Events that start before the first dose of IMP (pre-treatment) should be considered as not causally related. Where a pre-treatment event worsens in severity following the first dose of IMP, a new event record should be entered into the CRF.

Considering the explanation given above, Investigators are strongly encouraged to express their opinion on what the cause of an AE might be. For individual patients, the Investigator is usually in the best position to assess the underlying suspected cause of an AE. For all AEs and especially SAEs, it is important that the Investigator assess not only the possible role of the IMP but also other potential contributing factors. Factors for consideration of the underlying cause may include:
• Medical and disease history.
• Lack of efficacy/worsening of treated condition.
• Concomitant or previous treatment.
• Withdrawal of IMP.
• Protocol-related procedure.

12.6 Reporting Procedures for All Adverse Events

All AEs (including SAEs) occurring during the study will be reported on the running logs in the AE section of the CRF. This includes all events from the time following screening (Visit 1) up to and including the post study follow-up visit (Visit 11 or OLE Follow-up), whether or not attributed to IMP and observed by the Investigator or patient.

The following information will need to be provided for all AEs:

A) Adverse Event (Diagnosis or Syndrome if Known, or Signs and Symptoms)

Where the Investigator cannot determine a diagnosis, signs or symptoms should be recorded in the AE section of the CRF. Once a diagnosis has been determined the AE section of CRF must be updated to reflect the diagnosis in replacement of the original symptoms. In circumstances where only a provisional diagnosis is possible (working diagnosis), the CRF must be updated to reflect the provisional diagnosis in replacement of the original symptoms. In some circumstances it may be relevant for the Investigator to include the symptoms alongside the diagnosis in the verbatim event description. However, the diagnosis (full or provisional) should be clearly stated (e.g. *headache and fever due to pneumonia*).

B) Adverse Event Start Date and Stop Date

The start and stop dates of the event must be provided. All AEs require these fields to be completed in full. Partial dates or missing dates are not normally acceptable and significant effort must be undertaken to obtain any unknown information. If a precise date is not known an estimated date should be provided instead. When a complete date cannot be given then record as much information as possible (i.e., month and year or, in exceptional circumstances, just year). When the actual start date becomes known the CRF must be updated to replace the previously recorded date.

C) Outcome

The outcome of the event must be recorded accurately and classified into one for the following categories:

• Recovered.
• Recovered with sequelae.
• Continuing.
• Patient died.

D) Severity
When describing the severity of an AE the terms mild, moderate, or severe should be used. Clinical judgment should be used when determining which severity applies to any AE.

If the severity of an AE fluctuates day-to-day, e.g., a headache or constipation, the change in severity should not be recorded each time; instead, only the worst observed severity should be recorded with AE start and stop dates relating to the overall event duration, regardless of severity.

A severe AE is not the same as a SAE. For example, a patient may have severe vomiting but the event does not result in any of the SAE criteria above. Therefore, it should not be classed as serious.

E) Causality
See Section 12.5 above.

F) Action Taken with Study Medication
This question refers to the action taken with the IMP due to an AE. The action with the IMP must be classed as:

• None.
• Dose reduced temporarily.
• Dose reduced.
• Study medication interrupted.
• Study medication stopped.

12.7 Follow-up Procedures for Adverse Events
The Investigator may be asked to provide follow-up information to the GW PVD for any AEs reported or during the investigation of potential safety issues. Such requests for additional safety information may occur post Visit 11 or OLE Follow-up after the study.

AEs considered related to the IMP by the Investigator or the sponsor should be followed up until resolution or the event is considered stable.

It will be left to the Investigator’s clinical judgment whether or not an AE is of sufficient severity to require the patient’s removal from treatment. A patient may also
voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. Further details of withdrawal are presented in Section 10. If either of these occurs, the patient must undergo an end of treatment assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable. If a safety concern is identified following withdrawal of a participant, GW may contact the Investigator for additional follow-up information.

12.8 Potential Cases of Drug-Induced Liver Injury

All investigational centers are required to submit to the GW PVD the laboratory results for any patient after randomization that meet the criteria for the selected laboratory parameters as follows:

- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).
- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for more than two weeks.
- ALT or AST > 3 × ULN and (TBL > 2 × ULN or INR > 1.5).

These reports must be sent to the GW PVD using the fax number for SAE reporting within 24 hours of becoming aware of the results. In addition, please send a copy of the patient’s baseline laboratory results with all reports to the GW PVD.

Abnormal values in AST and/or ALT concurrent with abnormal elevations in TBL that meet the criteria outlined above are considered potential cases of drug-induced liver injury and will be considered as protocol defined criteria for withdrawal and important medical events. The Investigator will arrange for the patient to return to the investigational center as soon as possible (within 24 hours of notice of abnormal results) for repeat assessment of ALT, AST, TBL and alkaline phosphatase levels, detailed history and physical examination. Patients should be followed up in this way until all abnormalities have normalized (in the Investigator’s opinion) or returned to the baseline state.

Elevations in ALT or AST > 3 × ULN or TBL > 2 × ULN alone are not considered potential cases of drug-induced liver injury, but will be followed as detailed above, within 72 hours’ notice of abnormal results. If the participant cannot return to the investigational center, repeat assessments may be done at a local laboratory and the results sent to GW PVD.
12.9 Notification of Safety Information to Investigators, Regulatory Authorities and Ethics Committees.

In accordance with the EU Clinical Trials Directive\textsuperscript{60}, relevant parts of the FDA Code of Federal Regulations\textsuperscript{62} and any national regulations, GW will inform Investigators, Regulatory Authorities and relevant ECs/IRBs of all relevant safety information. This will include the reporting of relevant SAEs and all Suspected Unexpected Serious Adverse Drug Reactions (SUSARs).

This information will be provided through three sources:

1) IB\textsuperscript{51}: a compilation of the clinical and non-clinical safety data available on the IMP that is relevant to the study. The IB is updated annually.

2) Development Core Safety Information: this document forms the safety section of the IB\textsuperscript{51}, or is updated as an addendum to the IB\textsuperscript{51}. This document is revised if necessary, when new important safety information becomes available (potentially up to a few times a year).

3) Council for International Organizations of Medical Sciences (CIOMS) reports: these reports are issued every time a SUSAR is reported to GW. They provide information on individual case reports and are sent to all the Regulatory Authorities, the relevant central ECs/IRBs which have approved the study and Investigators. As required, the Investigator should notify their regional ECs/IRBs of SAEs or SUSARs occurring at their center and other AE reports, i.e., CIOMS reports and any additional safety documentation received from GW, in accordance with local procedures.

In the USA, Investigators are normally required to promptly report to their IRBs all unanticipated problems involving risks to human patients, or others, including AEs that should be considered unanticipated problems. Based on current FDA guidance\textsuperscript{57} the following clarification is provided in determining what constitutes an unanticipated problem:

In general, an AE observed during the conduct of a study should be considered an unanticipated problem involving risk to patients and reported to the IRB, \textit{only} if it were unexpected, serious, and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent/assent, or IB). An individual AE occurrence \textit{ordinarily} does not meet these criteria because, as an isolated event, its implications for the study cannot be understood.

The FDA guidance\textsuperscript{62} states that, accordingly, to satisfy the Investigator’s obligation to notify the IRB of unanticipated problems, any Investigators participating in a
multicenter study may rely on the sponsor’s assessment and provide to the IRB a report of the unanticipated problem prepared by the sponsor.

GW will inform Investigators, Regulatory Authorities and relevant ECs/IRBs of any safety issues or case reports that are considered to be unanticipated and provide such reports as mentioned above. It should be noted that a single SUSAR report notified to Investigators in the study does not necessarily constitute an unanticipated problem unless identified by GW in the submission cover letter.

As a minimum, the recipient will be sent all of the above and relevant updates between the period from ethical approval and final database lock.
13 STATISTICAL CONSIDERATIONS

A statistical analysis plan (SAP) will be produced prior to unblinding of the study. Any deviations from the original SAP will be described in the final clinical study report.

13.1 Sample Size, Power and Significance Levels

Blinded Phase:
A total of 144 patients will be enrolled. The 144 patients will be randomly allocated on a 1:1:1 basis (25 mg/kg/day GWP42003-P, 50 mg/kg/day and placebo, 48 patients per group). Patients in the placebo group will be split into two cohorts (24 patients 25 mg/kg/day dosing volumes and 24 patients receiving 50 mg/kg/day dosing volumes), but it is assumed that these two cohorts can be pooled for the analyses of efficacy.

If it is assumed that patients in the placebo group will experience a mean reduction in focal seizure frequency of 15% (from baseline), this sample size of 48 patients per group will be sufficient to detect a difference of 35% between treatments (i.e., patients receiving GWP42003-P will experience at least a 50% reduction in focal seizures). This is based on a standard deviation of 60%, using a two-sided 5% significance level and 80% power.

Open-Label Extension:
All patients who wish to continue on IMP following the blinded phase.

13.2 Interim Analysis

Blinded Phase:
No interim analysis is planned for this study.

Open-label Extension:
At least one interim analysis may be conducted to support New Drug Application and Marketing Authorization Application filings. Further interim analyses may be conducted as required.

13.3 Analysis Sets

Blinded Phase:
There will be up to three analysis sets in the blinded phase:

Intention to Treat (ITT)

- All patients who are randomized, receive IMP in the study and have post-baseline efficacy data will be included and analyzed according to their randomized treatment group.
• The ITT analysis set is the primary analysis set for all efficacy endpoints.

**Per Protocol (PP)**

If there are a sufficient number of significant protocol deviations in the study, a PP analysis set may also be presented.

• All patients who complete the study with no protocol deviations deemed to compromise the assessment of efficacy will be included and analyzed according to the treatment group they were randomized. The rules determining the PP analysis set will be fully defined prior to unblinding of the database.

**Safety**

All patients who received at least one dose of IMP in the study will be included and analyzed according to the treatment received. Only patients for whom it has been confirmed that they did not take any IMP will be excluded from this safety analysis set.

**Open-Label Extension:**

There will be one analysis set in the open-label extension phase:

**Safety**

All patients who received at least one dose of IMP in the open-label extension phase of the study will be included. Only patients for whom it has been confirmed that they did not take any IMP in the open-label extension phase will be excluded from this safety analysis set.

**13.3.1 Protocol Deviations**

Protocol deviations will be listed and reasons for exclusion from the analysis populations will be summarized.

**13.4 General Considerations**

Unless stated otherwise, continuous variables will be summarized showing the number of non-missing values ($n$), mean, standard deviation, median, minimum and maximum and categorical variables will be summarized showing the number and percentage of patients falling in each category.

Unless otherwise specified, tables for the blinded phases will be summarized by randomized treatment group, and for the open-label extension phase will be summarized overall.
13.5 Accountability and Background Characteristics

13.5.1 Enrollment and Disposition

All patients (screened, enrolled/randomized, prematurely terminated IMP) will be accounted for in the enrollment and disposition summary tables.

13.5.2 Baseline and Demographic Characteristics

Age, sex, ethnic origin (as allowed per local regulations) and any other demographic or baseline characteristics, including history of epilepsy and epilepsy-specific genetic testing, will be summarized, using appropriate summary statistics.

13.5.3 Medical History

Previous and current medical conditions will be summarized by System Organ Class (SOC), including details of epilepsy.

13.5.4 Concomitant Medication

Concomitant medications (including standard AED and rescue medication) taken prior to and during the study will be summarized separately, by medication class and active ingredients.

13.6 Endpoints and Statistical Methods

Blinded Phase:
Statistical hypothesis testing will be performed on the primary endpoint and other endpoints as appropriate. Since there is a single primary analysis endpoint, no formal adjustment of statistical significance for multiple testing on multiple endpoints is required, although such multiplicity should be allowed for when interpreting the results for secondary endpoints. However, there are three treatments, so multiple significance testing will occur when making comparisons between the treatments; the major comparisons of interest are those between each of the GWP42003-P Dose Levels and placebo and, in particular, the 50 mg/kg/day Dose Level and placebo. A step down procedure will be used to control the type I error. The comparison of 50 mg/kg/day GWP42003-P and placebo will be tested first and only if this is statistically significant at the 5% level will the comparison of 25 mg/kg/day GWP42003-P and placebo be tested.
13.6.1 Evaluable Period

Blinded Phase:
The start of the evaluable period of the study (Day 1) is defined as the first day the patient took IMP, as recorded on the CRF, or the day of randomization if this date is unknown.

The end of the evaluable period is defined as the earliest of:

- Day 113 of treatment for the IVRS reported efficacy data and the day of Visit 9 for the CRF-based efficacy data;
- The last day on which study IMP was taken (as stated on the study outcome CRF) for the IVRS reported efficacy data and the day after this for the CRF-based efficacy data;
- The day before a relevant change in prohibited or AED medications was made.

Open-Label Extension:
All data collected during this phase will be summarized across time, using appropriate descriptive statistical methods. Changes from pre-randomization baseline will also be presented. Treatment compliance and exposure to treatment will also be summarized.

13.6.2 Primary Endpoint(s)

Blinded Phase:
The primary endpoint is the percentage change from baseline in number of focal seizures (average per 28 days) during the treatment period (maintenance and titration) in patients taking GWP42003-P compared with placebo.

If the data are found to be normally distributed, they will be analyzed using an analysis of covariance (ANCOVA) approach. The model will include baseline and age group as covariates and treatment group as fixed factor.

The treatment difference, together with the 95% confidence intervals (CIs) will be presented. A step down procedure will be used to control the type I error as per Section 13.6.

However, due to the nature of seizure data, if a normal distribution cannot be assumed, the data will be analyzed using a Wilcoxon rank-sum test. An estimate of the median difference between 50 mg/kg/day GWP42003-P and placebo, together with approximate 95% CI, will be calculated using the Hodges-Lehmann approach. The comparison of 25 mg/kg/day GWP42003-P and placebo will be presented, but the Wilcoxon rank-sum test only performed if the comparison of 50 mg/kg/day GWP42003-P and placebo is statistically significant at the 5% level.
A graphical assessment of normality will be performed as well as computation of summary statistics for normality using the Shapiro-Wilk statistical test. If it is assumed that normality does hold, then a sensitivity analysis will be performed using the Wilcoxon rank-sum test as described above.

If a patient withdraws from the study, then the primary analysis variable will be calculated from the available data, during the treatment period, prior to the patient withdrawing.

**Open-Label Extension:**

The primary endpoint is the safety of GWP42003-P, evaluated by assessing the incidence, type and severity of AEs. Data will be presented as per Section 13.6.5.2.

### 13.6.2.1 Sensitivity Analysis for the Primary Endpoint

**Blinded Phase:**

The following sensitivity analyses will be conducted for the primary endpoint for the blinded phase:

- **Wilcoxon rank-sum test** on percentage change from baseline in number of focal seizures (average per 28 days) during the treatment period;
- **ANCOVA** on percentage change from baseline in number of focal seizures (average per 28 days) during the maintenance period (Day 22 to the end of the evaluable period);
- **ANCOVA** on percentage change from baseline in number of focal seizures (average per 28 days) during the treatment period, using the worst case of last observation carried forward (LOCF), next observation carried backward (NOCB) and the mean from the non-missing data for each patient to impute missing data arising from unreported days in IVRS.
  - Any intermittent missing data for the number of focal seizures arising from unreported days in IVRS will be imputed using the worst (highest number of seizures) of the following for each patient: LOCF, NOCB and the mean daily number of seizures during the treatment period based on non-missing data:
    \[
    \text{Number of seizures} \div \text{Number of reported days in IVRS}
    \]
- **Mixed Effect Model Repeated Measures (MMRM)** on percentage change from baseline in number of focal seizures (average per 28 days) during the treatment period:
  - The model will include baseline and age group as covariates and treatment group as a fixed factor. The time variable will be the assessment time point (nominal visit number, corresponding to each 21 days of the double-blind period) treated as a categorical repeated factor. The baseline-by-time and treatment-by-time interactions will also be included. The model will have an unstructured covariance matrix.
− The fitted model will then be used to produce a final time point comparison, which implicitly adjusts for missing observations under the assumption of missing at random (MAR); there will be no imputations for missing values at individual time points.

− The time course of the treatment effect will also be examined by estimating treatment differences, together with their 95% CIs, for each nominal visit during the randomized treatment period. A step down procedure will be used to control the type I error as per Section 13.6.

• MMRM on percentage change from baseline in number of focal seizures (average per 28 days) during the treatment period, using multiple imputation (MI) to impute data under the Missing Not at Random (MNAR) assumption.

− MNAR will be assumed for missing values resulting from two scenarios, discontinuation due to AEs, and discontinuation due to any reason in the GWP42003-P dose groups and MAR for others, including other patients discontinued in the GWP42003-P dose groups and patients in the placebo group.

− MI will be performed on the focal seizure frequency, based on time points corresponding to each 21 calendar days of the treatment period. Intermittent missing values for intermediate 21-day time points before the last 21-day time point will be imputed using the MCMC method in SAS PROC MI with an IMPUTE=MONOTONE statement for 100 times for each treatment group separately. Then, monotone missing data assumed under the MAR assumption at time point $t$ (i.e., patients in the placebo group and patients in the GWP42003-P groups who did not discontinue due to AEs or for any reason) will be imputed using the MI procedure with the ‘MONOTONE REG’ option, for each treatment group separately. The imputation model will include baseline focal seizure frequency and each 21-day time point up to time point $t$ (in chronological order). With the data imputed from above, monotone missing data of patients in the GWP42003-P groups under the MNAR assumption will be imputed. At each 21-day time point $t$, the input dataset for the MI procedure will include all placebo patients and those patients from the GWP42003-P groups that have values missing under MNAR at that time point. The imputation model will include focal seizure frequency at baseline and each 21-day time point up to time point $t$ (in chronological order) and will be performed for each GWP42003-P group separately.

• ANCOVA on percentage change from baseline in number of focal seizures (average per 28 days) during the treatment period, using MI to impute data under the MNAR assumption.

Full details for this sensitivity analysis will be provided in the SAP.
13.6.3 Secondary Endpoint(s)

The following endpoints will be compared between treatment groups over the treatment period, for the blinded phase, and during the open-label extension phase relative to the pre-randomization baseline of the blinded phase:

**Antiepileptic efficacy measures:**

- Percentage change from baseline in number of focal seizures (average per 28 days; open-label extension phase only).
- Number of patients considered treatment responders defined as those with a ≥25%, ≥50%, ≥75% or 100% reduction in focal seizure frequency.
- Number of patients experiencing a >25% worsening, −25 to +25% no change, 25–50% improvement, 50–75% improvement or >75% improvement in focal seizure frequency.
- Change in composite focal seizure score (frequency × severity).
- Change in number of focal seizure-free days.
- Change in number of seizures by subtype.
- Change in number of infantile/epileptic spasms.
- Change in use of rescue medication.
- Change in the number of episodes of status epilepticus (convulsive and non-convulsive).
- Changes in duration of seizure subtypes as assessed by the SGIC-SD or the CGIC-SD.

**Cognitive and Behavioral Function:**

- Changes in Vineland-II.
- Changes in Wechsler Scales (pre-school, primary, children, adult).
- Changes in CBCL and ABCL.

**Growth and Development (patients less than 18 years):**

- Change in serum IGF-1 levels.
- Change in Tanner Staging score (for patients aged 10–17 [inclusive]).

**Autistic Features:**

- Change in SCQ score.

**Quality of Life:**

- Changes in the QOLCE (patients 2–18 years) or QOLIE-31-P (patients 19+ years) score.
- Change in CGIC or SGIC score.
- Change in PGIC score.
Blinded Phase:
The number of patient responders and the number of patients seizure free will be summarized and analyzed using the difference in proportions and the odds ratio, together with 95% CIs, comparing the treatment groups.

For changes in composite focal seizure score, number of focal seizure-free days, number of seizures by subtype, number of infantile/epileptic spasms, use of rescue medication, number of episodes of status epilepticus, Vineland-II, Wechsler scales, CBCL, ABCL, SCQ, QOLCE, QOLIE-31-P, SGIC/CNIC and PGIC scores, the data will be summarized at baseline and over the treatment period, and at each time point (or 28-day period, as appropriate) during the maintenance period. Changes from baseline to the average over the treatment period (or at end of study) will be analyzed using ANCOVA, as with the primary endpoint (or appropriate non-parametric methods if data are found to be not normally distributed).

SGIC-SD/CNIC-SD assessments recorded at the end of treatment will be analyzed with ordinal logistic regression using the proportional odds model.

Changes from baseline for IGF-1 levels will be summarized by treatment group and plotted against the Tanner Stages, weight, and height.

Tanner Stages will be evaluated and summarized descriptively at each time point in terms of frequency and proportions. Number (%) of patients with changes in Tanner Stages will be summarized by treatment group.

The primary efficacy analysis uses the ITT analysis set over the evaluable period. ANCOVA analysis, using the LOCF approach, will be used to handle missing values.

In order to explore the robustness of the primary analysis, further sensitivity analysis (in addition to that already detailed in Section 13.6.2.1) may be specified in the SAP. Similar approaches, using the LOCF, will be applied if the data are analyzed using non-parametric methods.

Open-label Extension:
Secondary endpoints will be summarized across time, using appropriate statistical methods. Descriptive statistical methods will be used throughout. There will be no formal hypothesis testing.
13.6.4 Pharmacokinetics

Plasma concentrations for CBD, THC and their major metabolites, following single and multiple doses of GWP42003-P will be summarized by treatment group. Estimates of PK parameters will also be summarized using the appropriate statistics. Where available, plasma concentrations of concomitant AEDs will be summarized.

13.6.5 Safety

In the presentation of safety data for the blinded phase, data from the two cohorts of placebo patients (25 mg/kg/day and 50 mg/kg/day dosing volumes) will be presented separately and pooled together. This will allow the possibility to explore any effects of the volume of IMP on safety endpoints.

13.6.5.1 Treatment Compliance and Extent of Treatment Exposure

Treatment compliance and exposure to treatment will be summarized.

13.6.5.2 Adverse Events

AEs will be coded according to the Medical Dictionary for Regulatory Activities dictionary. A treatment emergent AE is one that started, or worsened in severity or seriousness, following the first dose of IMP. Descriptive presentations of treatment emergent AEs will be given by preferred term and SOC for the safety analysis. The number of patients reporting at least one AE will be provided.

The following summaries will be produced:

- All-causality AEs.
- Treatment related AEs.
- All-causality AEs by severity.
- All-causality serious AEs.
- Treatment related serious AEs.
- AEs reported as leading to permanent cessation of study treatment.
- Fatal AEs.

13.6.5.3 Clinical Laboratory Data

Clinical laboratory data at screening, during and at the end of treatment and the change from baseline to end of treatment will be summarized for the safety analysis set using appropriate summary statistics. Categorical shift tables will also be
presented, showing the numbers of patients with values outside the normal range. Baseline for the open-label extension will be pre-randomization baseline.

13.6.5.4 Vital Signs, 12-Lead Electrocardiogram, Physical Examination and Other Safety Data

Vital signs, ECG, physical examination, number of inpatient hospitalizations and C-SSRS data will be summarized for the safety analysis set, at screening, baseline and at each time point during the treatment period using appropriate summary statistics. Changes in the vital signs and number of inpatient hospitalizations from baseline to end of treatment will also be summarized. Details of menstruation cycles (in females) will be summarized and listed as appropriate.
14 SAFETY MONITORING COMMITTEE

An independent Safety Monitoring Committee (SMC) will be used in this study. Details of the composition and standard operating procedures of the SMC will be detailed in a separate charter.

Furthermore, an independent ESC will be instated to monitor the TSC diagnosis and verify the seizure types of screened patients on an ongoing basis in order to ascertain the correct study population is randomized. Investigators will submit a documented history of TSC directly to the ESC for confirmation of diagnosis and verification of seizure types. The ESC will provide written documentation of the confirmation of diagnosis directly to the investigator and guidance on seizure types, if applicable, for inclusion in the patient file. Details of the composition and standard operating procedures of the ESC will be detailed in a separate charter.
15 REGULATORY AND ETHICAL OBLIGATIONS

15.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformity with the current version and subsequent amendments of the Declaration of Helsinki56, the ICH Tripartite Guideline for GCP Topic E6(R1)52, the EU Clinical Trials Directive60, the EU GCP Directive61 and the clinical trial regulations adopting European Commission Directives into national legislation63,64,65,66,67.

15.2 Informed Consent/Assent

An initial generic ICF consent and assent form will be prepared by GW and provided to the Investigator, who will tailor these for their center by adding the center’s contact details and by using headed paper. The GW Clinical Manager will communicate updates to the template by letter. The written informed consent/assent documents should be prepared in the language(s) of the potential patient population.

Before a patient’s involvement in the trial, the Investigator is responsible for obtaining written informed consent/assent (if allowed per local regulations) from the patient and/or along with written parent(s)/legal representative consent after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study and before any protocol specific screening procedures or any IMPs are administered. The patient and/or parent(s)/legal representative should have ample time for review to consider the information provided before giving written consent/assent, more specific definitions of ample time may be in force if required by ECs/IRBs or local regulations.

The acquisition of informed consent/assent should be documented in the patient’s medical records and the ICF should be signed and personally dated by the patient and/or parent(s)/legal representative (as applicable) and by the person who conducted the informed consent/assent discussion. GW also requires a physician to be present for consent/assent and to sign the consent/assent forms. The original signed ICF should be retained and a copy provided to the patient and/or parent(s)/legal representative.

15.3 Ethics Committee/Institutional Review Board

A copy of the protocol, proposed ICF, other patient information material, any proposed advertising material and any further documentation requested must be submitted to the EC/IRB for written approval. GW must receive a copy of the written
approval of the protocol and ICF before recruitment of patients into the study and shipment of IMP.

The Investigator must submit and, where necessary, obtain approval from the EC/IRB for all subsequent protocol amendments and changes to the informed consent/assent documents. The Investigator should notify the EC/IRB of deviations from the protocol, SAEs occurring at the center and other AE reports received from GW, in accordance with local procedures.

The Investigator will be responsible for obtaining on-going EC/IRB approval/renewal throughout the duration of the study. Copies of the Investigator’s reports and the EC/IRB continuance of approval must be sent to GW.

15.4 Pre-Study Documentation Requirements

The Investigator is responsible for forwarding the following documents to GW for review before allowing any patients to consent/assent for entry into the study:

- Signed and dated protocol signature page.
- Copy of EC/IRB-approved ICF and other patient information material.
- Copy of the EC/IRB approval of the protocol, ICF and other patient information material.
- Up to date curricula vitae and medical licenses (as per local regulations) of the PI and all Sub-Investigators.
- The EC/IRB composition and/or written statement of the EC/IRB in compliance with the FDA regulations relating to GCP and clinical trials\(^57,58,59,68\) , the EU Clinical Trials Directive\(^60\), the EU GCP Directive\(^61\), or the ICH Tripartite Guidelines for GCP Topic E6(R1)\(^52\) where the EU Clinical Trials and GCP Directives do not apply.
- Signed laboratory normal ranges and documentation of laboratory certification (or equivalent) unless using central laboratory arranged by GW.
- Signed clinical trial agreement (including patient/Investigator indemnity insurance and financial agreement).
- Form FDA 1572, if required.
- Drug Enforcement Administration license (where applicable).
- Completed financial disclosure statements for the PI and all Sub-Investigators, if relevant.

15.5 Patient Confidentiality

The Investigator must ensure that the patient’s anonymity is maintained. In the CRFs and within the IVRS databases used to collect the trial data or other documents submitted to GW, patients should be identified by their initials and ethnic origin (if
allowed per local regulations) and their study screening number only. Documents that are not for submission to GW, e.g., signed ICFs, should be kept in strict confidence by the Investigator.

In compliance with the FDA regulations relating to good clinical practice and clinical trials, and the EU Clinical Trials Directive/ICH Tripartite Guidelines for GCP Topic E6(R1), it is required that the Investigator and institution permit authorized representatives of the company, the Regulatory Authorities and the EC/IRB have direct access to review the patient’s original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform the patient that his/her study-related records will be reviewed by the above named representatives without violating the confidentiality of the patient.

All information concerning the IMP and operations of GW such as patent applications, formulae, manufacturing processes, basic scientific data or formulation information supplied to the Investigator by the company and not previously published is considered confidential by the company and shall remain the sole property of the company. The Investigator will agree to use this information only in accomplishing the study and will not use it for any other purposes without the written consent of the company.
16 ADMINISTRATIVE AND LEGAL OBLIGATIONS

16.1 Protocol Amendments and End of Study or Termination

Protocol amendments must be made only with the prior approval of GW. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent/assent documents. The EC/IRB and Regulatory Authorities must be informed of all amendments and give approval for any substantial amendments. Amendments for administrational changes can be submitted to the EC/IRB for information only. The Investigator must send a copy of the approval letter from the EC/IRB to GW.

Both GW and the Investigator reserve the right to terminate the study, according to the clinical trial agreement. The Investigator should notify the EC/IRB in writing of the study’s completion or early termination and send a copy of the notification to GW.

16.2 Study Documentation and Storage

The Investigator should maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections in CRFs will be included on the GW Delegation of Authority and Signature form.

Source documents are original documents, data and records from which the patient’s CRF data are obtained. These include, but are not limited to, hospital records, clinical and office charts, laboratory and pharmacy records, diaries, electronic data captured by IVRS, microfiches, radiographs and correspondence. CRF entries may be considered source data if the CRF is the site of the original recording; that is, there is no other written or electronic record of data. A source data verification plan, identifying the source for each data point at each center, will be agreed with each center prior to patient recruitment. In the rare situations of data being recorded directly into the CRF in error, then the source data from the CRF should be transcribed into the patient’s notes with appropriate signature and date to provide a full audit trail.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related, essential documentation (as outlined in the ICH Tripartite Guidelines for GCP Topic E6(R1)\textsuperscript{52}, Section 8.2), suitable for inspection at any time by representatives from GW and/or applicable Regulatory Authorities. Elements should include:

- Patient files containing completed CRFs, ICFs and supporting copies of source documentation.
• Study files containing the protocol with all amendments, IB, copies of pre-study documentation (see Section 15.4) and all correspondence to and from the EC/IRB and GW.

• Proof of receipt, IMP accountability record, return of IMP for destruction, final IMP reconciliation statement and all drug-related correspondence.

In addition, all original source documents supporting entries in the CRFs, diary data and electronic data captured by IVRS must be maintained and be readily available.

Following completion or termination of a clinical study, GW will initiate proper archive of clinical study-related documentation and electronic records generated by the Investigator and/or GW. All clinical trial-related documents and electronic records will be retained within an archiving system for a period dependent upon need and for a minimum of 25 years. Essential documents should be retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least two years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or if needed by GW.

GW will inform the Investigators for each center in writing of the need for record retention. No study document should be destroyed without prior written agreement between GW and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify GW in writing of the new responsible person and/or the new location.

16.3 Study Monitoring and Data Collection

The GW representative and Regulatory Authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study, e.g., CRFs and other pertinent data, provided that patient confidentiality is respected.

The GW study monitor, or designee, is responsible for inspecting the CRFs and available IVRS/diary data at regular intervals throughout the study to verify adherence to the protocol, completeness, accuracy and consistency of the data and adherence to local regulations on the conduct of clinical research. The study monitor should have access to patient medical records and other study-related records needed to verify the entries in the CRFs.

The Investigator agrees to co-operate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.
To ensure the quality of clinical data across all patients and centers, a clinical data management review will be performed on patient data received at GW or a contract research organization (CRO). During this review, patient data will be checked for consistency, omissions and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and FDA regulations, ICH Tripartite Guidelines for GCP Topic E6(R1) and all other applicable regulatory requirements. To resolve any questions arising from the clinical data management review process, data queries and/or center notifications will be sent to the center for completion and then returned to GW or the CRO, as applicable.

16.4 Electronic Data collected by Interactive Voice Response System

Source data for the assessments collected via IVRS will be managed by the service provider in accordance with ICH Tripartite Guidelines for GCP Topic E6(R1) and in adherence to a quality management system. All data will be stored in a secure (e.g., redundant hardware, password control, limited physical access to servers), fully audit trailed environment with appropriate industry standard back-up and off-site storage practices.

Access for patients providing assessments and Investigators will be authenticated and meet industry standards and comply with the requirements outlined in the FDA Code of Federal Regulations Title 21, Part 11, Subpart B (Electronic Records).

After database lock, all Investigators will receive a certified copy of all IVRS assessment data. These data will be in an agreed, read-only format with a covering letter explaining the content of the data, a quality statement from the IVRS provider and the Investigator’s responsibilities.

Regulatory and sponsor auditors will have the ability to review, but not modify, IVRS data via an agreed means of access.

16.5 Quality Assurance

In accordance with the FDA regulations, EU Clinical Trials Directive, ICH Tripartite Guidelines for GCP Topic E6(R1) and the sponsor’s audit plans, representatives from GW’s Clinical Quality Assurance Department may select this study for audit. Inspection of center facilities, e.g., pharmacy, drug storage areas, laboratories, and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, the EU Clinical Trials Directive and applicable regulatory requirements.
16.6 Compensation

GW will indemnify the Investigator and the study center in the event of any claim in respect of personal injury arising due to a patient’s involvement in the study, providing that the study protocol has been adhered to. This would include claims arising out of or relating to the administration of the IMP or any clinical intervention or procedure provided for or required by the protocol to which the clinical study patient would not otherwise have been exposed, providing there is no evidence of negligence on behalf of the Investigator or their team. GW will not be liable for any claims arising from negligence on the part of the Investigator or their team.

16.7 Publication Policy

GW recognizes that there is a responsibility under the regulatory guidelines to ensure that results of scientific interest arising from this clinical study are appropriately published and disseminated. They will co-ordinate this dissemination and may solicit input and assistance from the chief/Principal Investigators. A summary of the results of this study will be made available on http://www.clinicaltrials.gov, as required by U.S. Law.

The raw data from this study may be obtained by the PIs or by their steering committee representatives on request. Should they wish, PIs are allowed to conduct their own analyses and are permitted to present such information along with methods and results of the clinical study at symposia, national or regional professional meetings and to publish it in theses or dissertations.

All publications, e.g., manuscripts, abstracts, oral/slide presentations or book chapters based on this study, must be submitted to the GW Medical Writing Department and, as applicable, GW Publication Committee for corporate review before release. To ensure adequate time for GW to make comments and suggestions where pertinent, all such material should be submitted to them at least 60 days prior to the date for submission for publication, public dissemination, or review by a publication committee. The PIs must then incorporate all reasonable comments made by GW into the publication.

GW also reserves the right to delay the submission of such information by a period of up to six months from the date of first submission to them in order to allow them to take steps to protect proprietary information where applicable.

16.8 Intellectual Property Rights

All Intellectual Property Rights owned by or licensed to either GW or the PIs, other than those arising from the clinical study, will remain their property. All Intellectual
Property Rights arising out of the clinical study will vest in or be exclusively licensed to GW and, as such, the PI should promptly disclose all knowledge to GW and refrain from using such knowledge without the prior written consent of GW.

16.9 Confidential Information

GW and the PI should ensure that only personnel directly concerned with the study should be party to confidential information and that any information coming to either party about the other during the course of the study should be kept strictly confidential and should not be disclosed to any third party or made use of without the prior written consent of the other.
17 REFERENCES


11 The Tuberous Sclerosis Alliance [Internet]. [cited 2015 Apr 01];Available from: http://www.tsalliance.org/


48 GWMD09112 Clinical Study Report. A randomized, partially-blind, placebo-controlled, pilot, dose-ranging study to assess the effect of Cannabidiol (CBD) on liver fat levels in subjects with fatty liver disease. 28 November 2013.


54 Clinical Trial Facilitation Group recommendations related to contraception and pregnancy testing in clinical trials. September 2014.


## APPENDIX 1  SCHEDULE OF ASSESSMENTS

### Blinded Phase

<table>
<thead>
<tr>
<th>Visit Number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10 (Tel.)</th>
<th>Safety Calls*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent/assent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eligibility Criteria</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital signs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postural BP</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination (including height and body weight)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical laboratory blood sampling</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical laboratory urine sampling (dipstick urinalysis)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine THC screen</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy test (if appropriate)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacokinetic blood sampling</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AED concentration</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Concomitant medications</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Inpatient epilepsy-related hospitalizations</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Suicidality / C-SSSRS/Children’s C-SSSRS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vineland-II</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGIC/CGIC</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGIC</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGIC-SD/CGIC-SD</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QOLCE/QOLIE-31-P</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wechsler Tests</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBCL/ABCL</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCQ</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanner Staging (where appropriate) and IGF-1 testing</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstruation question (where appropriate)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient diary review (seizures, AE information, concomitant AEDs, rescue medication, IMP dosing)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVRS and diary training</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMP dispensing</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collection of IMP</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Visit Number**

<table>
<thead>
<tr>
<th>Visit Number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>Safety Calls*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMP compliance review</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Medication Use and Behavior Survey</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

*Telephone safety calls will be completed every two days during titration, one week after the end of titration and, for patients not entering the OLE, weekly from Visit 9 to Visit 11.

### Open-label Extension

<table>
<thead>
<tr>
<th>Visit Number</th>
<th>B1</th>
<th>B2</th>
<th>B3</th>
<th>B4</th>
<th>Assessment Visits</th>
<th>Re-Supply Visits</th>
<th>End of Treatment</th>
<th>End of Taper</th>
<th>Follow up (Tel)</th>
<th>Safety Calls*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent/assent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital signs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination (including height and body weight)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical laboratory blood sampling</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical laboratory urine sampling (dipstick urinalysis)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine THC</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy test, where appropriate</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>AED concentration</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEIs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Concomitant medications</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Inpatient epilepsy-related hospitalizations</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Suicidality /C-SSRS/ Children’s C-SSRS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vineland-II</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGIC/CGIC</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGIC</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGIC-SD/CGIC-SD</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QOLCE/QOLIE-31-P</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wechsler Tests</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBCL/ABCL</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCQ</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanner Staging (where appropriate) and IGF-1 testing</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstruation question (where appropriate)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient diary review (seizures, AE information,</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Visit Number</td>
<td>B1</td>
<td>B2</td>
<td>B3</td>
<td>B4</td>
<td>Assessment Visits</td>
<td>Re-Supply Visits</td>
<td>End of Treatment</td>
<td>End of Taper</td>
<td>Follow up (Tel)</td>
<td>Safety Calls*</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>-------------------</td>
<td>------------------</td>
<td>------------------</td>
<td>-------------</td>
<td>----------------</td>
<td>---------------</td>
</tr>
<tr>
<td>concomitant AEDs, rescue medication, IMP dosing)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVRS and diary training</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMP dispensing</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collection of IMP</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMP compliance review</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Medication Use and Behavior Survey</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

*Telephone safety calls will be completed every two days during titration, one week after the end of titration and, for patients not entering the OLE, weekly from Visit 9 to Visit 11.
APPENDIX 2  TANNER STAGING

(Reproduced with permission from the New England Journal of Medicine)\textsuperscript{55}.

The following is to be completed for all female adolescent patients (i.e., 10 to less than 18 years of age at the time of signing the informed consent/assent form, or earlier if clinically indicated by onset of menarche or other signs of precocious puberty).

**Female Development & Pubic Hair**

<table>
<thead>
<tr>
<th>Stage 1 (Prepubertal, typically 10 years and younger)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No glandular tissue; areola follows the skin contours of the chest.</td>
</tr>
<tr>
<td>• No pubic hair at all.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 2 (10–11.5 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Breast bud forms, with small area of surrounding glandular tissue; areola begins to widen.</td>
</tr>
<tr>
<td>• Small amount of long, downy hair with slight pigmentation on the labia majora.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 3 (11.5–13 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Breast begins to become more elevated, and extends beyond the borders of the areola, which continues to widen but remains in contour with surrounding breast.</td>
</tr>
<tr>
<td>• Hair becomes more coarse and curly and begins to extend laterally.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A</th>
<th>Breast Development and Pubic Hair</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Stage 1" /></td>
<td><img src="image2" alt="Stage 2" /></td>
</tr>
<tr>
<td><img src="image6" alt="Pubic hair Stage 1" /></td>
<td><img src="image7" alt="Pubic hair Stage 2" /></td>
</tr>
</tbody>
</table>

Please check the box next to the most appropriate stage; in the event that qualifying characteristics are not within the same stage, defer to the lesser stage as the overall Tanner Score.
Tanner Stage 4 (13–15 years)

• Increased breast size and elevation; areola and papilla form a secondary mound projecting from the contour of the surrounding breast.
• Adult-like hair quality, extending across pubis but sparing medial thighs.

Tanner Stage 5 (15+ years)

• Breast reaches final adult size; areola returns to contour of the surrounding breast, with a projecting central papilla.
• Hair extends to medial surface of the thighs.

The following is to be completed for all male adolescent patients (i.e., 12 to less than 18 years of age at the time of signing the informed consent/assent form).

Male Genital Development & Pubic Hair

Please check the box next to the most appropriate stage.

Tanner Stage 1 (Prepubertal, typically 9 years and younger)

• Testicular volume less than 1.5 mL; small penis of 3 cm or less.
• No pubic hair at all.

Tanner Stage 2 (9–11 years)

• Testicular volume between 1.6 and 6 mL; skin on scrotum thins, reddens and enlarges; penis length unchanged.
• Small amount of long, downy hair with slight pigmentation at the base of the penis and scrotum.

Tanner Stage 3 (11–12.5 years)

• Testicular volume between 6 and 12 mL; scrotum enlarges further; penis begins to lengthen to about 6 cm.
• Hair becomes more coarse and curly and begins to extend laterally.

Tanner Stage 4 (12.5–14 years)
• Testicular volume between 12 and 20 mL; scrotum enlarges further and darkens; penis increases in length to 10 cm and circumference.
• Adult-like hair quality, extending across pubis but sparing medial thighs.

Tanner Stage 5 (14+ years)
• Testicular volume greater than 20 mL; adult scrotum and penis of 15 cm in length.
• Hair extends to medial surface of the thighs.
APPENDIX 3  STUDY PERSONNEL

Appendix 3.1  Investigator Details

At the time of protocol production, the participating Investigators had not been confirmed. A list of all Investigators will be maintained within the GW Master Files (electronically and added to the Trial Master File at the end of the study).

Appendix 3.2  Sponsor Contact Details

Pharmacovigilance Department — SAE Reporting: Fax:
USA Toll Free Fax:
Tel:

Sponsor: GW Research Ltd
Sovereign House
Vision Park
Chivers Way
Histon
Cambridge CB24 9BZ
United Kingdom
Tel:
Fax:

Medical Monitor: Refer to Study Contact List in the site file.

Clinical Project Manager/Clinical Operations Director:

Clinical Trial Supplies:
G-Pharm Ltd
Tel:
Fax:
Study Title: A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled seizures

Study Code: GWEP1521

EudraCT Number: 2015-002154-12

CLINICAL PROTOCOL

GW Research Ltd
Sovereign House
Vision Park
Chivers Way
Histon
Cambridge CB24 9BZ
United Kingdom

Tel: PPD
Fax: PPD

Confidentiality Statement

This document contains confidential information of GW Research Ltd (GW) that must not be disclosed to anyone other than the recipient study staff and members of the Institutional Review Board or Independent Ethics Committee. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW.
SPONSOR: GW RESEARCH LIMITED

Study Code: GWEP1521
EudraCT Number: 2015-002154-12
Protocol V8 23Apr19

Investigator Agreement

I have read the attached protocol entitled "A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled seizures", dated 23 April 2019, and agree to abide by all provisions set forth therein.

I agree to comply with applicable regulatory requirement(s); the U.S. Food and Drug Administration (FDA) regulations relating to good clinical practice (GCP) and clinical trials, the European Union (EU) Clinical Trials Directive (2001/20/EC), the EU Good Clinical Practice/GCP Directive (2005/28/EC) and subsequent applicable regulatory/statutory instruments, or the International Council for Harmonisation Tripartite Guideline for GCP where the EU Clinical Trials and GCP Directives do not apply, and to complete Form FDA 1572, if required.

I am not aware that any conflicts of interest, financial or otherwise, exist for myself, my spouse [or legal partner] and dependent children and agree to confirm this in writing if required and update as necessary.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW.

Center No: ____________________________

Print Name: ____________________________ Date: ____________________________

Principal Investigator (DD Month YYYY)

Signature: ____________________________

GW Authorization

Print Name: ____________________________ Date: ____________________________

Clinical Manager (DD Month YYYY)

Signature: ____________________________
1 PROTOCOL SYNOPSIS

<table>
<thead>
<tr>
<th>Study Title</th>
<th>A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled seizures.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Study Type</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Indication</td>
<td>Seizures* in patients with tuberous sclerosis complex (TSC). *Seizures include: focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures (tonic-clonic, tonic, clonic or atonic) that are countable.</td>
</tr>
</tbody>
</table>
| Primary Objective | **Blinded Phase:**  
To evaluate the efficacy of GWP42003-P as add-on therapy in reducing the frequency of seizures when compared with placebo in patients with TSC.  
**Open-label Extension:**  
To evaluate via the adverse events (AE) profile the long term safety and tolerability of GWP42003-P as add-on therapy in children and adults with TSC who experience inadequately-controlled seizures. |
| Secondary Objectives | **Blinded Phase:**  
• To evaluate the effect of GWP42003-P compared with placebo on antiepileptic measures.  
• To evaluate the effect of GWP42003-P on growth and development (in patients less than 18 years old) compared with placebo.  
• To evaluate the effects of GWP42003-P on quality of life compared with placebo.  
• To evaluate the safety and tolerability of GWP42003-P compared with placebo.  
**Open-label Extension:**  
• To evaluate the long term effects of GWP42003-P, as add-on therapy, on antiepileptic measures.  
• To evaluate the long term effect of GWP42003-P on growth and development (in patients less than 18 years old).  
• To evaluate the long term effects of GWP42003-P on quality of life.  
• To evaluate the long term safety and tolerability of |
### Exploratory Objectives

**Blinded Phase:**
- To evaluate the effect of GWP42003-P on TSC-associated neuropsychiatric disorders (TAND), including cognitive and behavioral function and autistic features compared with placebo.
- To determine the pharmacokinetics (PK) of CBD, and its major metabolites following single and multiple doses of GWP42003-P.
- To evaluate the effects of GWP42003-P on plasma concentrations of concomitant antiepileptic drugs (AEDs), if applicable.

**Open-label Extension:**
- To evaluate the long term effect of GWP42003-P on TAND, including cognitive and behavioral function and autistic features.

### Study Design

<table>
<thead>
<tr>
<th><strong>GWP42003-P.</strong></th>
<th><strong>This multicenter study consists of a randomized, placebo-controlled, double-blind phase followed by an open-label extension (OLE) phase.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blinded Phase:</strong></td>
<td>The blinded phase of the study is a randomized, double-blind, parallel-group, 16-week comparison of two doses of GWP42003-P versus placebo. Patients will complete a 1-week screening period and a 4-week baseline period before they are randomized to receive 25 mg/kg/day GWP42003-P, 50 mg/kg/day GWP42003-P or equivalent volumes of placebo. Randomization will be stratified by age according to the following ranges: 1–6, 7–11, 12–17 years and 18+ years. Patients will begin a 4-week dose escalation period, titrating up to their assigned dose, before continuing on a stable dose of blinded investigational medicinal product (IMP) for 12 weeks. Dose escalation for each patient is subject to the investigator’s assessment of safety and tolerability. If a dose becomes poorly tolerated, the investigator may consider temporarily or permanently reducing the dose for the remainder of the study. Clinic visits will occur for screening (Day −35), baseline (Day −28), randomization (Day 1) and, on Days 15 and 29 during titration and on Days 43, 57, 71 (telephone) and 85 until the end of treatment (Day 113). Safety telephone calls will be completed every two days during titration, one week after the end of titration and, for patients not entering the OLE, weekly from Visit 10 to Visit 12. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend.</td>
</tr>
</tbody>
</table>

---

**Confidential Page 4 of 154**

**Template: 231014.V1**
instead. Patients will be required to perform daily interactive voice response system (IVRS) telephone calls to record seizure information. They will also complete a paper diary daily with information about their IMP and concomitant AED administration.

Following completion of the blinded phase, patients will be invited to continue to receive GWP42003-P in an OLE. Those patients opting not to enter the OLE will complete a 10-day taper period (down-titrating 10% per day for 10 days).

**Open-label Extension Transition:**

In order to maintain consistent exposure to IMP and maintain the integrity of the blind, patients will enter a 2-week blinded transition to the OLE. OLE IMP will be titrated up to 25 mg/kg/day whilst blinded IMP is simultaneously tapered down to zero. All patients will complete the transition and enter the OLE taking 25 mg/kg/day GWP42003-P:

- Patients from the placebo group will titrate up to 25 mg/kg/day GWP42003-P.
- Patients from the 25 mg/kg/day GWP42003-P group will continue to take 25 mg/kg/day GWP42003-P.
- Patients from the 50 mg/kg/day GWP42003-P group will taper down (10% per day) to 25 mg/kg/day GWP42003-P.

Safety telephone calls will be completed every two days throughout the OLE transition. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead.

**Open-label Extension:**

The OLE consists of a 3-week titration period followed by a maintenance period and a 10-day taper period. The initial OLE period will last for a maximum of 1 year. Following titration according to the titration schedule, patients will continue with their optimal GWP42003-P dose. However, investigators may decrease the dose if a patient experiences intolerance, or increase the dose to a maximum of 50 mg/kg/day if required for better seizure control, until the optimal dose is found. Dose increases above 25 mg/kg/day are recommended to be done slowly, with maximum increments of 2.5 mg/kg/day every two days. Patients whose dose has been decreased can have their dose increased again provided there is adequate tolerance. Safety telephone calls will be completed every two days throughout the OLE titration and one week after the end of titration. If the call falls on a weekend, it is permitted to schedule the call for the
Primary Endpoint

**Blinded Phase:**
The primary endpoint is the change in number of TSC-associated seizures* during the treatment period (maintenance and titration) compared to baseline in patients taking GWP42003-P compared with placebo.

*Primary endpoint TSC-associated seizures include: focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures (tonic–clonic, tonic, clonic or atonic) that are countable.

**Open-label Extension:**
The safety of GWP42003-P will be evaluated by assessing the incidence, type and severity of AEs.

Secondary Endpoints

**Blinded Phase:**
The following endpoints will be compared between treatment groups over the 16-week, double-blind treatment period (all changes relative to baseline):

**Key:**
- Number of patients considered treatment responders defined as those with a ≥ 50% reduction in TSC-associated seizure frequency*.
- Change in Caregiver Global Impression of Change (CGIC) or Subject Global Impression of Change (SGIC) score.
- Change in total seizures.

**Other:**

**Antiepileptic Efficacy Measures:**
- Number of patients considered treatment responders defined as those with a ≥ 25%, ≥ 50%, ≥ 75% or 100% reduction in TSC-associated seizure* frequency.
- Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in TSC-associated seizure* frequency.
- Change in number of TSC-associated seizure*-free days.
- Change in number of ‘other’ seizures (absence, myoclonic,
focal sensory and infantile/epileptic spasms).

**Growth and Development (in patients less than 18 years old):**
- Change in serum insulin-like growth factor-1 (IGF-1) levels.
- Change in Tanner Staging score (for patients aged 10–17 [inclusive]).

**Quality of Life:**
- Changes in the Quality of Life in Childhood Epilepsy (QOLCE; patients 2–18 years) or Quality of Life in Epilepsy (QOLIE-31-P; patients 19+ years) score.
- Change in Physician Global Impression of Change (PGIC) score.

**Safety and Tolerability:**
- AEs.
- Clinical laboratory parameters.
- 12-lead electrocardiogram (ECG).
- Physical examination parameters (including height and weight).
- Vital signs.
- Columbia-Suicide Severity Rating Scale (C-SSRS; 19+ years) or C-SSRS Children’s (6–18 years) score, where applicable.
- Number of inpatient hospitalizations due to epilepsy.
- Abuse liability.
- Effects on menstruation cycles (in females).

**Open-label Extension:**
The following endpoints will be assessed relative to the pre-randomization baseline of the blinded phase:

**Antiepileptic Efficacy Measures:**
*TSC-associated seizures include: focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures (tonic–clonic, tonic, clonic or atonic) that are countable.

**Key:**
- Percentage change in number of TSC-associated seizures* (average per 28 days).
- Number of patients considered treatment responders defined as those with a ≥ 50% reduction in TSC-associated seizure frequency*. 
- Change in CGIC or SGIC score.
- Change in total seizures.

**Other:**
- Number of patients considered treatment responders defined as those with a ≥25%, ≥50%, ≥75% or 100% reduction in TSC-associated seizure* frequency.
- Number of patients experiencing a >25% worsening, −25 to +25% no change, 25–50% improvement, 50–75% improvement or >75% improvement in TSC-associated seizure* frequency.
- Change in number of TSC-associated seizure*-free days.
- Change in number of ‘other’ seizures (absence, myoclonic, focal sensory and infantile/epileptic spasms).

**Growth and Development (patients less than 18 years):**
- Change in serum IGF-1 levels.
- Change in Tanner Staging score (for patients aged 10–17 [inclusive]).

**Quality of Life:**
- Changes from baseline in the QOLCE (patients 2–18 years) or QOLIE-31-P (patients 19+ years) score.
- Change in PGIC score.

**Safety and Tolerability:**
- Clinical laboratory parameters.
- ECG.
- Physical examination parameters (including height and weight).
- Vital signs.
- C-SSRS (19+ years) or C-SSRS Children’s (6–18 years) score, where applicable.
- Number of inpatient hospitalizations due to epilepsy.
- Abuse liability.
- Effects on menstruation cycles (in females).

<table>
<thead>
<tr>
<th>Exploratory Endpoints</th>
<th>Double-blind and Open-label Extension: Antiepileptic Efficacy Measures:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change in composite focal seizure score (frequency × severity).</td>
</tr>
<tr>
<td></td>
<td>Change in number of seizures by subtype.</td>
</tr>
<tr>
<td></td>
<td>Change in use of rescue medication.</td>
</tr>
</tbody>
</table>
- Change in the number of episodes of *status epilepticus* (convulsive and non-convulsive).
- Changes in duration of seizure subtypes as assessed by the Subject Global Impression of Change in Seizure Duration (SGIC-SD) or the Caregiver Global Impression of Change in Seizure Duration (CGIC-SD).

**TAND:**

**Cognitive and Behavioral Function:**
- Changes in Wechsler Scales (pre-school, primary, children, adult).
- Changes in Achenbach Child Behavior Checklist (CBCL) and Adult Behavior Checklist (ABCL).

**Autistic Features:**
- Change in Social Communication Questionnaire (SCQ) score.

**PK (Double-blind only):**
- The plasma concentrations will be summarized by time window for CBD and its major metabolites following single and multiple doses of GWP42003-P. Where data allows, the area under the plasma concentration curve (AUC_0–t) from time zero to the last measurable time-point will be calculated.
- Plasma concentrations of concomitant AEDs before and after treatment with GWP42003-P, where available.

### Sample Size

**Blinded Phase:**
A total of 210 patients will be targeted to be enrolled. The 210 patients will be randomly allocated to one of four treatment groups (GWP42003-P 25 mg/kg/day, GWP42003-P 50 mg/kg/day, placebo 25 mg/kg/day dose volume equivalent, or placebo 50 mg/kg/day dose volume equivalent) at a 2:2:1:1 ratio. The placebo groups will be pooled for the analyses of efficacy.

If it is assumed that patients in the placebo group will experience a mean reduction in seizure frequency of 15% (from baseline), patients receiving GWP42003-P will experience at least a 50% reduction in seizures and a common standard deviation of 60%, then this sample size of 70 patients per group will be sufficient to detect a difference in response distributions with 90% power.

This test is based on a two-sided non-parametric Mann-Whitney-Wilcoxon test for continuous response data with a 5% significance level.

**Open-label Extension:**
All patients who wish to continue on IMP following completion.
**Summary of Patient Eligibility Criteria**

<table>
<thead>
<tr>
<th>Inclusion:</th>
<th>Patients meeting the following criteria will be considered eligible for this study:</th>
</tr>
</thead>
<tbody>
<tr>
<td>•</td>
<td>Patient is male or female aged between one and 65 years inclusive.</td>
</tr>
<tr>
<td>•</td>
<td>Patient and/or parent(s)/legal representative is willing and able to give informed consent/assent for participation in the study.</td>
</tr>
<tr>
<td>•</td>
<td>Patient and their caregiver are willing and able (in the investigator’s opinion) to comply with all study requirements (including accurate diary and IVRS completion).</td>
</tr>
<tr>
<td>•</td>
<td>Well-documented clinical history of epilepsy, which is not completely controlled by their current AEDs.</td>
</tr>
<tr>
<td>•</td>
<td>Clinical diagnosis of TSC according to criteria agreed by the 2012 International Tuberous Sclerosis Complex Consensus Conference.</td>
</tr>
<tr>
<td>•</td>
<td>Taking one or more AEDs at a dose which has been stable for at least four weeks prior to screening.</td>
</tr>
<tr>
<td>•</td>
<td>All medications or interventions for epilepsy (including ketogenic diet and any neurostimulation devices for epilepsy) must have been stable for one month prior to screening and the patient is willing to maintain a stable regimen throughout the study.</td>
</tr>
<tr>
<td>•</td>
<td>Patient is willing to keep any factors expected to affect seizures stable (such as the level of alcohol consumption and smoking).</td>
</tr>
<tr>
<td>•</td>
<td>Patient and/or parent(s)/legal representative is willing to allow the responsible authorities to be notified of participation in the study, if mandated by local law.</td>
</tr>
<tr>
<td>•</td>
<td>Patient and/or parent(s)/legal representative is willing to allow his or her primary care practitioner and consultant (if they have one) to be notified of participation in the study, if mandated by local law.</td>
</tr>
</tbody>
</table>

**At the end of the baseline period patients must also meet the following criteria:**

- Experienced **at least** eight seizures during the first 28 days of the baseline period with at least one seizure occurring in at least three of the four weeks (seizures include: focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures [tonic–clonic, tonic, clonic or atonic]) that are countable.
• Completed at least 90% of calls to IVRS during the first 28 days of the baseline period (a minimum of 25 completed calls).

Exclusion: The patient may not enter the study if ANY of the following apply:

• Patient has a history of pseudo-seizures.
• Patient has clinically significant unstable medical conditions other than epilepsy.
• Patient has an illness in the four weeks prior to screening or randomization, other than epilepsy, which in the opinion of the investigator could affect seizure frequency.
• Patient has undergone general anesthetic in the four weeks prior to screening or randomization.
• Patient has undergone surgery for epilepsy in the six months prior to screening.
• Patient is being considered for epilepsy surgery or any procedure involving general anesthesia during the blinded phase of the study.
• Patient has been taking felbamate for less than one year prior to screening.
• Patient is taking an oral mammalian target of rapamycin (mTOR) inhibitor.
• Patient has, in the investigator’s opinion, clinically significantly abnormal laboratory values.
• Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP, such as sesame oil.
• Any history of suicidal behavior or any suicidal ideation of type 4 or 5 on the C-SSRS in the last month or at screening.
• Patient is currently using or has in the past used recreational or medicinal cannabis, or cannabinoid-based medications, within the three months prior to screening and is unwilling to abstain for the duration of the study.
• Patient has tumor growth which, in the opinion of the investigator, could affect the primary endpoint.
• In the opinion of the investigator the patient has clinically significant abnormalities in the ECG measured at screening or randomization or any concurrent cardiovascular conditions, which will interfere with the ability to read their ECGs.
• Patient has significantly impaired hepatic function at the screening visit (Visit 1) or the randomization visit (Visit 3),
defined as any of the following:

- Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 × upper limit of normal (ULN).
- TBL* [serum total bilirubin] ≥ 2 × ULN or international normalized ratio [INR] > 1.5 (*TBL ≥ 2 × ULN exclusion will not apply for patients diagnosed with Gilbert’s disease).
- Serum ALT or AST ≥ 3 × ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

*This criterion can only be confirmed once the laboratory results are available.*

- Patient is female and of childbearing potential, or is male whose partner is of child bearing potential, unless willing to ensure that they or their partner use a highly effective method of birth control (e.g., hormonal contraceptives, intrauterine devices/hormone-releasing systems, bilateral tubal occlusion, vasectomized partner, sexual abstinence) during the study and for three months thereafter.
- Female patient who is pregnant (positive pregnancy test), lactating or planning pregnancy during the course of the study and for three months thereafter.
- Patient has received an IMP less than 12 weeks prior to the screening visit.
- Patient has any other significant disease or disorder which, in the opinion of the investigator, may either put the patient at risk because of participation in the study, may influence the result of the study, or may affect the patient’s ability to take part in the study.
- Any abnormalities identified following a physical examination of the patient that, in the opinion of the investigator, would jeopardize the safety of the patient if they take part in the study.
- Patient has donated blood during the past 12 weeks and is unwilling to abstain from donation of blood during the study.
- Patient has been previously randomized into this study.
- Patient has any known or suspected history of alcohol or substance abuse.
- Patient has travel outside the country and/or state of residence planned during the trial, unless the patient has confirmation that the IMP is permitted in the destination country/state.
<table>
<thead>
<tr>
<th>Criteria for Withdrawal</th>
<th>The patient must be withdrawn from the study if any of the following apply:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Administrative decision by the investigator, GW or regulatory authority.</td>
</tr>
<tr>
<td></td>
<td>• Pregnancy.</td>
</tr>
<tr>
<td></td>
<td>• Protocol deviation that is considered to potentially compromise the safety of the patient.</td>
</tr>
<tr>
<td></td>
<td>• Withdrawal of patient consent/assent.</td>
</tr>
<tr>
<td></td>
<td>• Withdrawal of parent(s)/legal representative consent.</td>
</tr>
<tr>
<td></td>
<td>• ALT or AST &gt; 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (&gt; 5%).</td>
</tr>
<tr>
<td></td>
<td>• ALT or AST &gt; 8 × ULN.</td>
</tr>
<tr>
<td></td>
<td>• ALT or AST &gt; 5 × ULN for more than two weeks.</td>
</tr>
<tr>
<td></td>
<td>• ALT or AST &gt; 3 × ULN and (TBL &gt; 2 × ULN or INR &gt; 1.5).</td>
</tr>
<tr>
<td></td>
<td>• Lost to follow-up.</td>
</tr>
<tr>
<td></td>
<td>Note: Prior to withdrawal for the transaminase elevations noted above, the investigator may choose to confirm the transaminase elevations by repeating the following laboratory tests within 24 to 48 hours: ALT, AST, TBL, INR, % eosinophils, gamma-glutamyl transferase and alkaline phosphatase. Should the above transaminase elevation criteria be confirmed, the patient must be withdrawn from the trial.</td>
</tr>
<tr>
<td></td>
<td>The patient may also be withdrawn from the study for any of the following:</td>
</tr>
<tr>
<td></td>
<td>• Did not meet eligibility criteria.</td>
</tr>
<tr>
<td></td>
<td>• Patient non-compliance.</td>
</tr>
<tr>
<td></td>
<td>• AE (including clinically significant laboratory result) which, in the opinion of the investigator, would compromise the continued safe participation of the patient in the study.</td>
</tr>
<tr>
<td></td>
<td>• Suicidal ideation or behavior of type 4 or 5 during the treatment period, as evaluated with the C-SSRS.</td>
</tr>
<tr>
<td></td>
<td>• Any evidence of drug abuse or diversion.</td>
</tr>
<tr>
<td></td>
<td>• General anesthesia (blinded phase only).</td>
</tr>
<tr>
<td></td>
<td>• Addition of a new AED (blinded phase only).</td>
</tr>
</tbody>
</table>

**Investigational Medicinal Product:**

**Formulation:**

GWP42003-P solution (100 mg/mL cannabidiol in sesame oil with anhydrous ethanol, sweetener [sucralose] and strawberry flavoring).

Placebo solution (sesame oil) containing the excipients anhydrous.
<table>
<thead>
<tr>
<th>Mode of Administration, Dose and Regimen</th>
<th>Ethanol, sweetener (sucralose) and strawberry flavoring.</th>
</tr>
</thead>
</table>

**Blinded Phase:**

Patients will titrate the IMP up to the required dose over four weeks as per randomization. Patients will then remain at this maintenance dose for 12 weeks.

Dose escalation for each patient is subject to the investigator’s assessment of safety and tolerability. If a dose becomes poorly tolerated, the investigator may consider temporarily or permanently reducing the dose for the remainder of the study.

Patients will be on treatment for a total of 16 weeks.

Patients not entering the OLE or who withdraw early will down-titrate over a period of 10 days. Patients who decide to enter the open-label extension will enter the Open-label Extension Transition.

**Titration from 0–25 mg/kg/day** will begin at 5 mg/kg/day and will be increased in increments of 5 mg/kg/day every two days (patients will remain on each dose level for two days before they progress on to the next dose).

**Titration from 25–50 mg/kg/day** will continue at smaller increments of 2.5 mg/kg/day every two days.

IMP will be taken twice daily (morning and evening).

**Open-label Extension Transition:**

This double-blind transition phase will take two weeks to complete. OLE IMP will be titrated up to 25 mg/kg/day whilst blinded IMP is simultaneously tapered down to zero. All patients will complete the transition and enter the OLE taking 25 mg/kg/day GWP42003-P:

- Patients from the placebo group will titrate up to 25 mg/kg/day.
- Patients from the 25 mg/kg/day group will continue to take 25 mg/kg/day.
- Patients from the 50 mg/kg/day will taper down (10% per day for 5 days) to 25 mg/kg/day.

**Open-label Extension:**

Patients may titrate the IMP up to the target dose of 50 mg/kg/day. Patients will then remain at this dose until the ‘End of Treatment’ visit, with the option for doses to be increased or decreased if deemed necessary by the investigator, to a maximum of 50 mg/kg/day. Following the ‘End of Treatment’ visit or decision to withdraw, doses of the IMP will be tapered down (10% per day for 10 days) at home until the ‘End of Taper’ visit. IMP will be taken twice daily (morning and evening).

In the UK, enrollment of patients between the ages of 12 and
23 months will only commence once 15 patients over the age of 23 months have been dosed for a minimum of 4 weeks and no new safety issues have been observed.

Control Group

The control group will receive equal volumes of matching placebo.

Procedures

**Screening Assessments (Blinded Phase) Will Include:**

- Informed consent/assent
- Demographic assessment
- Full medical history (including seizure information since diagnosis and all prior AEDs taken)
- Concomitant medication review (including AEDs)
- Physical examination
- Vital signs assessment
- Postural blood pressure
- Clinical laboratory samples (blood and urine) will be taken for:
  - Hematology
  - Biochemistry
  - Urinalysis
  - Urine/serum THC screen
  - Urine/serum pregnancy tests (if appropriate)
  - *TSC1* and *TSC2* mutation status (if not known previously) if the patient/parent(s)/legal representative provide consent
- ECG
- Suicidality

Patients who satisfy all inclusion and none of the exclusion criteria will be assigned a unique patient number.

After the screening visit, investigators will submit the patient’s documented history of seizures directly to the Epilepsy Study Consortium (ESC) for verification of seizure types. The ESC may ask the investigator for additional information to assist in their decision. The ESC will provide written confirmation directly to the investigator.

**Baseline Visit:**

Following written confirmation of seizure classification from the ESC patients will attend a Baseline Visit before beginning the 28-day baseline observation period. The patient’s attendance is preferred, but if this is not possible the primary caregiver can attend alone provided that this caregiver (not the patient) will be responsible for seizure identification, IVRS use, and paper diary
The following assessments will be completed:

- Concomitant medication review (including AEDs)
- AE review
- Epilepsy-related hospitalizations review
- IVRS training
- Patient diary issue and training

The investigator will review and train the patient or their caregiver to identify the patient’s expected seizure types. Patients or their caregivers will make a daily IVRS call to record daily seizure information including all seizures and episodes of status epilepticus. Patients or their caregivers will be given a paper diary to record usage of IMP, rescue medication, concomitant AEDs, and AEs and will be instructed on how to do so.

**Randomization Visit Assessments:**

Following the 28-day baseline observation period the investigator will assess the patient’s daily number of seizures from IVRS data. Patients who continue to satisfy all inclusion and none of the exclusion criteria will be randomized. Patients will then receive sufficient IMP, as assigned by IVRS, every 14 to 28 days for the 16-week treatment period. Before taking their first dose of IMP in clinic the following assessments will be completed:

- Concomitant medication review (including AEDs)
- AE review
- Epilepsy-related hospitalizations review
- Physical examination
- Tanner Staging (where appropriate)
- Details of menstruation (for females)
- ECG (including pre-dose baseline and +4 hours [±30 minutes] after first dose)
- Vital signs
- Postural blood pressure
- Suicidality
- SGIC-SD or CGIC-SD
- Vineland-II
- Wechsler Tests
- CBCL or ABCL
- SCQ
- QOLCE or QOLIE-31-P
- CGIC or SGIC
- PGIC
Clinical laboratory samples (blood and urine) will be taken for:
- Hematology
- Biochemistry
- Urinalysis
- Urine/serum pregnancy tests (if appropriate)
- Serum IGF-1
- PK (patients > 20 kg only)
- AED concentrations

- Review of IVRS and patient diary
- IMP dispensing

**Post Randomization Assessments:**
Clinic visits will occur on Day 15, Day 29, Day 43, Day 57, Day 85 and Day 113 with a telephone visit occurring on Day 71. Additional safety telephone calls will be completed every two days during titration and one week after the end of titration. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or the Monday after the weekend instead.
The following assessments will be completed at every clinic visit except where indicated:
- Concomitant medication review (including AEDs)
- AE review
- Epilepsy-related hospitalizations review
- Physical examination
- Tanner Staging, where appropriate (Visit 10)
- Details of menstruation (for females) (Visit 10)
- ECG
- Vital signs
- Postural BP (Visit 5)
- Suicidality
- SGIC-SD or CGIC-SD (Visit 10)
- Vineland-II (Visit 10)
- Wechsler Tests (Visit 10)
- CBCL or ABCL (Visit 10)
- SCQ (Visit 10)
- QOLCE or QOLIE-31-P (Visit 10)
- CGIC or SGIC (Visit 10)
- PGIC (Visit 10)
- Clinical laboratory samples (blood and urine) will be taken
for:
- Hematology
- Biochemistry
- Urinalysis
- Urine/serum pregnancy tests (Visits 5, 7, 9 and 10, if appropriate)
- Serum IGF-1 (Visit 10)
- PK (Visit 10; patients > 20 kg only)
- AED concentrations (Visits 5, 7, 9 and 10)
- Review of patient diary
- IMP dispensing, collection and compliance review

PK:
Blood sample collection for PK analysis of CBD and its major metabolites will be taken at Visits 3 and 10 for patients weighing more than 20 kg. Where appropriate, blood samples will be taken as follows:
- One sample pre-dose (i.e., prior to administration of IMP).
- One sample between 2 and 3 hours post-dose.
- One sample between 4 and 6 hours post-dose.
- One sample between 8 and 10 hours post-dose (patients 18 years and above only).
Blood samples will be collected for analysis of plasma concentrations of concomitant AEDs (if possible) ideally at the following time points:
- Visit 3 - Pre-IMP-dose.
- Visit 5 - Pre-IMP-dose.
- Visit 7 - Pre-IMP-dose.
- Visit 9 - Pre-IMP-dose.
- Visit 10 - Pre-IMP-dose.
Additional blood samples may be taken for AED monitoring if there is a suspicion of changes in AED levels, with the aim to keep the AED plasma levels within the patient’s therapeutic level.

Open-label Extension Transition and Open-label Extension:
Following completion of the blinded phase of the study, patients will enter a 2-week blinded transition followed by a 3-week titration. Safety telephone calls will be conducted every two days during this 5-week period and one week after the end of titration. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead. OLE visits will occur on Day 15, Day 36, Day 92 and then every 13 weeks up to 1 year. Additional IMP Re-supply Visits will be
scheduled between Assessment Visits.

The following assessments will be completed at all visits during the OLE, except where indicated (full listing by visit included in Section 9.1.2):

- Concomitant medication review (including AEDs)
- AE review
- Review of patient diary
- IMP dispensing, collection and compliance review
- Physical examination
- Tanner Staging, where appropriate (Visit B10)
- ECG
- Vital signs
- Suicidality
- SGIC-SD or CGIC-SD (Visits B4, B6, B8 and B10)
- Vineland-II (Visits B6 and B10)
- Wechsler Tests (Visits B6 and B10)
- CBCL or ABCL (Visits B6 and B10)
- SCQ (Visits B6 and B10)
- QOLCE or QOLIE-31-P (Visits B6 and B10)
- CGIC or SGIC (Visits B6 and B10)
- PGIC (Visits B6 and B10)
- Clinical laboratory samples (blood and urine) will be taken for:
  - Hematology
  - Biochemistry
  - Urinalysis
  - Urine/serum pregnancy tests (Visits B4, B6, B8 and B10, if appropriate)
  - Serum IGF-1 (Visits B6 and B10)
  - AED concentrations

Additional re-supply visits are scheduled during the OLE and will include a review of concomitant medications (including AEDs), AEs, patient diary and IMP dispensing, collection and compliance review.

**Monitoring of Drug Abuse Liability (for Patients 12 Years of Age and Older):**

During the routine collection of AEs in this study, if AEs are reported which can illuminate an abuse potential signal, then the investigator or study coordinator is required to complete an
additional Supplemental Adverse Event Form and Site Classification Form (investigator only) following further discussion of the event(s) with the patient/caregiver.

The second trigger that will require the investigator or study coordinator to discuss abuse potential signals with the patient/caregiver is drug accountability issues regarding overuse of the IMP or missing bottles.

Irrespective of the above, all patients/caregivers will be interviewed at their final dosing visit of the blinded phase (Visit 10 or 11) and again at their final dosing visit of the OLE (Visit B10 or B11). A Study Medication Use and Behavior Survey will be completed by the investigator or study coordinator.

A formal Adjudication Committee will be appointed and assigned to this initiative to classify triggered cases. The Adjudication Committee will meet on a periodic basis to review and assess all of the information collected on triggered cases.

### Statistical Considerations

#### Blinded Phase:

Each of the primary and secondary endpoints will be described and compared between treatment groups, using appropriate statistical methods, over the 16-week, double-blind maintenance and titration period.

Statistical hypothesis testing will be performed on the primary endpoint and other endpoints as appropriate. Each endpoint, including the primary will have 2 comparisons against placebo (25 mg/kg/day GWP42003-P and 50 mg/kg/day GWP42003-P vs. placebo). Also, 3 key secondary endpoints have been defined.

The primary and key secondary endpoints will be tested with their Type I error controlled by use of a hierarchical gate-keeping procedure. One must reject the null hypothesis of an endpoint at the level of 0.05 (2-sided) to test the hypothesis of the subsequent endpoint in the sequence at the level of 0.05 (2-sided). If a null hypothesis is not rejected then testing will stop and all subsequent analyses will be declared not statistically significant.

The secondary endpoints will be tested hierarchically, starting with the key secondary endpoints followed by all other and exploratory secondary endpoints. No multiplicity adjustments will be made for all other secondary endpoints.

All other statistical tests will be two-tailed and carried out at the 5% level of significance.

All safety data will be summarized using appropriate statistical methods.

#### Open-label Extension:

All data collected during this study will be summarized across
time, using appropriate statistical methods. Where baseline data are available from the blinded phase, changes from baseline will also be presented.

Descriptive statistical methods will be used throughout. There will be no formal hypothesis testing.

| Sponsor     | GW Research Ltd  
|             | Sovereign House  
|             | Vision Park      
|             | Chivers Way      
|             | Histon           
|             | Cambridge CB24 9BZ 
|             | United Kingdom   |
Figure 1-1  Study Design and Treatment Schema: Blinded Phase

Visit 1  Day -35  7 days  
Visit 2  Day -28  28 days  
Visit 3a  Day 1  14 days  
Visit 4a  Day 15  14 days  
Visit 5a  Day 29  14 days  
Visit 6a  Day 32  14 days  
Visit 7  Day 57  28 days  
Visit 8  Day 85 ±3  28 days  
Visit 9  Day 85 ±3  14 days  
Visit 10  Day 113 ±3  14 days  
Visit 11*  Up to Day 123 ±3  14 days  
Visit 12**  Day 151  14 days  

**S**  E  C  R  E  E  N  I  N  G  B  A  S  E  L  I  N  E  R  A  N  D  O  M  I  Z  A  T  I  O  N  

25 mg/kg/day GWP42003-P (n = 70)

50 mg/kg/day GWP42003-P (n = 70)

Placebo (n = 70 [35 × 25 mg/kg/day + 35 × 50 mg/kg/day dosing volumes])

Visit 1  Day -35 ±7  
Visit 2  Day -28 +3  
Visit 3a  Day 15 ±3  
Visit 4a  Day 29 ±3  
Visit 5a  Day 43 ±3  
Visit 6a  Day 57 ±3  
Visit 7  Day 71 ±3  
Visit 8  Day 85 ±3 (Telephone)  
Visit 9  Day 113 ±3  
Visit 10  Up to Day 123 ±3  
Visit 11*  Day 151 ±3  

* For patients not entering the open-label extension at Visit 10.
** For patients not entering the open-label extension; can be conducted by telephone.
# Safety telephone calls must be completed every two days during titration and one week after the end of titration. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead.

**Figure 1-2 Study Design and Treatment Schema: Open-label Extension**

- **Visit B1**
  - Day 1
  - (±3 days)

- **Visit B2**
  - Day 15
  - (±3 days)

- **Visit B3**
  - Day 36
  - (±3 days)

- **Visit B4**
  - Day 92
  - (±3 days)

- **Visit B6**
  - Day 183
  - (±7 days)

- **Visit B8**
  - Day 274
  - (±7 days)

- **End of Treatment Visit**
  - Day 365

- **Follow-up Visit**
  - (+3 days)

- **End of Taper Period**
  - Day 141

- **End of Taper Period**
  - Day 232

- **End of Taper Period**
  - Day 323

* To avoid double-dosing of IMP at Visit 1, patients will be instructed to begin titration of IMP the following day, which will be regarded as Day 1. As such, Visit 1 will occur on Day −1 with no clinic visit on Day 1.

†† Following the ‘End of Taper Period’ visit, a safety telephone call must be made two weeks later to collect seizure information, and to assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.

** Can be conducted by telephone.
ΔB5, B7 and B9 – Re-supply visits.

†† Safety telephone calls must be completed every two days during blinded transition, titration and one week after the end of titration. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead.
Table of Contents

Title Page ................................................................................................... 1

1 PROTOCOL SYNOPSIS ................................................................ 3

Table of Contents .................................................................................... 25

List of Appendices .................................................................................. 31

List of In-text Tables .............................................................................. 32

List of In-text Figures ............................................................................. 33

List of Abbreviations .............................................................................. 34

Definition of Terms ................................................................................. 37

2 OBJECTIVES ................................................................................ 38

2.1 Primary ........................................................................................................ 38

2.2 Secondary .................................................................................................... 38

2.3 Exploratory .................................................................................................. 39

3 BACKGROUND AND RATIONALE ......................................... 40

3.1 Disease ......................................................................................................... 40

3.2 GWP42003-P Background .......................................................................... 43

3.3 Rationale ...................................................................................................... 44

3.3.1 Selection of Study Dose ............................................................................ 44

3.4 Clinical Hypothesis ..................................................................................... 46

4 EXPERIMENTAL PLAN ............................................................. 47

4.1 Study Design ............................................................................................... 47

4.1.1 Primary Endpoint ...................................................................................... 48

4.1.2 Secondary Endpoint(s) .............................................................................. 49

4.2 Number of Centers ...................................................................................... 53

4.3 Number of Patients ...................................................................................... 53

5 INVESTIGATIONAL MEDICINAL PRODUCT ..................... 54

5.1 GWP42003-P Solution ................................................................................ 54

5.2 Placebo Solution .......................................................................................... 54

5.3 Packaging, Storage and Drug Accountability ............................................. 54

5.3.1 Packaging and Labeling .......................................................................... 54

5.3.2 Storage ...................................................................................................... 55
5.3.3 Supply and Return of Investigational Medicinal Product .......................... 56
5.3.4 Investigational Medicinal Product Accountability ................................. 56

6 PATIENT ELIGIBILITY .................................................................................. 58
6.1 Inclusion Criteria ....................................................................................... 58
6.2 Exclusion Criteria ....................................................................................... 59

7 PATIENT ENROLLMENT .............................................................................. 62
7.1 Treatment Assignment .............................................................................. 62
7.2 Randomization ......................................................................................... 62

8 TREATMENT PROCEDURES ..................................................................... 63
8.1 Investigational Medicinal Product Dosage, Administration and Schedule ........................................................................................................... 63
8.1.1 Dose Administration ............................................................................ 63
8.1.2 Dose Escalation and Dose Adjustments ............................................... 63
8.2 Concomitant Therapy ............................................................................... 66
8.3 Prohibited Therapy During Study Period ............................................... 67
8.4 Compliance in Investigational Medicinal Product Administration ............ 67
8.5 Access to Blinded Treatment Assignment (Blinded Phase and OLE Transition Only) ..................................................................................................... 68

9 STUDY PROCEDURES .................................................................................. 69
9.1 Study Procedures by Visit ......................................................................... 69
9.1.1 Blinded Phase ....................................................................................... 69
9.1.1.1 Visit 1 (Day −35, Screening) .......................................................... 69
9.1.1.2 Visit 2 (Day −28, Baseline) ............................................................. 70
9.1.1.3 Visit 3 (Day 1, Randomization) ...................................................... 70
9.1.1.4 Visit 4 (Day 15) ............................................................................ 72
9.1.1.5 Visit 5 (Day 29) ............................................................................ 72
9.1.1.6 Visit 6 (Day 43) ............................................................................ 73
9.1.1.7 Visit 7 (Day 57) ............................................................................ 73
9.1.1.8 Visit 8 (Day 71) ............................................................................ 74
9.1.1.9 Visit 9 (Day 85) ............................................................................ 74
9.1.1.10 Visit 10 (Day 113, End of Treatment/Withdrawal Visit) .............. 75
9.1.1.11 Visit 11 (Day 123, End of Taper) .................................................. 76
9.1.1.12  Visit 12 (Day 151, Safety Follow-up) ................................................... 77
9.1.2  Open-label Extension ........................................................................... 77
9.1.2.1  Visit B1 (Day 1) ............................................................................ 77
9.1.2.2  Visit B2 (Day 15) ........................................................................... 79
9.1.2.3  Visit B3 (Day 36) ........................................................................... 79
9.1.2.4  Visit B4 (Day 92) .......................................................................... 80
9.1.2.5  Visit B5 (Day 141, Re-supply Visit) ................................................. 81
9.1.2.6  Visit B6 (Day 183) .......................................................................... 81
9.1.2.7  Visit B7 (Day 232, Re-supply Visit) ................................................. 82
9.1.2.8  Visit B8 (Day 274) .......................................................................... 82
9.1.2.9  Visit B9 (Day 323, Re-supply Visit) .................................................. 83
9.1.2.10 Visit B10 (Day 365, End of Treatment/Withdrawal Visit) ............ 84
9.1.2.11 Visit B11 (Day 375, End of Taper Period Visit) ........................... 85
9.1.2.12 B12 (Day 389, Post-taper Safety Telephone Call) .................................. 85
9.1.2.13 Follow-up Visit .............................................................................. 86
9.1.2.14 Safety Telephone Calls ................................................................... 86
9.2  Study Procedure Listing ........................................................................ 86
9.2.1  Informed Consent/Assent ................................................................... 86
9.2.2  Contraception Requirements .............................................................. 87
9.2.3  Demographics .................................................................................. 88
9.2.4  Medical History ................................................................................ 88
9.2.5  Concomitant Medication ................................................................... 88
9.2.6  Physical Examination ....................................................................... 88
9.2.7  Vital Signs and Blood Pressure ............................................................ 88
9.2.8  12-Lead Electrocardiogram ................................................................. 89
9.2.9  Clinical Laboratory Sampling ............................................................... 89
9.2.9.1 Pharmacokinetic Blood Sampling .................................................... 91
9.2.9.2 Determination of Plasma Concentrations of Concomitant Antiepileptic Drugs ...................................................................................... 92
9.2.9.3 Determination of Mutation Status of the TSC1 and TSC2 Genes ....... 92
9.2.10 Interactive Voice Response System .................................................... 92
9.2.11 Patient Diary .................................................................................. 93
9.2.12 Questionnaires and Assessments Completed at Scheduled Visits .... 94
9.2.12.1 Subject/Caregiver Global Impression of Change .................................. 94
9.2.12.2 Physician Global Impression of Change ............................................... 95
9.2.12.3 Subject/Caregiver Global Impression of Change in Seizure Duration .............................................................................................................. 95
9.2.12.4 Quality of Life in Childhood Epilepsy (18 Years of Age and Younger) or Quality of Life in Epilepsy (19 Years of Age and Older) ........................................................................................................ 96
9.2.12.6 Child/Adult Behavior Checklist ........................................................................ 96
9.2.12.7 Social Communication Questionnaire .................................................. 96
9.2.12.8 Suicidality/ Children’s/Columbia-Suicide Severity Rating Scale (Six Years of Age and Older)........................................................................ 97
9.2.12.9 Wechsler Tests ...................................................................................... 97
9.2.13 Menstruation ............................................................................................. 98
9.2.14 Tanner Staging .......................................................................................... 98
9.2.15 Investigational Medicinal Product Accountability ....................................... 98
9.2.16 Adverse Events ......................................................................................... 98
9.2.17 Monitoring of Abuse Liability (for Patients 12 Years of Age and Older) .............................................................................................................. 99
9.2.17.1 Monitoring of Adverse Events .................................................................. 99
9.2.17.1.1 List of ‘Triggering Adverse Events of Interest’ ................................ 99
9.2.17.1.2 Supplemental Adverse Event Form ................................................. 100
9.2.17.1.3 Monitoring Drug Accountability Discrepancies ................................ 100
9.2.17.1.4 List of ‘Triggering Drug Accountability Discrepancies’ ................ 101
9.2.17.1.5 Supplemental Drug Accountability Form ....................................... 101
9.2.17.2 Site Classification Form ...................................................................... 101
9.2.17.3 Study Medication Use and Behavior Survey ....................................... 102
9.2.17.4 Adjudication Committee: Assessment of Abuse Potential of GWP42003-P ...................................................................................... 102

10 WITHDRAWAL ......................................................................................... 105

11 URGENT SAFETY MEASURES ................................................................ 107

12 ADVERSE EVENT REPORTING ............................................................... 108
12.1 Definitions .................................................................................................... 108
12.1.1 Adverse Event ........................................................................................ 108
12.1.2 Investigator ................................................................. 108
12.2 Serious Adverse Events .................................................. 108
12.3 Reporting Procedures for Serious Adverse Events .......... 109
12.4 Pregnancy ................................................................................ 110
12.5 Causality Assessment ............................................................ 110
12.6 Reporting Procedures for All Adverse Events ................. 111
12.7 Follow-up Procedures for Adverse Events ....................... 113
12.8 Potential Cases of Drug-induced Liver Injury .................. 113
12.9 Notification of Safety Information to Investigators, Regulatory
    Authorities and Ethics Committees .......................................... 114

13 STATISTICAL CONSIDERATIONS ................................. 117
13.1 Sample Size, Power and Significance Levels .................... 117
13.2 Interim Analysis ................................................................. 117
13.3 Analysis Sets ........................................................................ 118
13.3.1 Protocol Deviations ........................................................... 118
13.4 General Considerations ......................................................... 119
13.5 Accountability and Background Characteristics ............... 119
13.5.1 Enrollment and Disposition .............................................. 119
13.5.2 Baseline and Demographic Characteristics .................. 119
13.5.3 Medical History ............................................................... 119
13.5.4 Concomitant Medication ................................................. 119
13.6 Endpoints and Statistical Methods ................................. 119
13.6.1 Evaluable Period ............................................................... 120
13.6.2 Primary Endpoint(s) ........................................................ 121
13.6.2.1 Sensitivity Analysis for the Primary Endpoint ............. 122
13.6.3 Secondary Endpoint(s) ...................................................... 124
13.6.4 Pharmacokinetics ............................................................ 127
13.6.5 Safety ................................................................................. 127
13.6.5.1 Treatment Compliance and Extent of Treatment Exposure ........... 127
13.6.5.2 Adverse Events ............................................................. 127
13.6.5.3 Clinical Laboratory Data .............................................. 128
13.6.5.4 Vital Signs, 12-Lead Electrocardiogram, Physical Examination
    and Other Safety Data ......................................................... 128
14 SAFETY MONITORING COMMITTEE ................................ 129

15 REGULATORY AND ETHICAL OBLIGATIONS ............ 130

15.1 Declaration of Helsinki ....................................................... 130
15.2 Informed Consent/Assent ..................................................... 130
15.3 Ethics Committee/Institutional Review Board ...................... 130
15.4 Pre-study Documentation Requirements ............................... 131
15.5 Patient Confidentiality ......................................................... 132

16 ADMINISTRATIVE AND LEGAL OBLIGATIONS .......... 133

16.1 Protocol Amendments and End of Study or Termination .......... 133
16.2 Study Documentation and Storage ........................................ 133
16.3 Study Monitoring and Data Collection ................................... 134
16.4 Electronic Data collected by Interactive Voice Response System .... 135
16.5 Quality Assurance ............................................................... 135
16.6 Compensation ................................................................. 136
16.7 Publication Policy ............................................................... 136
16.8 Intellectual Property Rights ................................................ 137
16.9 Confidential Information ..................................................... 137

17 REFERENCES ........................................................................... 138
List of Appendices

APPENDIX 1  SCHEDULE OF ASSESSMENTS........................................... 143
APPENDIX 2  TANNER STAGING.......................................................... 149
APPENDIX 3  STUDY PERSONNEL...................................................... 152
Appendix 3.1  Investigator Details .................................................... 152
Appendix 3.2  Sponsor Contact Details ............................................ 152
APPENDIX 4  IVRS CALLS FOLLOWING END OF TREATMENT/WITHDRAWAL ........................................... 153
List of In-text Tables

Table 5.1-1  Formulation of GWP42003-P Solution ....................................... 54
Table 5.2-1  Formulation of Placebo Solution ............................................. 54
Table 8.1.2-1 Dose Titration Regimen* .......................................................... 64
Table 8.1.2-2 Blinded Transition ................................................................... 65
Table 8.1.2-3 OLE Titration Schedule ........................................................... 65
Table 9.2.9-1 Biochemistry, Hematology, Urinalysis and THC Screen ........ 90
Table 13.6-1 Hierarchy for Analysis............................................................... 120
List of In-text Figures

Figure 1-1  Study Design and Treatment Schema: Blinded Phase .......... 22
Figure 1-2  Study Design and Treatment Schema: Open-label Extension .................................................................................. 23
Figure 9.2.17.4-1 Flow Diagram for Identifying and Evaluating Clinical Trial Adverse Event Data Through Systematic Categorization, Tabulation and Analysis which can Illuminate an Abuse Potential Signal (for Patients 12 Years of Age and Older) .................................................. 104
List of Abbreviations

ABCL  Adult Behavior Checklist
ACTH  Adrenocorticotropic hormone
AE    Adverse Event
AED   Antiepileptic Drug(s)
ALT   Alanine Aminotransferase
ANCOVA  Analysis of Covariance
AST   Aspartate Aminotransferase
CBCL  Child Behavior Checklist
CBD   Cannabidiol
CGIC  Caregiver Global Impression of Change
CGIC-SD Caregiver Global Impression of Change in Seizure Duration
CI    Confidence Interval
CIOMS Council for International Organizations of Medical Sciences
CRF   Case Report Form
CRO   Contract Research Organization
C-SSRS Columbia-Suicide Severity Rating Scale
DRF   Diagnostic Review Form for Epilepsy Study Consortium
EAP   Expanded Access IND Program
EC    Ethics Committee
ECG   12-Lead Electrocardiogram
EEG   Electroencephalogram
ESC   Epilepsy Study Consortium
EU    European Union
FDA   U.S. Food and Drug Administration
GABA $\gamma$-aminobutyric acid
GCP   Good Clinical Practice
GW    GW Research Ltd
IB    Investigator’s Brochure
ICF   Informed Consent Form
ICH   International Council for Harmonisation
IGF-1 Insulin-like growth factor-1
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug</td>
</tr>
<tr>
<td>INR</td>
<td>International Normalized Ratio</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention to treat</td>
</tr>
<tr>
<td>IVRS</td>
<td>Interactive Voice Response System</td>
</tr>
<tr>
<td>MAR</td>
<td>Missing at Random</td>
</tr>
<tr>
<td>MNAR</td>
<td>Missing Not at Random</td>
</tr>
<tr>
<td>mTOR</td>
<td>Mammalian target of rapamycin</td>
</tr>
<tr>
<td>MI</td>
<td>Multiple Imputation</td>
</tr>
<tr>
<td>OLE</td>
<td>Open-label Extension</td>
</tr>
<tr>
<td>PGIC</td>
<td>Physician Global Impression of Change</td>
</tr>
<tr>
<td>PI</td>
<td>Principal investigator</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>PP</td>
<td>Per protocol</td>
</tr>
<tr>
<td>PRN</td>
<td>Packaging Reference Number</td>
</tr>
<tr>
<td>PVD</td>
<td>Pharmacovigilance Department</td>
</tr>
<tr>
<td>QOLCE</td>
<td>Quality of Life in Childhood Epilepsy</td>
</tr>
<tr>
<td>QOLIE-31-P</td>
<td>Quality of Life in Epilepsy</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
</tr>
<tr>
<td>SCQ</td>
<td>Subject Communication Questionnaire</td>
</tr>
<tr>
<td>SGIC</td>
<td>Subject Global Impression of Change</td>
</tr>
<tr>
<td>SGIC-SD</td>
<td>Subject Global Impression of Change in Seizure Duration</td>
</tr>
<tr>
<td>SEGAs</td>
<td>Subependymal giant-cell astrocytomas</td>
</tr>
<tr>
<td>SENS</td>
<td>Subependymal nodules</td>
</tr>
<tr>
<td>SMC</td>
<td>Safety Monitoring Committee</td>
</tr>
<tr>
<td>SOC</td>
<td>System Organ Class</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>TAND</td>
<td>TSC-associated neuropsychiatric disorders</td>
</tr>
<tr>
<td>TBL</td>
<td>Total Bilirubin</td>
</tr>
<tr>
<td>THC</td>
<td>Δ⁹-Tetrahydrocannabinol</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>TSC</td>
<td>Tuberous sclerosis complex</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper Limit of Normal</td>
</tr>
<tr>
<td>VFDs</td>
<td>Visual field defects</td>
</tr>
<tr>
<td>VGB</td>
<td>Vigabatin</td>
</tr>
</tbody>
</table>
# Definition of Terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>The 28-day (+3 days) period from screening to randomization.</td>
</tr>
<tr>
<td>Day 1</td>
<td>The day a patient first receives investigational medicinal product in this study.</td>
</tr>
<tr>
<td>End of study</td>
<td>Last patient last visit or last contact, whichever occurs last.</td>
</tr>
<tr>
<td>Enrolled patient</td>
<td>Patient is considered enrolled in the study from the time of providing written informed consent.</td>
</tr>
<tr>
<td>IMP</td>
<td>Investigational Medicinal Product (Study Medication).</td>
</tr>
<tr>
<td>International Normalized Ratio</td>
<td>A calculation made to standardize prothrombin time.</td>
</tr>
<tr>
<td>Investigator</td>
<td>Study principal investigator or a formally delegated study physician.</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>Any seizure lasting 30 minutes or longer.</td>
</tr>
</tbody>
</table>
2 OBJECTIVES

2.1 Primary

Blinded Phase:
To evaluate the efficacy of GWP42003-P as add-on therapy in reducing the frequency of seizures when compared with placebo in patients with tuberous sclerosis complex (TSC).

Open-label Extension:
To evaluate via the adverse events (AE) profile the long term safety and tolerability of GWP42003-P as add-on therapy in children and adults with TSC who experience inadequately-controlled seizures.

2.2 Secondary

Blinded Phase:
- To evaluate the effect of GWP42003-P compared with placebo on antiepileptic measures.
- To evaluate the effect of GWP42003-P on growth and development (in patients less than 18 years old) compared with placebo.
- To evaluate the effects of GWP42003-P on quality of life compared with placebo.
- To evaluate the safety and tolerability of GWP42003-P compared with placebo.

Open-label Extension:
- To evaluate the long term effects of GWP42003-P, as add-on therapy, on antiepileptic measures.
- To evaluate the long term effect of GWP42003-P on growth and development (in patients less than 18 years old).
- To evaluate the long term effects of GWP42003-P on quality of life.
- To evaluate the long term safety and tolerability of GWP42003-P.
2.3 Exploratory

Blinded Phase:

- To evaluate the effect of GWP42003-P on TSC-associated neuropsychiatric disorders (TAND), including cognitive and behavioral function and autistic features compared with placebo.

- To determine the pharmacokinetics (PK) of CBD, and its major metabolites following single and multiple doses of GWP42003-P.

- To evaluate the effects of GWP42003-P on plasma concentrations of concomitant antiepileptic drugs (AEDs), if applicable.

Open-label Extension:

- To evaluate the long term effect of GWP42003-P on TAND, including cognitive and behavioral function and autistic features.
3 BACKGROUND AND RATIONALE

3.1 Disease

TSC is a genetic disorder characterized by the formation of nonmalignant tumors (tubers) in multiple organ systems. The clinical signs of TSC arise as a result of inactivating mutations in either of two tumor suppressor genes: TSC1 (located on chromosome 9q34.13) or TSC2 (located on chromosome 16p13.3). TSC1 encodes the 130-kDa protein TSC1 (hamartin) whilst TSC2 encodes the 200-kDa protein TSC2 (tuberin). TSC1 and TSC2 share no homology yet bind to each other with high affinity to form a functional heterodimer which suppresses the mammalian target of rapamycin (mTOR), a key regulator of cell growth and proliferation. Thus, inactivating mutations in TSC1 and TSC2 lead to inadequate suppression of mTOR signaling, resulting in abnormal cellular growth and tumorigenesis. TSC is transmitted in an autosomal dominant pattern of inheritance, although two-thirds of all cases are caused by de novo mutations. Mutations in TSC1 account for approximately 15% of all cases of TSC whilst approximately 70% of all cases are due to mutations in TSC2; ~15% of TSC patients have no identifiable mutation in the coding regions of either gene. Generally, TSC2 mutations result in a more severe disease phenotype compared with TSC1 mutations. The birth incidence of TSC is estimated to be 1 in 6,000 with approximately 50,000 individuals in the United States and 1 million individuals worldwide affected.

Tumors in TSC patients can occur in any major organ yet develop primarily in the brain, eyes, heart, kidney, skin and lungs. The random location, number, size and distribution of tumors result in a great variety of clinical manifestations, yet most patients exhibit dermatological, renal and/or neurological abnormalities, which appear at distinct developmental points. Dermatological abnormalities generally first appear in infancy or early childhood and include hypomelanotic macules, which are present in more than 90% of TSC patients, and facial angiofibromas, found in approximately 75% of TSC patients. In contrast, renal abnormalities tend not to develop until late childhood/adolescence and include angiomylipomas (found in 50–70% of TSC patients), renal cysts (found in 25–35% of TSC patients) and, very rarely, renal-cell carcinomas (found in 2–3% of TSC patients). Neurological abnormalities first appear during embryogenesis and include cerebral cortical tubers and subependymal nodules (SENs), each of which are found in 80–90% of TSC...
patients, as well as subependymal giant-cell astrocytomas (SEGAs), which are presumed to derive from SENs and are found in 5–15% of TSC patients\textsuperscript{19}. Whereas SENs and SEGAs are usually asymptomatic, the presence of cortical tubers is widely believed to underlie the neurologic manifestations of TSC, which include epilepsy, cognitive disability and autism\textsuperscript{12,13,19}.

Epileptic seizures are the most common clinical manifestation of TSC, affecting more than 70% of patients\textsuperscript{9,20,21,22}. Seizure onset occurs within the first year of life in approximately two-thirds of TSC patients and occurs within the first 3 years of life in 80% of TSC patients\textsuperscript{13,20}. The onset of epilepsy in TSC commonly manifests as focal motor seizures, which in approximately one-third of TSC patients coexist with infantile spasms\textsuperscript{20}. Intercital electroencephalogram (EEG) recordings at onset typically show hypsarrhythmia, characterized by focal or multifocal spike discharges and irregular slow-wave activity\textsuperscript{23}. Virtually all TSC patients with infantile spasms and approximately half of all epileptic TSC patients without them develop multiple seizure types, including complex focal seizures (with or without secondary generalization), generalized tonic–clonic seizures, atonic seizures, and atypical absences\textsuperscript{20}. Although infantile spasms resolve with time, the frequency and severity of other seizures tend to increase throughout early childhood and nearly two-thirds of TSC patients develop medically intractable epilepsy, including Lennox–Gastaut syndrome\textsuperscript{20}. Cognitive impairment (intelligence/developmental quotient < 70) is observed in around 60% of all TSC patients with a history of seizures and in approximately three-quarters of all TSC patients with a history of refractory epilepsy\textsuperscript{20}. Early management of seizures is therefore important in preventing subsequent epileptic encephalopathy and in reducing the associated cognitive and neuropsychiatric consequences\textsuperscript{22,24}.

In both the European Union and the United States, the drug of first choice for the treatment of infantile spasms secondary to TSC is vigabatrin (VGB), which was approved by the U.S. Food and Drug Administration (FDA) in 2009 (as Sabril\textsuperscript{®}) to treat infantile spasms in children aged 1 month to 2 years\textsuperscript{25}. VGB is a structural analog of γ-aminobutyric acid (GABA; the major inhibitory neurotransmitter in the central nervous system) that irreversibly inhibits GABA-transaminase and thereby increases brain levels of GABA\textsuperscript{26}. The initial prospective clinical study compared VGB (100–150 mg/kg/day) with adrenocorticotropic hormone (ACTH; 10 IU/day) in 42 patients with infantile spasms, only 4 of whom were diagnosed with TSC (3
received VGB; 1 received ACTH)\(^{27}\). Although all 4 TSC patients became spasm-free after 20 days’ treatment (irrespective of which therapy was received), VGB was considered more effective than ACTH for the treatment of infantile spasms due to TSC\(^{27}\). In a separate randomized trial which compared VGB (150 mg/kg/day, \(n = 11\)) with the oral steroid hydrocortisone (15 mg/kg/day, \(n = 11\)) for the treatment of infantile spasms due to TSC, 100% of patients taking VGB were spasm-free after 1 month’s treatment compared with 45% taking hydrocortisone\(^{28}\). Furthermore, of the non-responders who received hydrocortisone, all became spasm-free on switching to VGB therapy\(^{28}\). A larger study compared 2 doses of VGB in treatment-naïve patients with infantile spasms\(^{29,30}\). Of the patients with TSC, 52% were spasm-free after 2 weeks’ treatment compared with 16% of patients with other etiologies\(^{29}\). Furthermore, 92% of TSC patients who began VGB therapy were spasm-free after 71 days’ treatment, although whether these patients received additional treatments during this time is unclear\(^{29}\). Following recruitment of more patients into the trial and use of intent-to-treat analysis, however, only 21% of TSC patients could be classed as primary responders after 2 weeks’ treatment compared with 9% of patients with other etiologies\(^{30}\). Although VGB is generally well tolerated, long term treatment with VGB is associated with irreversible peripheral visual field defects (VFDs), the risk of which increases with increasing dose and cumulative exposure\(^{26}\). The prevalence of VGB-associated VFDs in children with refractory complex focal seizures is approximately 15%\(^{26}\); however, a very recent study found that 60% of TSC patients who received VGB treatment for infantile spasms subsequently developed VFDs\(^{31}\). Furthermore, there is evidence that spasms may relapse and become refractory to VGB following discontinuation of treatment in children with focal cortical dysplasia/TSC\(^{32}\).

ACTH (corticotropin) is a long-established therapy for infantile spasms and was approved by the FDA in 2010 (as Acthar\(^{\text{®}}\) Gel) as monotherapy in infants and children younger than 2 years. Although a number randomized controlled trials have demonstrated efficacy for ACTH in the treatment of infantile spasms and resolution of hypsarrhythmia, many of these studies do not provide TSC-specific data\(^{33}\). Side effects are common with ACTH treatment and long term exposure is associated with serious adverse events (SAEs), including fulminant infections secondary to immunosuppression, hypertension, glucosuria and metabolic abnormalities\(^{25,34}\). Furthermore, there is evidence that ACTH may contribute to the enlargement of
cardiac rhabdomyoma in TSC patients\textsuperscript{35,36}. ACTH treatment is therefore generally short-term (~2 weeks followed by taper) and close monitoring is required in TSC patients with cardiac rhabdomyoma. Relapse rates following effective ACTH treatment range from 15–60\%\textsuperscript{33}. Oral corticosteroids (prednisone/prednisolone) have also been used to treat infantile spasms, although randomized controlled trials demonstrate that even at very high doses only ~30–60\% of patients achieve freedom from spasms\textsuperscript{37,38,39,40}.

The mTOR inhibitor everolimus (the 40-O-[2-hydroxyethyl] derivative of sirolimus/rapamycin) has demonstrated efficacy in reducing seizure frequency in TSC patients with SEGA\textsuperscript{41}. In an open-label study of add-on everolimus (3 mg/m\textsuperscript{2}/day; \(n = 16\)), 56\% of patients had a clinically-relevant reduction in total seizure frequency at 6 months\textsuperscript{42}. In a randomized controlled trial comparing everolimus (4.5 mg/m\textsuperscript{2}/day; \(n = 78\)) with placebo (\(n = 39\)), analysis of change in seizure frequency was inconclusive because most patients had no seizures at baseline or at 24 weeks’ follow-up\textsuperscript{43}. As both studies demonstrated significant reductions in SEGA volume, the FDA approved everolimus in 2010 (as Afinitor\textsuperscript{R}) and in 2012 (as Afinitor Disperz\textsuperscript{TM}) for the treatment of TSC patients with SEGA who are not eligible for curative surgical resection. In addition to resective surgery, other non-pharmacological treatments of TSC-associated epilepsy include vagus nerve stimulation and the introduction of a ketogenic diet\textsuperscript{22}.

### 3.2 GWP42003-P Background

The investigational medicinal product (IMP), GWP42003-P, is formulated from extracts prepared from \textit{Cannabis sativa} L. plants that have a defined chemical profile and contain consistent levels of CBD as the principal phytocannabinoid. Extracts from these plants are processed to yield purified (\(\geq 98\%\)) CBD that typically contains less than 0.15\% (w/w) THC (for oral formulations). The purified CBD is subsequently dissolved in excipients with added sweetener and flavoring.

The pharmacological effects of phytocannabinoids are thought to be mediated primarily via their interaction with the endocannabinoid system, which consists of cannabinoid receptors, endogenous ligands (endocannabinoids) and enzymes for endocannabinoid synthesis and degradation. To date, 2 G-protein-coupled receptors for cannabinoids have been identified, designated CB\textsubscript{1} receptor and CB\textsubscript{2} receptor. CBD does not bind to either of these receptors with any great affinity but does
modulate the metabolizing enzymes of the endocannabinoid system. CBD also affects conduction of ion channels and acts on other G-protein-coupled receptors such as the transient receptor potential channel TRPV1 and the orphan receptor GPR55. Importantly, CBD lacks the psychoactivity associated with THC. Further to this, CBD has demonstrated anticonvulsant, antipsychotic, anxiolytic, neuroprotective, antioxidant and anti-inflammatory activity. Very little data concerning AEs of CBD in humans currently exist; however, in the small number of placebo-controlled trials published to date investigating the anticonvulsant effects of CBD, few side effects have been reported after 4–12 months of 200–300 mg/day CBD.

3.3 Rationale

The pharmacological therapies currently available for TSC-associated epilepsy often produce serious adverse effects, and a significant proportion of patients (37–63%) become resistant to treatment. Consequently, there is a clear need for new, efficacious pharmaceutical treatments for refractory epilepsy. Given the limitations of current synthetic AEDs, it has been suggested that CBD should be tested for anticonvulsive efficacy in randomized controlled clinical trials, especially in infantile epileptic syndromes. Although there are no published reports to date investigating the efficacy of CBD for seizures in TSC patients, a recent parent survey has reported that 84% of children with treatment-resistant epilepsy experienced a reduction in seizures whilst taking CBD-enriched cannabis, with over half of those reporting > 80% reduction in seizure frequency. The CBD-enriched cannabis was behaviorally well tolerated and children often experienced improved sleep, increased alertness, and better mood.

3.3.1 Selection of Study Dose

Doses up to 800 mg CBD per day for up to 8 weeks have been well tolerated in adults in the GW Research Ltd (GW) clinical study GWMD09112, which — assuming an average weight of 70 kg — equates to 11.4 mg/kg. In the literature, doses of CBD have been given up to 1500 mg CBD per day for 4 weeks in adults, which, in a 70 kg human, equates to a daily dose of 21.4 mg/kg CBD.

At the time of dose selection, GWP42003-P was being used by physicians for treatment of patients with intractable epilepsy resulting from a variety of etiologies in a number of Individual and Intermediate Expanded Access Investigational New Drug (IND) studies. In the ongoing Individual Expanded Access IND studies, the initial
dosing had been cautious (100 mg [morning] + 150 mg [afternoon/evening]), progressively increasing to 400 mg/day CBD; doses up to 22 mg/kg/day had been well tolerated in an individual pediatric patient. The sponsor reviews all safety information on an ongoing basis from the patients in the Individual Expanded Access IND studies and is not aware of any safety issues arising from the dosing used to date.

In the Expanded Access IND program (EAP), clinical dosing is determined on a case-by-case basis, balancing seizure control with tolerability, and shows that patients had tolerated doses up to 50 mg/kg/day. In a data review of the EAP, the median dose was 25 mg/kg/day among 230 patients treated for at least 12 weeks (EAP; data cut Sep 2015).

The first patient was dosed on 22 Jan 2014 and at the Sep 2015 data cut 350 patients with severe treatment-resistant epilepsies in the EAP (predominantly children) had received CBD oral solution; the median duration of exposure was 202 days. The available safety data collected from these patients showed that the reported AEs were usually mild or moderate in severity and resolved without treatment. There had been few withdrawals due to AEs. The median dose of CBD oral solution was 25 mg/kg/day after 12 weeks of treatment. 24 patients achieved a dose > 30 mg/kg up to and including 40 mg/kg and 37 patients were dosed in the higher category > 40 mg/kg up to and including 50 mg/kg. The highest dose had been 51 mg/kg (1 patient).

Doses of 25 and 50 mg/kg/day have been chosen for the GWEP1521 study to cover the doses of CBD oral solution most likely to have an effect in controlling multiple seizure types in TSC. The two doses will also allow demonstration of a possible dose response in TSC. Dose escalation for each patient in this study is subject to the investigator’s assessment of safety and tolerability. If AEs become dose limiting, the investigator may consider temporarily or permanently reducing the dose for the remainder of the study. Dose limiting AEs have so far recovered/were resolving with dose adjustment or cessation.

The maximum dose patients can receive during the maintenance period of the blinded phase will be 50 mg/kg/day. During the open-label phase, the maximum dose patients can receive will be 50 mg/kg/day although all patients will initially titrate to 25 mg/kg/day. The maximum dose was based on data from the Intermediate EAP at the time of initiation of GWEP1521.

Please refer to the Investigator’s Brochure (IB)\textsuperscript{51} and Development Core Safety Information for the most current safety data.
3.4 Clinical Hypothesis

The primary clinical hypothesis is that there will be a difference between the GWP42003-P dose groups and placebo in their effect on focal seizure frequency.

This study will also evaluate the effect of GWP42003-P compared with placebo on further measures of antiepileptic efficacy (responder analysis, focal seizure score, number of focal seizure-free days, number of seizures by subtype, number of infantile/epileptic spasms, usage of rescue medication, number of episodes of status epilepticus, duration of seizure subtypes), cognitive and behavioral function, autistic features, and quality of life. These endpoints are among those recommended by the European Medicines Agency guideline on clinical investigation of medicinal products in the treatment of epileptic disorders\textsuperscript{50}.

The dose response relationship between two GWP42003-P Dose Levels (25 mg/kg/day and 50 mg/kg/day) and placebo will also be explored.
4 EXPERIMENTAL PLAN

4.1 Study Design

This multicenter study consists of a randomized, placebo-controlled, double-blind phase followed by an open-label extension (OLE) phase.

Blinded Phase:

The blinded phase of the study is a randomized, double-blind, parallel-group, 16-week comparison of two doses of GWP42003-P versus placebo. Patients will complete a 1-week screening period and a 4-week baseline period before they are randomized to receive 25 mg/kg/day GWP42003-P, 50 mg/kg/day GWP42003-P or equivalent volumes of placebo. Randomization will be stratified by age according to the following ranges: 1–6, 7–11, 12–17 years and 18+ years. Patients will begin a 4-week dose escalation period, titrating up to their assigned dose, before continuing on a stable dose of blinded IMP for 12 weeks.

Dose escalation for each patient is subject to the investigator’s assessment of safety and tolerability. If a dose becomes poorly tolerated, the investigator may consider temporarily or permanently reducing the dose for the remainder of the study.

Clinic visits will occur for screening (Day −35), baseline (Day −28), randomization (Day 1) and, on Days 15 and 29 during titration and on Days 43, 57, 71 (telephone) and 85 until the end of treatment (Day 113). Safety telephone calls will be completed every two days during titration, one week after the end of titration and, for patients not entering the OLE, weekly from Visit 10 to Visit 12 (refer to Section 9.1.2.14 for further details on safety telephone calls). If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead.

Patients will be required to perform daily interactive voice response system (IVRS) telephone calls to record seizure information. They will also complete a daily paper diary with information about their IMP and concomitant AED administration.

Following completion of the blinded phase, patients will be invited to continue to receive GWP42003-P in an OLE.

Those patients opting not to enter the OLE will complete a 10-day taper period (down-titrating 10% per day for 10 days).

Open-label Extension Transition:

In order to maintain consistent exposure to IMP and maintain the integrity of the blind, patients will enter a 2-week blinded transition to the OLE. OLE IMP will be
titrated up to 25 mg/kg/day whilst blinded IMP is simultaneously tapered down to zero. All patients will complete the transition and enter the OLE taking 25 mg/kg/day GWP42003-P:

- Patients from the placebo group will titrate up to 25 mg/kg/day GWP42003-P.
- Patients from the 25 mg/kg/day GWP42003-P group will continue to take 25 mg/kg/day GWP42003-P.
- Patients from the 50 mg/kg/day GWP42003-P group will taper down (10% per day) to 25 mg/kg/day GWP42003-P.

Safety telephone calls will be completed every two days throughout the OLE transition. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead.

**Open-label Extension:**

The OLE consists of a 3-week titration period followed by a maintenance period and a 10-day taper period. The initial OLE period will last for a maximum of 1 year.

Following titration according to the titration schedule, patients will continue with their optimal GWP42003-P dose. However, investigators may decrease the dose if a patient experiences intolerance, or increase the dose to a maximum of 50 mg/kg/day if required for better seizure control, until the optimal dose is found. Dose increases above 25 mg/kg/day are recommended to be done slowly, with maximum increments of 2.5 mg/kg/day every two days. Patients whose dose has been decreased can have their dose increased again provided there is adequate tolerance. Safety telephone calls will be completed every two days throughout the OLE titration and one week after the end of titration. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead. If seizure freedom is achieved with use of GWP42003-P during the study, the investigator should consider reducing the dose of concomitant AEDs after six months of seizure freedom.

**4.1.1 Primary Endpoint**

**Blinded Phase:**

The primary endpoint is the change in number of TSC-associated seizures* during the treatment period (maintenance and titration) compared to baseline in patients taking GWP42003-P compared with placebo.
*Primary endpoint TSC-associated seizures include: focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures (tonic–clonic, tonic, clonic or atonic) that are countable.

Open-label Extension:
The safety of GWP42003-P will be evaluated by assessing the incidence, type and severity of AEs.

4.1.2 Secondary Endpoint(s)

Blinded Phase:
The following endpoints will be compared between treatment groups over the 16-week, double-blind treatment period (all changes relative to baseline):

Key:
- Number of patients considered treatment responders defined as those with a $\geq 50\%$ reduction in TSC-associated seizure* frequency.
- Change in Caregiver Global Impression of Change (CGIC) or Subject Global Impression of Change (SGIC) score.
- Change in total seizures.

Other:
Antiepileptic Efficacy Measures:
- Number of patients considered treatment responders defined as those with a $\geq 25\%, \geq 50\%, \geq 75\%$ or 100% reduction in TSC-associated seizure* frequency.
- Number of patients experiencing a $> 25\%$ worsening, $-25$ to $+25\%$ no change, 25–50% improvement, 50–75% improvement or $> 75\%$ improvement in TSC-associated seizure* frequency.
- Change in number of TSC-associated seizure*--free days.
- Change in number of ‘other’ seizures (absence, myoclonic, focal sensory and infantile/epileptic spasms).

Growth and Development (in patients less than 18 years old):
- Change in serum insulin-like growth factor-1 (IGF-1) levels.
- Change in Tanner Staging score (for patients aged 10–17 [inclusive]).

**Quality of Life:**

- Changes in the Quality of Life in Childhood Epilepsy (QOLCE; patients 2–18 years) or Quality of Life in Epilepsy (QOLIE-31-P; patients 19+ years) score.
- Change in Physician Global Impression of Change (PGIC) score.

**Safety and Tolerability:**

- AEs.
- Clinical laboratory parameters.
- 12-lead electrocardiogram (ECG).
- Physical examination parameters (including height and weight).
- Vital signs.
- Columbia-Suicide Severity Rating Scale (C-SSRS; 19+ years) or C-SSRS Children’s (6–18 years) score, where applicable.
- Number of inpatient hospitalizations due to epilepsy.
- Abuse liability.
- Effects on menstruation cycles (in females).

**Open-label Extension:**

The following endpoints will be assessed relative to the pre-randomization baseline of the blinded phase:

*TSC-associated seizures include: focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures (generalized tonic–clonic, tonic, clonic or atonic) that are countable.

**Key:**

- Percentage change in number of TSC-associated seizures * (average per 28 days).
- Number of patients considered treatment responders defined as those with a \( \geq 50\% \) reduction in TSC-associated seizure frequency*.

- Change in CGIC or SGIC score.

- Change in total seizures.

**Other:**

**Antiepileptic Efficacy Measures:**

- Number of patients considered treatment responders, defined as those with a \( \geq 25\% \), \( \geq 50\% \), \( \geq 75\% \) or \( 100\% \) reduction in TSC-associated seizure* frequency.

- Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in TSC-associated seizure* frequency.

- Change in number of TSC-associated seizure*-free days.

- Change in number of ‘other’ seizures (absence, myoclonic, focal sensory and infantile/epileptic spasms).

**Growth and Development (patients less than 18 years):**

- Change in serum IGF-1 levels.

- Change in Tanner Staging score (for patients aged 10–17 [inclusive]).

**Quality of Life:**

- Changes from baseline in the QOLCE (patients 2–18 years) or QOLIE-31-P (patients 19+ years) score.

- Change in PGIC score.

**Safety and Tolerability:**

- Clinical laboratory parameters.

- ECG.

- Physical examination parameters (including height and weight).

- Vital signs.

- C-SSRS (19+ years) or C-SSRS Children’s (6–18 years) score, where applicable.
Number of inpatient hospitalizations due to epilepsy.

Abuse liability.

Effects on menstruation cycles (in females).

Exploratory Endpoints (Double-blind and OLE)

Antiepileptic Efficacy Measures:

- Change in composite focal seizure score (frequency × severity).
- Change in number of seizures by subtype.
- Change in use of rescue medication.
- Change in the number of episodes of status epilepticus (convulsive and non-convulsive).
- Changes in duration of seizure subtypes as assessed by the Subject Global Impression of Change in Seizure Duration (SGIC-SD) or the Caregiver Global Impression of Change in Seizure Duration (CGIC-SD).

TAND:

Cognitive and Behavioral Function:

- Changes in Wechsler Scales (pre-school, primary, children, adult).
- Changes in Achenbach Child Behavior Checklist (CBCL) and Adult Behavior Checklist (ABCL).

Autistic Features:

- Change in Social Communication Questionnaire (SCQ) score.

PK (Double-blind only):

- The plasma concentrations will be summarized by time window for CBD and its major metabolites following single and multiple doses of GWP42003-P. Where data allows, the area under the plasma concentration curve (AUC0-t) from time zero to the last measurable time-point will be calculated.
- Plasma concentrations of concomitant AEDs before and after treatment with GWP42003-P, where available.
4.2 Number of Centers

Approximately 40 centers are expected to participate in this study.

4.3 Number of Patients

Blinded Phase:

A total of 210 patients will be targeted to be enrolled. The 210 patients will be randomly allocated to one of four treatment groups (GWP42003-P 25 mg/kg/day, GWP42003-P 50 mg/kg/day, placebo 25 mg/kg/day dose volume equivalent, or placebo 50 mg/kg/day dose volume equivalent) at a 2:2:1:1 ratio. The placebo groups will be pooled for the analyses of efficacy. If it is assumed that patients in the placebo group will experience a mean reduction in seizure frequency of 15% (from baseline), patients receiving GWP42003-P will experience at least a 50% reduction in seizures and a common standard deviation of 60%, then this sample size of 70 patients per group will be sufficient to detect a difference in response distributions with 90% power. This test is based on a two-sided non-parametric Mann-Whitney-Wilcoxon test for continuous response data with a 5% significance level.

Open-label Extension:

All patients who wish to continue on IMP following the blinded phase.

The sample size calculation is explained fully in Section 13.1.
5 INVESTIGATIONAL MEDICINAL PRODUCT

Please refer to the separate Pharmacy Manual for more detailed information on the IMP.

5.1 GWP42003-P Solution

GWP42003-P solution is presented as a clear, colorless to yellow solution containing 100 mg/mL CBD dissolved in the excipients sesame oil and anhydrous ethanol (10% v/v) with added sweetener (sucralose) and strawberry flavoring (Table 5.1-1).

<table>
<thead>
<tr>
<th>Material</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBD</td>
<td>100 mg/mL</td>
</tr>
<tr>
<td>Anhydrous ethanol</td>
<td>79 mg/mL</td>
</tr>
<tr>
<td>Sucralose</td>
<td>0.5 mg/mL</td>
</tr>
<tr>
<td>Strawberry flavoring</td>
<td>0.2 mg/mL</td>
</tr>
<tr>
<td>Sesame oil</td>
<td>make up to 1 mL</td>
</tr>
</tbody>
</table>

5.2 Placebo Solution

Placebo solution is presented as a clear, colorless to yellow oily solution containing the excipients sesame oil and anhydrous ethanol (10% v/v) with added sweetener (sucralose) and strawberry flavoring (Table 5.2-1).

<table>
<thead>
<tr>
<th>Material</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anhydrous ethanol</td>
<td>79 mg/mL</td>
</tr>
<tr>
<td>Sucralose</td>
<td>0.5 mg/mL</td>
</tr>
<tr>
<td>Strawberry flavoring</td>
<td>0.2 mg/mL</td>
</tr>
<tr>
<td>Sesame oil</td>
<td>make up to 1 mL</td>
</tr>
</tbody>
</table>

5.3 Packaging, Storage and Drug Accountability

5.3.1 Packaging and Labeling

The IMP will be manufactured, packaged, labeled and/or distributed by G-Pharm or delegated contractors. The IMP will be presented in 100 mL amber glass bottles with child-resistant caps and packed in cartons. Sufficient IMP will be dispensed at each relevant visit considering the dose group and weight of each patient. A unique identification number will be used to identify each box and the IMP it contains. The unique identification number together with the packaging reference number (PRN) will permit full traceability of manufacture, pack and label activities conducted at or on behalf of G-Pharm and the IMP information held on the IVRS. G-Pharm will
ensure that all IMP provided is fully labeled and packaged. Label text will include the following information, as a minimum:

- Sponsor’s name.
- Product identification (e.g., “GWP42003-P/placebo”).
- Dose and/or Potency.
- Expiry date.
- Storage conditions.
- Instruction: “For clinical trial use only”.
- Instruction: “Keep out of the sight and reach of children”.

In addition, any local country requirements in accordance with local Drug Law or Regulatory Requirement will be included in the final label text.

The IMP labels for the blinded phase and the open-label phase of the trial will have different colors, so these can be easily distinguished by the patients. Directions of use, name, address and the telephone number of the investigator (or main contact for information about the product or the clinical trial) will be provided separately to the patient. Patients will be instructed to retain and carry this information with them at all times.

5.3.2 Storage

The IMP must be stored upright at room temperature (< 30°C) and must not be refrigerated or frozen. It must also be kept away from heat and direct sunlight.

The IMP must be stored in compliance with the local regulations for a controlled drug (if applicable to country). The sponsor must approve storage location and facilities. Temperature records of the clinical site storage location must be maintained (recording a minimum of Monday–Friday, excluding public holidays) from date of receipt of first shipment until end of study dispensing period at each center. These records must contain at least the minimum and maximum daily temperatures and should be made available to the appropriate GW personnel for review throughout the study. Temperature records taken during transit of IMP to center must be checked on receipt.

Should storage conditions deviate from these specified requirements, the GW study monitor must be contacted immediately to confirm if the IMP remains suitable for
use. IMP should be placed under quarantine until written confirmation is received that IMP is suitable for use.

IMP will be transported to country depots and clinical sites in compliance with Good Distribution Practice guidelines.

5.3.3 Supply and Return of Investigational Medicinal Product

All IMP will be shipped to approved depot facilities and clinical sites with a Product Release Certificate that includes a physical description of the product for confirmation of identity on receipt.

Once a center has been activated via the IVRS at study initiation, IMP will be shipped to the identified responsible person, such as the pharmacist, at the investigator’s center, who will check the amount received (against the IVRS Shipment Request) and condition of the drug (i.e., integrity, physical appearance, temperature during transit). Details of IMP received will be recorded in the IMP accountability record (see Section 5.3.4). The center will acknowledge IMP receipt via the IVRS and will complete any receipt forms required. IMP will be dispensed and returned as detailed in Section 8.4 with further IMP shipments to be initiated by IVRS. As directed, all supplies, including unused, partially used, or empty containers, will be returned to G-Pharm/depot or destroyed at a G-Pharm-approved site if agreed in writing by the study monitor.

5.3.4 Investigational Medicinal Product Accountability

The investigator has overall responsibility for the accountability of all used and unused IMP. A drug accountability record for the IMPs must be kept current and should contain:

- Study Code.
- PRN, Treatment number, date of receipt and quantity of IMP received.
- Patient’s trial identification and/or Treatment number.
- Date and quantity of IMP dispensed.
- The initials of the dispensing/dosing party.
- Date and quantity of IMP returned to the investigator.
- IMP expiry dates.
IMP will be dispensed at Visits 3, 4, 5, 6, 7, 9 and 10 (patients not entering the OLE) during the blinded phase and Visits B1, B2, B3, B4, B5, B6, B7, B8 and B9. All patients will be asked to return all IMP (used and unused) to each subsequent visit. Any discrepancies will be discussed with the patient or their caregiver at the time of the visit and documented accordingly within the patient’s source documents.

The investigator must inform GW promptly of all missing or unaccountable IMP.

A record of returned IMP must be completed and included in the shipment of used and unused IMP to GW or the relevant Drug Distribution Depot. At the end of the study, a record/statement of reconciliation must be completed and provided to GW.

These inventories must be made available for inspection by an authorized GW representative and local officials or regulatory agency inspectors.

Please refer to the separate Pharmacy Manual for more detailed information on the IMP.
6 PATIENT ELIGIBILITY

Investigators are responsible for confirming patient eligibility and will be required to maintain a log that includes limited information about all screened patients (initials, age, sex; as allowed per local regulations) and outcome of screening. After the screening visit, investigators will submit the patient’s documented history of seizures directly to the Epilepsy Study Consortium (ESC) for verification of seizure types. The ESC may ask the investigator for additional information to assist in their decision. The decision will be made within 14 days of receipt of all required information and the ESC will provide written confirmation directly to the investigator.

6.1 Inclusion Criteria

For inclusion in the study, patients must fulfil ALL of the following criteria:

6.1.1 Patient is male or female aged between one and 65 years inclusive.

6.1.2 Patient and/or parent(s)/legal representative is willing and able to give informed consent/assent for participation in the study (see Section 15.2).

6.1.3 Patient and their caregiver are willing and able (in the investigator’s opinion) to comply with all study requirements (including accurate diary and IVRS completion).

6.1.4 Well-documented clinical history of epilepsy, which is not completely controlled by their current AEDs.

6.1.5 Clinical diagnosis of TSC according to the criteria agreed by the 2012 International Tuberous Sclerosis Complex Consensus Conference19.

6.1.6 Taking one or more AEDs at a dose which has been stable for at least four weeks prior to screening.

6.1.7 All medications or interventions for epilepsy (including ketogenic diet and any neurostimulation devices for epilepsy) must have been stable for one month prior to screening and the patient is willing to maintain a stable regimen throughout the study.

6.1.8 Patient is willing to keep any factors expected to affect seizures stable (such as the level of alcohol consumption and smoking).

6.1.9 Patient and/or parent(s)/legal representative is willing to allow the responsible authorities to be notified of participation in the study, if mandated by local law.
6.1.10 Patient and/or parent(s)/legal representative is willing to allow his or her primary care practitioner and consultant (if they have one) to be notified of participation in the study, if mandated by local law.

At the end of the baseline period, patients must also meet the following criteria:

6.1.11 Experienced at least eight seizures during the first 28 days of the baseline period, with at least one seizure occurring in at least three of the four weeks (seizures include: focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures ([tonic–clonic, tonic, clonic or atonic] that are countable).

6.1.12 Completed at least 90% of calls to IVRS during the first 28 days of the baseline period (a minimum of 25 completed calls).

6.2  Exclusion Criteria

The patient may not enter the study if ANY of the following apply:

6.2.1 Patient has a history of pseudo-seizures.

6.2.2 Patient has clinically significant unstable medical conditions other than epilepsy.

6.2.3 Patient has an illness in the four weeks prior to screening or randomization, other than epilepsy, which in the opinion of the investigator could affect seizure frequency.

6.2.4 Patient has undergone general anesthetic in the four weeks prior to screening or randomization.

6.2.5 Patient has undergone surgery for epilepsy in the six months prior to screening.

6.2.6 Patient is being considered for epilepsy surgery or any procedure involving general anesthesia during the blinded phase of the study.

6.2.7 Patient has been taking felbamate for less than one year prior to screening.

6.2.8 Patient is taking an oral mTOR inhibitor.

6.2.9 Patient has, in the investigator’s opinion, clinically significantly abnormal laboratory values.
6.2.10 Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP, such as sesame oil.

6.2.11 Any history of suicidal behavior or any suicidal ideation of type 4 or 5 on the C-SSRS in the last month or at screening.

6.2.12 Patient is currently using or has in the past used recreational or medicinal cannabis, or cannabinoid-based medications, within the three months prior to screening and is unwilling to abstain for the duration for the study.

6.2.13 Patient has tumor growth which, in the opinion of the investigator, could affect the primary endpoint.

6.2.14 In the opinion of the investigator the patient has clinically significant abnormalities in the ECG measured at screening or randomization or any concurrent cardiovascular conditions, which will interfere with the ability to read their ECGs.

6.2.15 Patient has significantly impaired hepatic function at the screening visit (Visit 1) or the randomization visit (Visit 3), defined as any of the following:

i) Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 × upper limit of normal (ULN).

ii) TBL* [serum total bilirubin] ≥ 2 × ULN or international normalized ratio [INR] > 1.5 (*TBL ≥ 2 × ULN exclusion will not apply for patients diagnosed with Gilbert’s disease).

iii) Serum ALT or AST ≥ 3 × ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

This criterion can only be confirmed once the laboratory results are available.

6.2.16 Patient is female and of child bearing potential, or is male whose partner is of child bearing potential, unless willing to ensure that they or their partner use a highly effective method of birth control (e.g., hormonal contraceptives, intrauterine devices/hormone-releasing systems, bilateral tubal occlusion, vasectomized partner, sexual abstinence) during the study and for three months thereafter.

6.2.17 Female patient who is pregnant (positive pregnancy test), lactating or planning pregnancy during the course of the study and for three months thereafter.

6.2.18 Patient has received an IMP less than 12 weeks prior to the screening visit.
6.2.19 Patient has any other significant disease or disorder which, in the opinion of the investigator, may either put the patient at risk because of participation in the study, may influence the result of the study, or may affect the patient’s ability to take part in the study.

6.2.20 Any abnormalities identified following a physical examination of the patient that, in the opinion of the investigator, would jeopardize the safety of the patient if they take part in the study.

6.2.21 Patient has donated blood during the past 12 weeks and is unwilling to abstain from donation of blood during the study.

6.2.22 Patient has been previously randomized into this study.

6.2.23 Patient has any known or suspected history of alcohol or substance abuse.

6.2.24 Patient has travel outside the country and/or state of residence planned during the trial, unless the patient has confirmation that the IMP is permitted in the destination country/state.
7 PATIENT ENROLLMENT

Before patients may be entered into the study, GW requires a copy of the relevant center’s Ethics Committee (EC) or Institutional Review Board (IRB) written approval of the protocol, informed consent/assent forms (ICF) and other patient information material. Patients will be considered enrolled in the study from the time of providing written informed consent/assent. All patients and/or parent(s)/legal representatives, where appropriate, must personally sign and date the consent and, if allowed per local regulations, assent forms prior to any procedures being performed (refer to Section 9.2.1 and Section 15.2).

In the UK, enrollment of patients between the ages of 12 and 23 months will only commence once 15 patients over the age of 23 months have been dosed for a minimum of 4 weeks and no new safety issues have been observed.

7.1 Treatment Assignment

At the start of Visit 1, enrolled patients will be allocated a unique patient number using an IVRS. After confirmation of eligibility at Visit 3, patients will be randomly allocated to 25 mg/kg/day, 50 mg/kg/day or placebo using the IVRS. G-Pharm will provide all IMP in a packed and labeled state and the IVRS will identify the pack number to be dispensed to the patient at each relevant visit, according to the treatment assigned in the randomization schedule.

7.2 Randomization

The allocation of IMP to treatment number will be done according to a randomization schedule produced by an independent statistician. The randomization schedule will be held centrally and not divulged to any other person involved in the study until the database has been locked and unblinding authorized by the relevant GW personnel. For access to blinded treatment assignment, see Section 8.5.

The randomization will be stratified by age group (1–6 years, 7–11 years, 12–17 years and 18–65 years).
8 TREATMENT PROCEDURES

8.1 Investigational Medicinal Product Dosage, Administration and Schedule

The use of placebo in the current study was deemed necessary to determine the efficacy and safety of the current intervention, since the best proven intervention had already been tried or may be given as an adjuvant treatment, failing to fully alleviate the patient’s symptoms. For details regarding IMP formulations, see Section 5.

Patients will be assigned to receive GWP42003-P 25 mg/kg/day, GWP42003-P 50 mg/kg/day, placebo 25 mg/kg/day dose volume equivalent, or placebo 50 mg/kg/day dose volume equivalent at a 2:2:1:1 ratio. The placebo groups will be pooled for the analyses of efficacy.

8.1.1 Dose Administration

The IMP will be administered by the patient or their caregiver twice each day (morning and evening) using the syringe(s) provided and may be taken with other concomitant medications, as directed by the investigator.

Patients may not be randomized into the study if using a gastrostomy/nasogastric tube, unless the patient is able to still take medication orally. Dosing through gastrostomy/nasogastric tubes may be allowed after consultation with the GW medical monitor. Alteration in dosing frequency may also be considered after consultation with the GW medical monitor.

8.1.2 Dose Escalation and Dose Adjustments

All patients will be weighed during Visit 3 and the daily volumes of IMP solution to be taken during the maximum four-week titration period and for the remainder of the blinded phase maintenance period will be calculated via the IVRS and the dosing regimen provided to the patient and/or caregiver. Doses may be altered during the OLE according to changes in patient weight. Further information on dispensing procedures will be provided in a separate Pharmacy Manual.

Titration from 0–25 mg/kg/day will begin at 5 mg/kg/day and will be increased in increments of 5 mg/kg/day every two days (patients will remain on each dose level for two days before they progress on to the next dose). Titration from 25–50 mg/kg/day will continue at smaller increments of 2.5 mg/kg/day every two days.
### Table 8.1.2-1  Dose Titration Regimen*

<table>
<thead>
<tr>
<th>Day</th>
<th>Dose Level 1 (25 mg/kg/day)</th>
<th>Dose Level 2 (50 mg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.0 mg/kg</td>
<td>5.0 mg/kg</td>
</tr>
<tr>
<td>2</td>
<td>5.0 mg/kg</td>
<td>5.0 mg/kg</td>
</tr>
<tr>
<td>3</td>
<td>10.0 mg/kg</td>
<td>10.0 mg/kg</td>
</tr>
<tr>
<td>4</td>
<td>10.0 mg/kg</td>
<td>10.0 mg/kg</td>
</tr>
<tr>
<td>5</td>
<td>15.0 mg/kg</td>
<td>15.0 mg/kg</td>
</tr>
<tr>
<td>6</td>
<td>15.0 mg/kg</td>
<td>15.0 mg/kg</td>
</tr>
<tr>
<td>7</td>
<td>20.0 mg/kg</td>
<td>20.0 mg/kg</td>
</tr>
<tr>
<td>8</td>
<td>20.0 mg/kg</td>
<td>20.0 mg/kg</td>
</tr>
<tr>
<td>9</td>
<td>25.0 mg/kg</td>
<td>25.0 mg/kg</td>
</tr>
<tr>
<td>10</td>
<td>25.0 mg/kg</td>
<td>25.0 mg/kg</td>
</tr>
<tr>
<td>11</td>
<td>25.0 mg/kg</td>
<td>27.5 mg/kg</td>
</tr>
<tr>
<td>12</td>
<td>25.0 mg/kg</td>
<td>27.5 mg/kg</td>
</tr>
<tr>
<td>13</td>
<td>25.0 mg/kg</td>
<td>30.0 mg/kg</td>
</tr>
<tr>
<td>14</td>
<td>25.0 mg/kg</td>
<td>30.0 mg/kg</td>
</tr>
<tr>
<td>15</td>
<td>25.0 mg/kg</td>
<td>32.5 mg/kg</td>
</tr>
<tr>
<td>16</td>
<td>25.0 mg/kg</td>
<td>32.5 mg/kg</td>
</tr>
<tr>
<td>17</td>
<td>25.0 mg/kg</td>
<td>35.0 mg/kg</td>
</tr>
<tr>
<td>18</td>
<td>25.0 mg/kg</td>
<td>35.0 mg/kg</td>
</tr>
<tr>
<td>19</td>
<td>25.0 mg/kg</td>
<td>37.5 mg/kg</td>
</tr>
<tr>
<td>20</td>
<td>25.0 mg/kg</td>
<td>37.5 mg/kg</td>
</tr>
<tr>
<td>21</td>
<td>25.0 mg/kg</td>
<td>40.0 mg/kg</td>
</tr>
<tr>
<td>22</td>
<td>25.0 mg/kg</td>
<td>40.0 mg/kg</td>
</tr>
<tr>
<td>23</td>
<td>25.0 mg/kg</td>
<td>42.5 mg/kg</td>
</tr>
<tr>
<td>24</td>
<td>25.0 mg/kg</td>
<td>42.5 mg/kg</td>
</tr>
<tr>
<td>25</td>
<td>25.0 mg/kg</td>
<td>45.0 mg/kg</td>
</tr>
<tr>
<td>26</td>
<td>25.0 mg/kg</td>
<td>45.0 mg/kg</td>
</tr>
<tr>
<td>27</td>
<td>25.0 mg/kg</td>
<td>47.5 mg/kg</td>
</tr>
<tr>
<td>28</td>
<td>25.0 mg/kg</td>
<td>47.5 mg/kg</td>
</tr>
<tr>
<td>29</td>
<td>25.0 mg/kg</td>
<td>50.0 mg/kg</td>
</tr>
</tbody>
</table>

* IMP is to be taken twice daily. Total daily doses are shown.

Each patient will take their first dose of IMP at Visit 3 (Day 1) and their final maintenance dose of IMP at Visit 10 (Day 113). If an unacceptable AE develops at any time during the titration period, dosing should initially be suspended or amended, at the investigator’s discretion, until the event has resolved. During the maintenance period, patients should continue on a stable dosing regimen at the target Dose Level. If that dose becomes poorly tolerated or an AE occurs (e.g., somnolence, transaminase elevation not meeting withdrawal criteria specified in Section 10 and Section 12.8), the investigator may consider temporarily or permanently reducing the dosage for the remainder of the maintenance period following discussion with the GW medical monitor. It is recommended that patients with poor tolerability have their daily dose reduced by 10 mg/kg every seven days unless, in the investigator’s opinion, smaller or
larger or more rapid dose reductions are clinically indicated. Where possible, the patient should be encouraged to return to the target Dose Level.

Patients entering the OLE will first complete a two-week blinded transition phase. OLE IMP will be titrated up to 25 mg/kg/day whilst blinded IMP is simultaneously tapered down to zero. All patients will complete the transition and enter the OLE taking 25 mg/kg/day GWP42003-P.

Following completion of the blinded transition patients may complete a three-week titration up to a target dose of 50 mg/kg/day. Beginning at 25 mg/kg/day the dose will increase in increments of 2.5 mg/kg/day every two days.

Table 8.1.2-2 is an example of the OLE transition (Visit B1 to Visit B2) for patients transitioning from each group of the randomized phase.

<table>
<thead>
<tr>
<th>Day Blinded Transition/OLE</th>
<th>Patients randomized to 25 mg/kg/day group</th>
<th>Patients randomized to 50 mg/kg/day group</th>
<th>Patients randomized to placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blinded</td>
<td>Open-label</td>
<td>Blinded</td>
</tr>
<tr>
<td>1</td>
<td>25</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>22.5</td>
<td>0</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>17.5</td>
<td>5</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>12.5</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>7.5</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>2.5</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>0</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>0</td>
<td>25</td>
<td>0</td>
</tr>
</tbody>
</table>

Following completion of the blinded transition patients may complete a three-week titration up to a target dose of 50 mg/kg/day. Beginning at 25 mg/kg/day the dose will increase in increments of 2.5 mg/kg/day every two days (Table 8.1.2-3).

<table>
<thead>
<tr>
<th>OLE Day</th>
<th>Daily Dose (mg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 (Visit B2)</td>
<td>26.25a</td>
</tr>
<tr>
<td>16</td>
<td>27.5</td>
</tr>
<tr>
<td>17</td>
<td>30</td>
</tr>
<tr>
<td>18</td>
<td>30</td>
</tr>
</tbody>
</table>
### Table 8.1.2-3  OLE Titration Schedule

<table>
<thead>
<tr>
<th>OLE Day</th>
<th>Daily Dose (mg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>32.5</td>
</tr>
<tr>
<td>20</td>
<td>32.5</td>
</tr>
<tr>
<td>21</td>
<td>35</td>
</tr>
<tr>
<td>22</td>
<td>35</td>
</tr>
<tr>
<td>23</td>
<td>37.5</td>
</tr>
<tr>
<td>24</td>
<td>37.5</td>
</tr>
<tr>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td>26</td>
<td>40</td>
</tr>
<tr>
<td>27</td>
<td>42.5</td>
</tr>
<tr>
<td>28</td>
<td>42.5</td>
</tr>
<tr>
<td>29</td>
<td>45</td>
</tr>
<tr>
<td>30</td>
<td>45</td>
</tr>
<tr>
<td>31</td>
<td>47.5</td>
</tr>
<tr>
<td>32</td>
<td>47.5</td>
</tr>
<tr>
<td>33</td>
<td>50</td>
</tr>
<tr>
<td>34</td>
<td>50</td>
</tr>
<tr>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>36 (Visit B3)</td>
<td>50</td>
</tr>
</tbody>
</table>

* Derived from an AM dose based on 25 mg/kg/day and a PM dose based on 27.5 mg/kg/day.

Patients who do not enter the OLE study at Visit 10 or withdraw early will have their dose of IMP tapered gradually (10% each day) over a period of 10 days unless continued dosing is not possible due to an AE. Patients not entering the OLE will return used and unused IMP to the clinic at Visit 11.

### 8.2 Concomitant Therapy

It is theoretically possible that GWP42003-P may modify the metabolism of other drugs (including AEDs) administered concurrently and there remains the possibility of pharmacological interactions between GWP42003-P and other concurrently administered drugs. Doses of any concomitant AEDs must have been stable for at least four weeks prior to screening and must remain stable throughout the blinded study period. If during the blinded or OLE phase plasma concentrations of concomitant AEDs are found to be altered following administration of IMP, or if there are side-effects suspected of being related to an elevation in the concomitant AED concentration, the investigator must contact the GW medical monitor to discuss best management. Decisions should be based on clinical symptoms and not plasma levels of AEDs. Further information on drug interactions can be found in the IB\(^5\). Concomitant AED dose reductions are permitted on clinical grounds (e.g., due to AEs or transaminase elevations *not meeting* withdrawal criteria specified in Section 10 and Section 12.8) following discussion with the GW medical monitor.
Additional new AEDs (including oral mTOR inhibitors) are not allowed to be added during the randomized phase of the trial but may be considered on a case-by-case basis for the OLE phase in accordance with local licensing and after consultation with the GW medical monitor.

The use of rescue medication is allowed when necessary. Any medication, other than the IMP, taken during the study must be recorded on the Case Report Form (CRF).

Any non-pharmacological therapies (e.g., ketogenic diet, vagus nerve stimulation) must also be stable up to four weeks prior to screening and throughout the duration of the study.

8.3 Prohibited Therapy During Study Period

The following medications are prohibited for the duration of the study beginning from acquisition of patient consent/assent. However, any patients taking these medications after randomization should not be withdrawn from the study unless there are safety concerns. If applicable, the possible effects of these medications on the primary endpoint will be considered during the assessment of the evaluable period (see Section 13.6.1).

- Any new medications or interventions for epilepsy (including ketogenic diet and vagus nerve stimulation) or changes in dosage.
- Recreational or medicinal cannabis or synthetic cannabinoid-based medications (including Sativex®).
- Any other IMP taken as part of a clinical trial.

Care should be taken with drugs, or their metabolites, that are cytochrome P450 2C19 substrates, such as N-desmethyloclobazam. Care should also be taken with drugs, or their metabolites, that are solely or primarily metabolized by UDP-glucuronosyltransferase 1A9 and 2B7.

8.4 Compliance in Investigational Medicinal Product Administration

The IMP is dispensed to the patient at each of the following visits:

- Visit 3 (Day 1)
- Visit 4 (Day 15)
- Visit 5 (Day 29)
- Visit 6 (Day 43)
• Visit 7 (Day 57)
• Visit 9 (Day 85)
• Visit 10 (Day 113) (patients not entering the OLE)
• All OLE visits until the end of treatment

The patient or their caregiver will record the volume of solution taken on each treatment day in the diary.

Patients should return all IMP (used and unused) at each of visits 4, 5, 6, 7, 9, 10 and 11 during the blinded phase and at all OLE visits. The usage recorded in the diary and the usage projected in the dose calculator will be checked and any discrepancies discussed with the patient or their caregiver at the time of the visit and documented accordingly within the patient’s source documents.

Records of IMP accountability will be maintained according to Section 5.3.4.

8.5 Access to Blinded Treatment Assignment (Blinded Phase and OLE Transition Only)

The identity of IMP assigned to patients will be held by the IVRS. The principal investigator (PI) at each center, or his/her designee, is responsible for ensuring that information on how to access the IVRS for an individual patient is available to the relevant staff in case of an emergency and unblinding is required. A patient’s treatment assignment should only be unblinded when knowledge of the treatment is essential to make a decision on the medical management of the patient. Unblinding for any other reason will be considered a protocol deviation.

The investigator is encouraged to contact GW to discuss the rationale for unblinding prior to doing so. However, to prevent delays to the investigator or medical personnel responding to a potentially emergent situation, unblinding of study medication will not be dependent upon the investigator receiving approval from GW (i.e., the investigator will be able to obtain the code break information independent of contacting GW).

If the investigator does unblind, they must contact GW within one working day of the event and must document the time, date and reason(s) for unblinding on the patient’s CRF.
9  STUDY PROCEDURES

A list of the required study procedures is provided in the subsections that follow; refer also to the Schedule of Assessments (APPENDIX 1). Assessments or tests that are not done and examinations that are not conducted must be reported as such in the CRFs.

The location of the source data for the following procedures will be documented, per center, in a signed ‘Source Data Verification’ plan; for further details see Section 16.2.

9.1  Study Procedures by Visit

Patients and their parent(s)/legal representative will be invited to take part in the study and will be issued with the patient information and informed consent/assent or the patient/parent(s)/legal representative information and informed consent. Following adequate time to discuss the study with the investigator, nurse, relatives or caregiver, as wished, patients/parent(s)/legal representatives who provide written informed consent/assent will be screened for entry into the study.

9.1.1  Blinded Phase

9.1.1.1  Visit 1 (Day −35, Screening)

Eligibility must be assessed according to the criteria specified in Section 6.

The following observations will be made at Visit 1: demographics, medical history (including seizure information since diagnosis, history of epilepsy-specific genetic testing and all prior AEDs taken), concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, postural blood pressure and visit procedure-related AEs. With the patient/parent(s)/legal representative’s consent, a further blood test will be carried out to determine the mutation status of TSC1 and TSC2, if it is unknown.

The patient’s documented history of TSC will be sent to the ESC to confirm seizure classification.

Clinical laboratory samples (blood and urine [where possible]), including pregnancy tests if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry, urinalysis, and a urine/serum THC screen. Suicidality will be assessed in accordance with Section 9.2.12.8.
The investigator must record the patient’s attendance at the visit and confirm the outcome of screening on the CRF.

9.1.1.2 Visit 2 (Day −28, Baseline)

This visit will occur 7 days after Visit 1. A visit window of ±7 days from the scheduled visit is permitted to ensure ESC confirmation of seizure classification, but it is preferred that the visit is performed on the scheduled visit day where possible.

Attendance of the patient is not required for this visit provided the primary caregiver is able to attend and that this caregiver (not the patient) will be responsible for seizure identification, IVRS use, and paper diary completion. However, it is preferred that the patient attend where possible.

The following observations will be made at Visit 2: review of concomitant medications (including AEDs), AEs and epilepsy-related hospitalizations.

Patients who satisfy all inclusion and none of the exclusion criteria specified in Section 6 will begin the 28 (+3)-day baseline period. The investigator will review and train the patient or their caregiver to identify the patient’s expected seizure types. Patients or their caregivers will be issued with IVRS details and will be instructed on how to use it to record daily seizure information. Patients or their caregivers will also be given a paper diary to record usage of IMP, rescue medication, concomitant AEDs and AEs and will be instructed on how to do so.

9.1.1.3 Visit 3 (Day 1, Randomization)

This visit will occur 28 days after Visit 2. A visit window of +3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

The following observations will be made at Visit 3: concomitant medications, (including AEDs), physical examination (including height and body weight), details of menstruation (for females), Tanner Staging (for patients aged 10–17 years [inclusive], or earlier if clinically indicated by onset of menarche or other signs of precocious puberty), ECG, vital signs, postural blood pressure, epilepsy-related hospitalizations, AEs and paper diary review. The ECG will be repeated four hours (±30 minutes) after the first dose of IMP.

Clinical laboratory samples (blood and urine [where possible]), including pregnancy tests if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry, urinalysis, and determination of serum IGF-1 levels (for
patients less than 18 years of age). Provided that the risk/benefit outcome is favorable in the investigator’s opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs. PK samples (patients > 20 kg in weight only) will be taken in accordance with Section 9.2.9.1.

The investigator must assess the patient’s daily number of seizures from the patient’s IVRS data, record the patient’s attendance at the visit, and confirm the outcome of the visit prior to randomization. Patients who have experienced at least eight seizures during the first 28 days of the baseline period, and who meet all of the other inclusion and none of the exclusion criteria specified in Section 6, will be eligible to continue in the study.

Eligible patients will then be randomized to receive GWP42003-P 25 mg/kg/day, GWP42003-P 50 mg/kg/day, placebo 25 mg/kg/day dose volume equivalent, or placebo 50 mg/kg/day dose volume equivalent at a 2:2:1:1 ratio.

Following randomization at Visit 3, patients will remain at the clinic where the following baseline assessments will be performed prior to the administration of study medication: QOLCE/QOLIE-31-P, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II. Suicidality will be assessed in accordance with Section 9.2.12.8.

Patients/caregivers and investigators will be asked to write a brief description of their/the patient’s overall condition and assess the average duration of seizure subtypes as a memory aid for the PGIC, SGIC/CGIC and SGIC-S/CGIC-SD; these will be referred to at relevant, subsequent visits or withdrawal.

IMP will be dispensed for the following 2 weeks and patients or their caregivers will be provided with individual dosing schedules as described in Section 8.1 Each patient will then receive a titration regimen. The first dose of IMP will be administered in clinic.

Following Visit 3, during titration, safety telephone calls must be made every two days. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead. A further call must be completed one week after the end of titration. During these calls, caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The investigator must retain oversight of safety telephone calls.
9.1.1.4 Visit 4 (Day 15)

This visit will occur 14 days after Visit 3 (randomization). A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

The following observations will be made at Visit 4: concomitant medications, (including AEDs), physical examination (including height and body weight), ECG, vital signs, epilepsy-related hospitalizations and AEs.

Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry and urinalysis.

Suicidality will be assessed in accordance with Section 9.2.12.8.

The investigator must assess adherence to the titration regimen by reviewing the patient’s diary and IVRS data and record the patient’s attendance at the visit.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients will then receive a new treatment pack of the IMP.

Following Visit 4, during titration, safety telephone calls must be made every two days. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead. During these calls, caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The investigator must retain oversight of safety telephone calls.

9.1.1.5 Visit 5 (Day 29)

This visit will occur 28 days after Visit 3. A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

The following observations will be made at Visit 5: concomitant medications, (including AEDs), physical examination (including height and body weight), ECG, vital signs, postural BP, epilepsy-related hospitalizations and AEs.

Clinical laboratory samples (blood and urine [where possible]), including pregnancy tests if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry and urinalysis. Provided that the risk/benefit outcome is favorable in the investigator’s opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs.
Suicidality will be assessed in accordance with Section 9.2.12.8.

The investigator must assess adherence to the titration regimen by reviewing the patient’s diary and IVRS data and record the patient’s attendance at the visit.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients will then receive a new treatment pack of the IMP.

A safety telephone call must be made one week after the end of titration (Visit 5). During this call, caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The investigator must retain oversight of the safety telephone call.

**9.1.1.6 Visit 6 (Day 43)**

This visit will occur 42 days after Visit 3 (randomization). A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

The following observations will be made at Visit 6: concomitant medications, (including AEDs), physical examination (including height and body weight), ECG, vital signs, epilepsy-related hospitalizations and AEs.

Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry and urinalysis. Suicidality will be assessed in accordance with Section 9.2.12.8.

The investigator must assess adherence to the dosing regimen by reviewing the patient’s diary and IVRS data and record the patient’s attendance at the visit.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients will then receive new IMP.

**9.1.1.7 Visit 7 (Day 57)**

This visit will occur 56 days after Visit 3 (randomization). A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

The following observations will be made at Visit 7: concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, epilepsy-related hospitalizations and AEs.
Clinical laboratory samples (blood and urine [where possible]), including pregnancy tests if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry and urinalysis. Provided that the risk/benefit outcome is favorable in the investigator’s opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs.

Suicidality will be assessed in accordance with Section 9.2.12.8.

The investigator must assess adherence to the dosing regimen by reviewing the patient’s diary and IVRS data and record the patient’s attendance at the visit.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients will then receive new IMP.

9.1.1.8 Visit 8 (Day 71)

This visit will occur 70 days after Visit 3 (randomization). A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

Visit 8 will be completed by telephone and will comprise a review of concomitant medications (including AEDs), epilepsy-related hospitalizations and AEs.

9.1.1.9 Visit 9 (Day 85)

This visit will occur 84 days after Visit 3 (randomization). A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

The following observations will be made at Visit 9: concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, epilepsy-related hospitalizations and AEs.

Clinical laboratory samples (blood and urine [where possible]), including pregnancy tests if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry and urinalysis. Provided that the risk/benefit outcome is favorable in the investigator’s opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs.

Suicidality will be assessed in accordance with Section 9.2.12.8.

The investigator must assess adherence to the dosing regimen by reviewing the patient’s diary and IVRS data and record the patient’s attendance at the visit.
All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients will then receive new IMP.

**9.1.1.10 Visit 10 (Day 113, End of Treatment/Withdrawal Visit)**

This visit will occur 112 days after Visit 3 (randomization) or earlier if the subject withdraws from the study. A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible. Patients will be instructed to record the dosing time of their concomitant AEDs in the diary.

The following observations will be made at Visit 10/the Withdrawal visit: concomitant medications (including AEDs), physical examination (including height and body weight), Tanner Staging (for patients aged 10–17 years [inclusive], or earlier if clinically indicated by onset of menarche or other signs of precocious puberty), details of menstruation (for females), ECG, vital signs, epilepsy-related hospitalizations and AEs.

Clinical laboratory samples (blood and urine [where possible]), including pregnancy tests if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry, urinalysis, and determination of serum IGF-1 levels (for patients less than 18 years of age) to be performed by the central laboratory. Provided that the risk/benefit outcome is favorable in the investigator’s opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs. PK samples (patients > 20 kg in weight only) will be taken in accordance with Section 9.2.9.1.

The following assessments will also be performed: QOLCE/QOLIE-31-P, PGIC, SGIC/CGIC, SGIC-SD/CGIC-SD, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II. Suicidality will be assessed in accordance with Section 9.2.12.8.

The investigator must assess adherence to the dosing regimen by reviewing the patient’s diary and IVRS data, record the patient’s attendance at the visit and confirm the outcome of the visit.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made.

For patients 12 years of age and older who do not enter the taper period, the trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.
For patients who withdraw early, the IVRS will be contacted to confirm withdrawal from the study. Patients who withdraw should have their dose of IMP tapered gradually (10% each day) over a period of 10 days, beginning at the time the decision is made to discontinue. In some cases, tapering the dose of IMP may be inadvisable (e.g., continued dosing is not possible due to an AE). The decision on whether or not to taper IMP will be left to the investigator’s clinical judgment. If tapering is undertaken, a 10-day supply of IMP (if required) and instructions for tapering the dose will be provided. Patients/caregivers should continue to complete the IVRS (see APPENDIX 4) and paper diary and should return for Visit 11 (the ‘End of Taper Period’ visit), if possible.

Patients who have completed all of the scheduled study visits will be offered the option of entering an OLE. Entry is to be on the same day as Visit 10 (Day 113).

Patients not entering the OLE at this visit will be given a 10-day supply of IMP (if required) and instructions for tapering the dose, during which time IVRS (see APPENDIX 4) and paper diary information will continue to be recorded.

9.1.1.11 Visit 11 (Day 123, End of Taper)

This visit is required only for those patients who do not enter the OLE on the day of Visit 10 or for those who withdraw early and taper IMP. For patients who complete the study but opt not to enter the OLE, Visit 11 should occur 10 (+3) days after Visit 10 (i.e., on Day 123 [+3]). For patients who withdraw early and taper IMP, this visit should occur 10 (+3) days after the Withdrawal visit. For patients who begin to taper IMP but subsequently withdraw/do not complete the full taper period, this visit should occur on the final day of dosing or as soon as possible after this date.

The following observations will be made at Visit 11: concomitant medications (including AEDs), epilepsy-related hospitalizations and AEs, physical examination (including height and body weight), vital signs, ECG and clinical laboratory samples (blood and urine for hematology, biochemistry and urinalysis). Suicidality will be assessed in accordance with Section 9.2.12.8.

For patients 12 years of age and older, the trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.

The investigator must assess adherence to the dosing regimen by reviewing the patient’s diary and IVRS data and record the patient’s attendance at the visit.
All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. The patient diaries will be collected.

Following Visit 11 (or date of final dosing) the IVRS seizure reporting diary should only be completed once more (see APPENDIX 4).

9.1.1.12 Visit 12 (Day 151, Safety Follow-up)

This visit is required for patients who do not enter the OLE or who withdraw from the study early. This visit should occur four weeks after Visit 11 (+3 days), or date of final dosing, and can be conducted over the telephone. The following observations will be made at Visit 12: concomitant medications (including AEDs), epilepsy-related hospitalizations and AEs.

9.1.2 Open-label Extension

Patients who successfully complete the blinded phase will be invited to participate in the OLE when they reach the End of Treatment visit (Visit 10) of the blinded phase. They will be issued with the OLE patient information and informed assent or the patient/parent(s)/legal representative information and informed consent (as applicable). Following adequate time to discuss the study with the investigator, nurse, relatives or caregiver, patients/parent(s)/legal representatives who provide written informed consent/assent at Visit B1 will be enrolled into the OLE. The OLE period will last for a maximum of 1 year; however, patients in the US and Poland may have the opportunity to continue in the OLE beyond this.

On-label use of mTOR inhibitors (for the treatment of seizures or tumors) and general anesthesia are permitted in the OLE phase of the trial.

9.1.2.1 Visit B1 (Day 1)

Day 1 is regarded as the first day of IMP dosing. The following data collected at the ‘End of Treatment’ visit of the blinded phase will also be considered as Visit B1 data: vital signs, physical examination (including height and body weight), details of menstruation (for females), Tanner Staging (patients aged 10–17 [inclusive]), ECG, clinical laboratory samples (blood and urine for hematology, biochemistry, urinalysis, determination of serum IGF-1 levels [patients less than 18 years of age], and pregnancy tests [if appropriate]), IVRS and paper diary information from the blinded phase (including information regarding seizures, AEs, usage of rescue medication, concomitant AEDs, IMP dosing), epilepsy-related hospitalizations, AEs, concomitant medications and/or changes to medication, QOLCE/QOLIE-31-P, PGIC,
SGIC/CGIC, SGIC-SD/CGIC-SD, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II. Suicidality will be assessed in accordance with Section 9.2.12.8.

Patients will take their final dose of the blinded phase IMP in the morning of Visit B1, followed by collection of the blinded phase ‘End of Treatment’ assessments. Patients will be instructed to begin the Blinded Open-label transition, taking their first dose of Blinded Transition OLE IMP in the evening of Visit B1 (Day 1).

Patients or their caregivers will receive sufficient IMP for two weeks’ home dosing together with a blinded transition phase. If an unacceptable AE develops at any time during transition, dosing should initially be suspended or amended, at the investigator’s discretion, until the event has resolved or is well tolerated.

Patients or their caregivers will be given a paper diary to record information regarding AEs, IMP, usage of rescue medication, concomitant AEDs and IMP dosing. In addition, patients/caregivers will be instructed to complete a weekly seizure reporting diary until the Follow-up visit using the IVRS.

The investigator should review the laboratory results as soon as these become available. If the results raise any safety concerns, the investigator should consider whether it will be appropriate for the patient to continue to participate in the extension study, or if the patient should be withdrawn.

In order to complete the SGIC/CGIC, the patient/caregiver is to compare to the memory aid from the Baseline of the blinded phase. If the memory aid is not available from the Baseline of the blinded phase then the patient/caregiver should do this from memory, if possible, and complete a memory aid at Visit B1.

In order to complete the SGIC-SD/CGIC-SD, the patient/caregiver would have been asked to assess and note the average duration of the patient’s seizures at the Baseline of the blinded phase as a memory aid for subsequent visits. If the memory aid is not available from the Baseline of the blinded phase then the patient/caregiver should do this from memory, if possible, and complete a memory aid at Visit B1.

Following Visit B1, during the blinded transition, safety telephone calls must be made every two days. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead. During these calls, caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The investigator must retain oversight of safety telephone calls.
9.1.2.2 Visit B2 (Day 15)

Visit B2 will take place 14 days after Visit B1. A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

The following assessments will be made at Visit B2: concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, epilepsy-related hospitalizations, and AEs. Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry and urinalysis. Provided that the risk/benefit outcome is favorable in the investigator’s opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs. Suicidality will be assessed in accordance with Section 9.2.12.8.

The investigator must assess adherence to the titration regimen by reviewing the patient’s diary and IVRS data and record the patient’s attendance at the visit.

Upon completion of the two-week blinded transition at Visit B2 all patients will be taking 25 mg/kg/day. All blinded IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients/caregivers will then receive sufficient open-label IMP for three weeks’ home dosing together with a titration schedule. Patients may titrate up to the target dose of 50 mg/kg/day according to the defined titration schedule. If an unacceptable AE develops at any time during titration, dosing should initially be suspended or amended, at the investigator’s discretion, until the event has resolved or is well tolerated.

Following Visit B2, during titration, safety telephone calls must be made every two days. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead. An additional call should be completed one week after the end of titration. During these calls, caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The investigator must retain oversight of safety telephone calls.

9.1.2.3 Visit B3 (Day 36)

Visit B3 will take place 35 days after Visit B1. A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.
The following assessments will be made at Visit B3: concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, postural blood pressure, epilepsy-related hospitalizations, and AEs. Suicidality will be assessed in accordance with Section 9.2.12.8. Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry and urinalysis. Provided that the risk/benefit outcome is favorable in the investigator’s opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs.

The investigator must assess adherence to the titration regimen by reviewing the patient’s diary and IVRS data and record the patient’s attendance at the visit.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients/caregivers will then receive sufficient open-label IMP for eight weeks’ home dosing.

9.1.2.4 Visit B4 (Day 92)

This visit will occur 91 days after Visit B1. A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

The following observations will be made at Visit B4: concomitant medications, (including AEDs), physical examination (including height and body weight), ECG, vital signs, epilepsy-related hospitalizations and AEs.

Clinical laboratory samples (blood and urine [where possible]), including pregnancy tests if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry and urinalysis to be performed by the central laboratory. Provided that the risk/benefit outcome is favorable in the investigator’s opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs.

The following assessments will also be performed: SGIC-SD/CGIC-SD. Suicidality will be assessed in accordance with Section 9.2.12.8.

The investigator must assess adherence to the dosing regimen by reviewing the patient’s diary and IVRS data, record the patient’s attendance at the visit and confirm the outcome of the visit.
All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients/caregivers will then receive sufficient open-label IMP until the next scheduled visit.

**9.1.2.5 Visit B5 (Day 141, Re-supply Visit)**

This visit will occur 140 days after Visit B1. A visit window of ±7 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

Attendance of the patient is not required for this re-supply visit provided the primary caregiver is able to attend. However, it is preferred that the patient attend where possible.

The visit will comprise a review of concomitant medications (including AEDs), epilepsy-related hospitalizations and AEs.

The investigator must assess adherence to the dosing regimen by reviewing the patient’s diary and IVRS data, record the patient’s/caregiver’s attendance at the visit and confirm the outcome of the visit.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients/caregivers will then receive sufficient IMP until the next scheduled visit.

**9.1.2.6 Visit B6 (Day 183)**

This visit will occur 182 days after Visit B1. A visit window of ±7 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

The following observations will be made at Visit B6: concomitant medications, (including AEDs), physical examination (including height and body weight), ECG, vital signs, epilepsy-related hospitalizations and AEs.

Clinical laboratory samples (blood and urine [where possible]), including pregnancy tests if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry, urinalysis and determination of serum IGF-1 levels (for patients less than 18 years of age) to be performed by the central laboratory. Provided that the risk/benefit outcome is favorable in the investigator’s opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs.
The following assessments will also be performed: QOLCE/QOLIE-31-P, PGIC, SGIC/CGIC, SGIC-SD/CGIC-SD, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II. Suicidality will be assessed in accordance with Section 9.2.12.8.

The investigator must assess adherence to the dosing regimen by reviewing the patient’s diary and IVRS data, record the patient’s attendance at the visit and confirm the outcome of the visit.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients/caregivers will then receive sufficient open-label IMP until the next scheduled visit.

**9.1.2.7 Visit B7 (Day 232, Re-supply Visit)**

This visit will occur 231 days after Visit B1. A visit window of ±7 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

Attendance of the patient is not required for this re-supply visit provided the primary caregiver is able to attend. However, it is preferred that the patient attend where possible.

The visits will comprise a review of concomitant medications (including AEDs), epilepsy-related hospitalizations and AEs.

The investigator must assess adherence to the dosing regimen by reviewing the patient’s diary and IVRS data, record the patient’s/caregiver’s attendance at the visit and confirm the outcome of the visit.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients/caregivers will then receive sufficient IMP until the next scheduled visit.

**9.1.2.8 Visit B8 (Day 274)**

This visit will occur 273 days after Visit B1. A visit window of ±7 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

The following observations will be made at Visit B8: concomitant medications, (including AEDs), physical examination (including height and body weight), ECG, vital signs, epilepsy-related hospitalizations and AEs.
Clinical laboratory samples (blood and urine [where possible]), including pregnancy tests if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry and urinalysis to be performed by the central laboratory. Provided that the risk/benefit outcome is favorable in the investigator’s opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs.

The following assessments will also be performed: SGIC-SD/CGIC-SD. Suicidality will be assessed in accordance with Section 9.2.12.8.

The investigator must assess adherence to the dosing regimen by reviewing the patient’s diary and IVRS data, record the patient's attendance at the visit and confirm the outcome of the visit.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients/caregivers will then receive sufficient open-label IMP until the next scheduled visit.

9.1.2.9 Visit B9 (Day 323, Re-supply Visit)

This visit will occur 322 days after Visit B1. A visit window of ±7 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

Attendance of the patient is not required for this re-supply visit provided the primary caregiver is able to attend. However, it is preferred that the patient attend where possible.

The visits will comprise a review of concomitant medications (including AEDs), epilepsy-related hospitalizations and AEs.

The investigator must assess adherence to the dosing regimen by reviewing the patient’s diary and IVRS data, record the patient’s/caregiver’s attendance at the visit and confirm the outcome of the visit.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients/caregivers will then receive sufficient IMP until the next scheduled visit.

Patients in the US and Poland may have the opportunity to continue in the OLE beyond Visit B10. Please refer to Protocol Annex 1 (US based patients) or Protocol Annex 2 (Poland based patients) for the remaining visit schedule.
9.1.2.10 Visit B10 (Day 365, End of Treatment/Withdrawal Visit)

This visit will occur 364 days after Visit B1 or following early withdrawal from the study. A visit window of $\pm 7$ days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible. The following assessments will be made at the ‘End of Treatment’/Withdrawal visit: vital signs, physical examination (including height and body weight), details of menstruation (for females), Tanner Staging (patients aged 10–17 [inclusive]), ECG, clinical laboratory samples (blood and urine for hematology, biochemistry, urinalysis, determination of serum IGF-1 levels [patients less than 18 years of age] and pregnancy tests if appropriate [using both a serum sample and a urine dipstick]), IVRS and paper diary information (including information regarding seizures, AEs, usage of rescue medication, concomitant AEDs, IMP dosing), epilepsy-related hospitalizations, concomitant medications and/or changes to medication, AEs, QOLCE/QOLIE-31-P, SGIC/CGIC, PGIC, SGIC-SD/CGIC-SD, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II. Suicidality will be assessed in accordance with Section 9.2.12.8. Provided that the risk/benefit outcome is favorable in the investigator’s opinion, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs. The investigator must assess adherence to the dosing regimen.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. For patients who withdraw early, the IVRS will be contacted to confirm withdrawal from the study. For patients who immediately continue to use GWP42003-P following the ‘End of Treatment’ visit outside of the GWEP1521 study, the IVRS will be contacted to confirm the patient’s completion of this study and the paper diaries will be collected.

For patients who do not immediately continue to use GWP42003-P following the ‘End of Treatment’ visit outside of the GWEP1521 study, IMP will be tapered at home (10% per day for 10 days). Additional IMP will be dispensed, if required, and instructions for tapering the dose will be provided. Patients who withdraw early should also begin the taper period following the Withdrawal visit (unless continued dosing is not possible due to an AE). Information will continue to be recorded in the paper diary during the taper period.

For patients 12 years of age and older who do not enter the taper period, the trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.
Following the End of Treatment/Withdrawal visit, the IVRS seizure reporting diary should be completed according to APPENDIX 4.

For patients in the US and Poland who continue in the OLE beyond Visit B10, assessments are described in Protocol Annex 1 (US) and Protocol Annex 2 (Poland).

**9.1.2.11 Visit B11 (Day 375, End of Taper Period Visit)**

This visit will take place 10 (+3) days after the ‘End of Treatment’ visit or Withdrawal visit for patients who withdraw early and taper IMP. For patients who begin to taper IMP but subsequently withdraw/do not complete the full taper period, this visit should occur on the final day of dosing or as soon as possible after this date.

The following assessments will be made: concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, epilepsy-related hospitalizations, and AEs. Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry, and urinalysis. Suicidality will be assessed in accordance with Section 9.2.12.8. The investigator must assess adherence to the dosing regimen by reviewing the patient’s diary and IVRS data and record the patient’s attendance at the visit.

For patients 12 years of age and older, the trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made.

Following Visit B11 (or date of final dosing), the IVRS seizure reporting diary should only be completed once more (see APPENDIX 4).

**9.1.2.12 B12 (Day 389, Post-taper Safety Telephone Call)**

A safety telephone call must be made two weeks (±3 days) after the ‘End of Taper Period’ visit or date of final dosing. Patients or their caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.

Following this call, the IVRS seizure reporting diary should be completed up to the Follow-up visit.
9.1.2.13  Follow-up Visit

This visit is required for patients who withdraw from the study or complete treatment but do not wish to continue to use GWP42003-P. The Follow-up visit will be performed four weeks (+3 days) after the patient’s last dose of GWP42003-P (including final taper period dose) and can be conducted over the telephone. During this visit/call, caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.

9.1.2.14  Safety Telephone Calls

Safety telephone calls must be made every two days during the two-week blinded transition and the two-week OLE titration period and one week after the end of titration to assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead.

The investigator must retain oversight of safety telephone calls.

9.2  Study Procedure Listing

9.2.1  Informed Consent/Assent

Adult patients with an adequate level of understanding must personally sign and date the EC/IRB-approved / ICF before any study-specific procedures are performed or any patient-related data are recorded for the study. For adult patients with an insufficient level of understanding of what is proposed, only parent(s)/legal representative consent will be sought. If an adult patient is unable to read (illiterate or visually impaired), or is physically unable to speak or write, an impartial witness should be present during the entire informed consent discussion. After the ICF is read and explained to the patient and after the patient has orally consented to participation in the trial and has signed and dated the ICF (if capable of doing so), the witness should also sign and personally date the ICF. By signing the ICF, the witness attests that the information in the ICF was accurately explained to and apparently understood by the patient and that informed consent was freely given by the patient (as outlined in the International Council for Harmonisation [ICH] Tripartite Guideline for GCP Topic E6(R2)52, section 4.8.9).

The parent(s)/legal representative of minor patients must personally sign and date the EC/IRB-approved ICF before any study-specific procedures are performed or any patient-related data is recorded for the study. In addition, in cases where the patient
possesses adequate understanding, assent will be taken (if allowed per local regulations) along with parent(s)/legal representative consent, using EC/IRB-approved assent forms. Assent is defined as the minor’s permission or affirmative agreement to participate in the study. The explicit wish of a minor, who is capable of forming an opinion and assessing the information provided, to refuse participation in or to be withdrawn from the clinical trial at any time must be considered by the investigator.

For patients who go from being a minor to an adult (as per the country or state’s age-of-majority regulation) during the course of the study, a new ICF will be signed if the patient possesses adequate understanding to do so.

If the patient cannot write, they can give consent/assent by “making their mark” on the consent/assent form (e.g., writing an “X”).

GW requires a physician to be present for consent and assent and to sign the consent and assent forms also. Patients/parent(s)/legal representatives will be given the option of being informed about the summary outcome and results of the trial as part of the ICF. For further details, see Section 15.2.

### 9.2.2 Contraception Requirements

To be eligible for the study, the patient must have agreed that if they or their partner are of childbearing potential they are willing to use highly effective contraception for the duration of the study and for three months thereafter. Highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly\(^{53}\). Such methods include hormonal contraceptives, intrauterine devices/hormone-releasing systems, bilateral tubal occlusion, vasectomized partner (provided that partner is the sole sexual partner of the trial patient and that the vasectomized partner has received medical assessment of the surgical success), or sexual abstinence\(^{54}\). Abstinence, as referenced above, is only acceptable as true abstinence: when this is in line with the preferred and usual lifestyle of the patient; periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception\(^{54}\).
9.2.3 Demographics

Patient demographics will be recorded at Visit 1. The following information will be obtained for each patient: date of birth, sex and ethnic origin (if allowed per local regulations).

9.2.4 Medical History

Relevant, significant medical history (including seizure information since diagnosis, history of epilepsy-specific genetic testing and all prior AEDs taken) will be obtained during Visit 1 and is defined as any condition or disease that:

- May affect the condition under study.
- Is ongoing on entry into the study.
- Has occurred within one year prior to screening (Visit 1).

The mutation status of the \( TSC1 \) and \( TSC2 \) genes, if known, will be obtained through the patient's medical records.

9.2.5 Concomitant Medication

Details of all current and recent medication (i.e., taken within the previous 14 days) including AEDs will be recorded at the screening visit (Visit 1) and reviewed at each subsequent visit. AEDs used during the study should be maintained at a stable dose.

Any changes in concomitant medication during the study must be recorded in the CRF at study visits. Patients should stop taking any prohibited therapy prior to enrollment, as defined in Section 8.2.

9.2.6 Physical Examination

A physical examination will be performed at the screening visit (Visit 1) to ensure that the patient is eligible to enter the study. To ensure patient safety, further physical examinations will be performed during subsequent visits. Physical examinations will include height and body weight measurements.

9.2.7 Vital Signs and Blood Pressure

Vital sign measurements (body temperature, pulse rate, respiration rate), including blood pressure taken in a sitting position at rest for five minutes, will be completed alongside the physical examination. Where postural blood pressure is required it should be measured after five minutes in supine position followed by two minutes in
standing position, if it is possible for the patient to stand. Blood pressure must be recorded using the same arm throughout the study, where possible.

### 9.2.8 12-Lead Electrocardiogram

A 12-lead ECG will be performed after five minutes in a supine position, if possible. A physician must review the ECG and any abnormal findings considered to indicate significant medical history or AEs must be recorded appropriately in the CRF. Additional ECG measurements can be taken at any time during the study, if clinically indicated.

### 9.2.9 Clinical Laboratory Sampling

Laboratory tests will include hematology, biochemistry, urinalysis (provided urine can be obtained), urine/serum THC screening and a serum pregnancy test (if appropriate). In addition to serum pregnancy tests, urine dipstick pregnancy tests will also be performed (if appropriate) at the study center. Analysis of all clinical blood samples, pregnancy tests (using serum) and tests to detect the presence of THC will be conducted at a central clinical laboratory.

Urine samples for biochemistry will be analyzed at the study center by use of a dipstick with any relevant findings being sent for further urinalysis at the central laboratory (urinalysis, microscopy, culture and sensitivity, as applicable). In cases where urine samples cannot be analyzed at center due to local regulations, a full set of urine samples should be sent to the central laboratory for analysis. Sample volume requirements and processing procedures will be detailed in a separate laboratory manual.

The investigator and study monitor will be provided with a list of the normal ranges used by the testing laboratory for all variables assayed during the study and a statement of accreditation (or similar) for the laboratory. Clinical laboratory sample parameters are detailed in Table 9.2.9-1.
### Table 9.2.9-1  Biochemistry, Hematology, Urinalysis and THC Screen

<table>
<thead>
<tr>
<th>Biochemistry (Serum)</th>
<th>Biochemistry (Serum)</th>
<th>Hematology (Whole Blood)</th>
<th>Urinalysis (Urine)</th>
<th>Pregnancy Test (Serum / Urine)</th>
<th>THC Screen (Serum / Urine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine aminotransferase (ALT)</td>
<td>Insulin-like growth factor-1 (IGF-1)</td>
<td>Hematocrit</td>
<td>Bilirubin</td>
<td>Serum and urine</td>
<td>THC</td>
</tr>
<tr>
<td>Albumin</td>
<td></td>
<td>Hemoglobin</td>
<td>Blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td></td>
<td>Mean cell volume</td>
<td>Glucose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase (AST)</td>
<td></td>
<td>Mean corpuscular hemoglobin</td>
<td>Ketones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td></td>
<td>Platelets</td>
<td>Nitrites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
<td>Red blood cell count</td>
<td>pH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimates of glomerular filtration rate</td>
<td></td>
<td>White blood cell count with automated differential</td>
<td>Protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gamma-glutamyl transferase</td>
<td></td>
<td></td>
<td>Specific gravity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
<td></td>
<td>Urobilinogen</td>
<td></td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolactin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prothrombin time (PT/INR) (plasma)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bilirubin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea (blood urea nitrogen [BUN])</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatine Kinase (CK)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Analyzed at a central laboratory.
2 Analyzed at the study center by use of a dipstick (if allowed per local regulations).
3 Only analyzed at Visits 3, 10/B1, B6 and B10).

Investigators at study centers will be notified of safety laboratory test results. All laboratory results will be reviewed and the reports signed by an investigator. Any results considered to be of clinical significance must be addressed and followed up as clinically appropriate. The results of THC screening will be reported back to the study site to permit confirmation of eligibility. Any samples reported to be THC-positive at screening must be sent for analysis by gas chromatography–mass spectrometry at the central laboratory.
All laboratory results considered to represent an AE must be documented in the CRF. See Section 12.8 for guidance on evaluation of potential drug-induced liver injury.

Repeat samples will be taken, if required, for clinical follow-up or if the sample is lost or damaged. Any abnormal end of treatment clinical laboratory result of clinical significance must be repeated at regular intervals until it returns to normal, or until an investigator is satisfied that the abnormality is not related to the IMP and needs no further investigation.

Sample volume requirements and processing procedures will be detailed in a separate laboratory manual. The patient/caregiver must be advised that it may not be safe for them to undertake further blood tests within one month of any study-related blood draws and to inform the investigator if they suffered any blood loss. The volume of blood drawn at each visit should be tracked. Where the required blood draw volume for study samples exceeds guidance at a particular visit, safety parameters (biochemistry and hematology) should be prioritized.

9.2.9.1 Pharmacokinetic Blood Sampling

The plasma concentration/time curves of CBD and its major metabolites will be assessed at Visits 3 and 10 for patients weighing more than 20 kg. Where appropriate, blood samples will be taken as follows:

- One sample pre-dose (i.e., prior to administration of IMP).
- One sample between 2 and 3 hours post-dose.
- One sample between 4 and 6 hours post-dose.
- One sample between 8 and 10 hours post-dose (patients 18 years and above only).

There must be a minimum period of at least two hours between each of the blood sampling time points. In the event of an AE that, in the opinion of the investigator, is related to a concomitant AED, additional blood samples may be collected.

For patients who undergo PK blood sampling, the patient/caregiver will record all meal times and the types of meals consumed by the patient during all PK testing days (Visits 3 and 10).

Analysis of all pharmacokinetic samples will be conducted at a central clinical laboratory. Sample volume requirements and processing procedures will also be detailed in a separate laboratory manual.
The patient/caregiver must be advised that it may not be safe for them to undertake further blood tests within one month of any study-related blood draws and to inform the investigator if they suffered any blood loss during the one-month period leading up to a planned blood draw.

**9.2.9.2 Determination of Plasma Concentrations of Concomitant Antiepileptic Drugs**

Plasma concentrations of concomitant AEDs will be assessed at Visits 3, 5, 7, 9 and 10/ the Withdrawal visit (if possible) during the blinded phase and at Visits B2, B3, B4 and all subsequent Assessment Visits during the OLE. Samples will be collected for all patients provided that the risk/benefit outcome is favorable in the investigator’s opinion. At each visit, blood samples will be taken prior to administration of IMP. Patients will be instructed to record the dosing time of their concomitant AEDs in the diary.

Additional blood samples may be taken for AED monitoring if there is a suspicion of changes in AED levels, with the aim to keep the AED plasma levels within the patient’s therapeutic level. AED doses should be adjusted, as appropriate, following discussion with the GW medical monitor in order to maintain stable AED plasma concentrations.

**9.2.9.3 Determination of Mutation Status of the TSC1 and TSC2 Genes**

If the mutation status of TSC1 and TSC2 is unknown at screening, genetic analysis will be carried out if the patient/parent(s)/legal representative provides consent (a blood sample will be taken during Visit 1).

**9.2.10 Interactive Voice Response System**

The IVRS will be used to collect patient reported diary data (refer to Section 9.2.11), to assign patients to treatment groups and to provide treatment allocation information in the event of patient unblinding. The IVRS will also be used to manage IMP supply.

A member of the study team must contact the IVRS at each clinic visit in order to:

- Allocate a patient number at screening (Visit 1).
- Randomize a patient (Visit 3).
- Obtain dispensing information (Visits 3, 4, 5, 6, 7, 9 and during OLE).
• Provide completion/taper/premature termination information (Visit 10).

Training will be given to all centers prior to the start of the study.

9.2.11 Patient Diary

A diary will be completed daily throughout the study. Patients or their caregivers will be instructed on how to complete the diary and will be asked to record information daily. The number and type of seizures and the severity of focal seizures as well as information on AEs, concomitant AEDs and rescue medication will be collected each day from baseline (Visit 2). Information on IMP intake will also be recorded each day from randomization (Visit 3) until completion of dosing or withdrawal (Visit 10/Withdrawal visit).

Seizure information, including the number and seizure subtype, as well as the severity of focal seizures and the number of episodes of status epilepticus will be collected through an IVRS telephone diary completed daily throughout the blinded phase of the study by the patient or their caregiver. This IVRS telephone diary will be completed on a weekly basis during the OLE. The patient or their caregiver will also complete a paper diary daily to record AEs, concomitant AEDs, IMP intake and rescue medication throughout the study.

The following seizure subtypes will be collected daily in the IVRS telephone diary:

• Focal motor seizures without impairment of consciousness or awareness#

• Focal seizures with impairment of consciousness or awareness#

• Focal seizures evolving to bilateral generalized convulsive seizures#

• Generalized seizures:
  – Tonic–clonic#
  – Tonic#
  – Clonic#
  – Atonic#

• ‘Other’ seizures:
  – Absence seizures**
  – Myoclonic seizures**
− Focal sensory seizures**
  − Infantile/epileptic spasms**
  • Episodes of status epilepticus

# To be included in primary seizure endpoint.
** To be included in composite ‘other’ seizure count.

For the purposes of calculating the composite seizure score, the severity of focal seizures will be assessed according to the following criteria:

• Type 1 - Focal motor seizures without impairment of consciousness or awareness.
• Type 2 - Focal seizures with impairment of consciousness or awareness.
• Type 3 - Focal seizures evolving to bilateral convulsive seizures.

9.2.12 Questionnaires and Assessments Completed at Scheduled Visits

Questionnaires should be completed by the patient or the caregiver, as appropriate. The same person should answer/complete the questionnaires/assessments in order to maintain consistency. The C-SSRS/Children’s C-SSRS (where applicable) will be administered by a trained rater.

9.2.12.1 Subject/Caregiver Global Impression of Change

The SGIC/CGIC, as appropriate, will be performed for all patients. At Visit 3 the patient or patient’s caregiver will be asked to write a brief description of the patient’s overall condition as a memory aid for the SGIC/CGIC at subsequent visits. It is preferred that the same person performs this assessment at each visit.

The CGIC comprises the following question to be rated on a seven-point scale:

• Since your child started treatment, please assess the status of your child’s overall condition (comparing their condition now to their condition before treatment) using the scale below.

The SGIC comprises the following question to be rated on a seven-point scale:

• Since you started treatment, please assess the status of your overall condition (comparing your condition now to your condition before treatment) using the scale below.
The markers are: Very Much Improved; Much Improved; Slightly Improved; No Change; Slightly Worse; Much Worse; Very Much Worse.

If the main caregiver is not available at the appropriate visit then this information can be captured over the telephone, ideally on the day of the visit or otherwise within three days.

### 9.2.12.2 Physician Global Impression of Change

The PGIC will be performed for all patients. At Visit 3 the investigator will be asked to write a brief description of the patient’s overall condition as a memory aid for the PGIC at subsequent visits. It is preferred that the same investigator performs this assessment at each visit.

The PGIC comprises the following question to be rated on a seven-point scale:

- Please assess the change in the patient’s general functional abilities since Visit 3 (prior to the commencement of study medication).

The markers are: Very Much Improved; Much Improved; Slightly Improved; No Change; Slightly Worse; Much Worse; Very Much Worse.

If the main caregiver is not available at the appropriate visit then this information can be captured over the telephone, ideally on the day of the visit or otherwise within three days.

### 9.2.12.3 Subject/Caregiver Global Impression of Change in Seizure Duration

The caregiver will be asked to assess the average duration of the patient’s seizures at Visit 3 (i.e., prior to commencement of IMP) as a memory aid for subsequent visits.

The SGIC-SD/CGIC-SD comprises a question to be rated on a three-point scale for each seizure subtype:

The markers are: Average duration of seizures has decreased; Average duration of seizures has stayed the same; Average duration of seizures has increased.

If the main caregiver is not available at the appropriate visit then this information can be captured over the telephone, ideally on the day of the visit or otherwise within three days.

**CGIC-SD**:
• Since the patient started treatment, please assess the average duration of the patient’s seizures (comparing their condition now to their condition before treatment) using the scale below.

**SGIC-SD:**

• Since you started treatment, please assess the average duration of your seizures (comparing their condition now to their condition before treatment) using the scale below.

### 9.2.12.4 Quality of Life in Childhood Epilepsy (18 Years of Age and Younger) or Quality of Life in Epilepsy (19 Years of Age and Older)

The QOLCE and the QOLIE-31-P are composed of 16 and 31 subscales, respectively, assessing seven domains of Health Related Quality of Life (physical function, social function, emotional well-being, cognition, behavior, general health and general quality of life). The QOLCE (and QOLIE-31-P, if completed by the caregiver) must be completed by a person who interacts with the patient on a consistent, daily basis. Quality of life assessments will be performed for all patients. The questionnaires should take 20–30 minutes to complete.


The Vineland-II is an individually administered instrument for assessing adaptive behaviors. Communication, Daily Living Skills, Socialization, and Motor Skills will be assessed by the caregiver using a rating scale. Vineland-II assessments will be performed for all patients.

### 9.2.12.6 Child/Adult Behavior Checklist

Achenbach CBCL and ABCL, for ages 1½–5, 6–18 and 18–59 examine internalizing behaviors (such as depression and anxiety), externalizing behaviors (such as aggression), stress, obsessive-compulsive behaviors and ‘sluggish cognitive tempo’. Statements about the patient’s behavior are recorded on a Likert scale: 0 = Not True, 1 = Somewhat or Sometimes True, 2 = Very True or Often True.

The age appropriate checklist will be used for all patients.

### 9.2.12.7 Social Communication Questionnaire

The current version of the SCQ will be completed by the caregiver for all patients above the age of 4 years with a mental age of at least 2 years. The scale provides
sub-scores to assess the domains Reciprocal Social Interaction, Communication and Restricted, Repetitive and Stereotyped Patterns of Behavior. The scale assesses behavior over the most recent three month period using 40 questions, each to be answered ‘yes’ or ‘no’.

9.2.12.8 Suicidality/Children's/Columbia-Suicide Severity Rating Scale (Six Years of Age and Older)

Suicidality will be assessed either by using the C-SSRS/Children’s C-SSRS or, in patients with profound cognitive impairment, by the investigator’s clinical judgment following interview of the patient. Where the C-SSRS/Children’s C-SSRS is not considered appropriate and clinical interview is used instead, the reason must be clearly documented by the investigator.

The definitions of behavioral suicidal events used in this scale are based on those used in the Columbia Suicide History Form. Questions are asked on suicidal behavior, suicidal ideation and intensity of ideation. During the screening visit (Visit 1), questions will be in relation to lifetime experiences, and all subsequent questioning will be in relation to the last assessment (Since Last Visit).

The C-SSRS is to be completed by the investigator or his/her qualified delegate at every visit as indicated in the Schedule of Assessments (see APPENDIX 1); “qualified delegate” is defined as anyone who has completed the C-SSRS training within the past two years or has continually administered the C-SSRS assessments throughout this trial since obtaining the training certificate. The survey should be completed by the same assessor, where possible, throughout the study. The Children’s C-SSRS will be used for patients aged 6–18 (inclusive) whilst the C-SSRS will be used for patients aged 19 and older.

9.2.12.9 Wechsler Tests

The Wechsler Tests are age specific and will only be administered at a sub-group of centers that have the expertise to conduct the assessments (ideally before any other study procedures but can be completed on a separate day, if necessary, within three days of the visit). Each assessment will need to be conducted by an experienced psychometrician. The age of the patient at entry will be the age used when choosing the items to be administered. Children and adults are to complete the tests as able. The following Wechsler Subtests will be used:

**Age 2–6:**
• WPPSI-4 - Vocabulary and Matrix Reasoning

**Age 6–Adult:**

• WASI-2 - Vocabulary and Matrix Reasoning
• WISC-4 and WAIS-4 Digit Span and Coding

### 9.2.13 Menstruation

Caregivers will be asked if the female patient is menstruating and details will be recorded as part of their baseline (Visit 3); any changes in normal cycles will be captured at Visit 10/Withdrawal visit and subsequent OLE visits.

### 9.2.14 Tanner Staging

The pubic hair growth (both sexes), genital (males only) and breast (females only) development of all adolescent patients (i.e., 10 to 17 years of age at the time of signing the informed consent form, or earlier if clinically indicated by onset of menarche or other signs of precocious puberty) will be assessed using Tanner Staging\(^5\) (see APPENDIX 2). The patients will undergo a discreet physical examination and be assigned a value under each category of Pubic Hair Growth (both sexes), Genitals (male patients only), and Breasts (female patients only).

Once a patient reaches a score of V (i.e., 5) the examination need not be performed again.

### 9.2.15 Investigational Medicinal Product Accountability

Records of IMP accountability will be maintained according to Section 5.3.4.

### 9.2.16 Adverse Events

Any adverse changes in the patient’s medical condition, following completion of the consent form by the patient, will be recorded on the CRF as AEs, questioning the patient further if necessary. All AEs\(^*\) occurring during the study, whether or not attributed to the IMP, observed by the investigator or reported by the patient will be recorded in the CRF.

*For the patient’s expected seizure types, these do not routinely require documentation as AEs. However, any worsening, including change in the pattern or severity of seizures, must be documented as an AE. As part of the ongoing safety review, the SMC will monitor any worsening of seizures, including change in the
pattern or severity. Any AE which meets SAE criteria should still be reported as a SAE.

SAEs must be reported to GW Pharmacovigilance Department (PVD) within 24 hours of discovery or notification of the event, and recorded in the CRF.

Refer to Section 12 for definitions, procedures and further information.

The number of inpatient hospitalizations that are, in the investigator’s opinion, due to epilepsy will be recorded in the patient’s CRF and through the SAE reporting process.

9.2.17 Monitoring of Abuse Liability (for Patients 12 Years of Age and Older)

There are two triggers that will require the investigator or study coordinator to discuss abuse potential signals with the patient or their caregiver. These are either AEs of interest that may be reported by the patient/caregiver, or drug accountability issues regarding overuse of the IMP or missing bottles. Different questionnaires will be completed by the site depending upon which trigger occurs (see Figure 9.2.17.4-1, Section 9.2.17.4). Irrespective of the above, all patients/caregivers will be interviewed at their final dosing visit (‘End of Treatment’/Withdrawal visit or ‘End of Taper Period’ visit, as applicable) of the blinded phase and again at their final dosing visit of the OLE, and a Study Medication Use and Behavior Survey will be completed by the investigator or study coordinator. Investigators and study coordinators will be provided with training on how to complete and perform the processes outlined in this section. This training must be completed and documented by the relevant site staff prior to implementation at site.

9.2.17.1 Monitoring of Adverse Events

AE information will be collected according to Section 9.2.16.

9.2.17.1.1 List of ‘Triggering Adverse Events of Interest’

During the collection of AEs, if the patient reports an AE consistent with any of the following categories, then the investigator or study coordinator is required to complete an additional Supplemental Adverse Event Form and a Site Classification Form (investigator only) following further discussion of the event(s) with the patient or their caregiver. The categories are:

- Euphoria or inappropriate elation.
- Inappropriate laughter or exhilaration.
• Mood changes.
• Drunk, high or intoxicated.
• Hallucinations (visual or auditory), dissociations, disorientation, agitation.
• Disturbance in cognition, memory, or attention.
• Drug abuse.
• Drug withdrawal or drug withdrawal syndrome.
• Addiction.
• Overdose.
• Misuse of IMP.
• Thoughts of suicide, attempted suicide or suicide.

An AE that is consistent with the above categories will be known as a ‘triggering AE of interest’ for the purposes of this study.

9.2.17.1.2 Supplemental Adverse Event Form

This form consists of 15 questions regarding the AE and use of IMP. It is completed as part of an interview with the patient/caregiver when a triggering AE of interest is reported. It is important that this is completed by a trained investigator or study coordinator with the patient/caregiver present. The answers on the Supplemental Adverse Event Form will then be transcribed into the patient’s CRF for the study. If the Supplemental Adverse Event Form cannot be completed at the time the triggering AE of interest is reported, then the site should contact the patient/caregiver to obtain the required answers as soon as possible.

9.2.17.1.3 Monitoring Drug Accountability Discrepancies

Any time after enrollment until final collection of study data, drug accountability discrepancies are monitored as follows:

• At routine Drug Accountability collection times:
  the site personnel will collect the IMP clinical supplies and make sure the usage is in line with the expectations reported within the paper diary.

• At any time that the site is informed by either the IVRS or by the patient/caregiver about any overuse of IMP, suspected misuse, abuse, or diversion.
9.2.17.1.4 List of ‘Triggering Drug Accountability Discrepancies’

If there are any discrepancies in drug accountability as outlined by the criteria below, known as ‘triggering drug accountability discrepancies’, then the trained investigator or study coordinator will complete a Supplemental Drug Accountability Form and Site Classification Form (investigator only) following further discussion of the event(s) with the patient/caregiver. The triggering drug accountability discrepancies are as follows:

- Missing bottle(s).
- Compliance issues where one or more bottles are used compared to what was the expected use, according to the paper diary.
- Returned IMP supply with evidence of tampering.
- Greater than the target daily dose as recorded in the paper diary.

9.2.17.1.5 Supplemental Drug Accountability Form

This form consists of eight questions regarding various aspects of drug accountability and patient usage. It is completed as part of an interview with the patient/caregiver when a triggering drug accountability discrepancy is identified. It is important that this is completed by a trained investigator or study coordinator with the patient/caregiver present. The answers on the Supplemental Drug Accountability Form will then be transcribed into the patient’s CRF for the study. The accountability reporting procedures will still occur. If the Supplemental Drug Accountability Form cannot be completed at the time the triggering drug accountability discrepancy is identified, then the site should contact the patient/caregiver by telephone to obtain the required answers as soon as possible. (Note: IMP refers to GWP42003-P, not other concomitant medications).

9.2.17.2 Site Classification Form

The investigator should review the applicable Supplemental Adverse Event Form or Supplemental Drug Accountability Form, and then complete the Site Classification Form. For each Supplemental Adverse Event Form or Supplemental Drug Accountability Form completed, there should be an associated Site Classification Form.

The Site Classification Form requires the investigator to assign the finding to an appropriate classification and then to also assign the possible relationship to the IMP.
The investigator is also required to indicate the level of the certainty of the classification. The answers from the Site Classification Form will then be transcribed into the patient’s CRF for the study.

9.2.17.3 Study Medication Use and Behavior Survey

This form consists of 18 questions regarding the use of the IMP. The trained investigator or study coordinator will complete this survey as an interview with the patient/caregiver at the final dosing visit (‘End of Treatment’/Withdrawal visit or ‘End of Taper Period’ visit, as applicable) of the blinded phase and again at the final dosing visit of the OLE. The answers on the Study Medication Use and Behavior Survey will then be transcribed into the patient’s CRF for the study.

The Study Medication Use and Behavior Survey will be completed for all patients 12 years of age and older in the study and not only those that have reported a triggering AE or drug accountability discrepancy.

9.2.17.4 Adjudication Committee: Assessment of Abuse Potential of GWP42003-P

A formal Adjudication Committee will be appointed and assigned to this initiative to classify triggered cases. The Adjudication Committee will meet on a periodic basis to review and assess all of the information collected on triggered cases.

A detailed charter will be agreed, which will describe the roles, responsibilities and duties of the members of Adjudication Committee. The Committee will review all of the information collected in the process and in the assessment of the abuse potential of GWP42003-P, such as:

- All triggering AE information.
- Supplemental Adverse Event Form (if applicable).
- All triggering drug accountability discrepancies.
- Supplemental Drug Accountability Form (if applicable).
- Site Classification Form.
- Study Medication Use and Behavioral Survey.
- Additional information from site(s) as requested by the Committee.
The Adjudication Committee will assess all of the information. It will form a position on the classification of each event and will write a study-related report, detailing the conclusions and recommendations.

The overall process is summarized in Figure 9.2.17.4-1.
Figure 9.2.17.4-1  Flow Diagram for Identifying and Evaluating Clinical Trial Adverse Event Data Through Systematic Categorization, Tabulation and Analysis which can Illuminate an Abuse Potential Signal (for Patients 12 Years of Age and Older)

Stage 1

- Patients with ‘Triggering Adverse Events of Interest’
- Patients with ‘Triggering Drug Accountability Discrepancy’
- All patients

Stage 2

- When a Triggering Adverse Event of Interest is identified, a patient interview is conducted with the Supplemental Adverse Event Form and, if applicable, the Supplemental Drug Accountability Form.
- When a Triggering Drug Accountability discrepancy is identified, a patient interview is conducted with the Supplemental Drug Accountability Form and, if applicable, the Supplemental Adverse Event Form.

Stage 3

- Investigator completes a Site Classification Form after supplemental information is collected, drug accountability evaluated, and the patient evaluated. One Site Classification Form is completed per Supplemental Adverse Event Form or Drug Accountability Form.

Stage 4

- Site completes Study Medication Use and Behavior Survey at end of dosing.

Stage 5

Adjudication Committee

Evaluates all of the information collected (as detailed above in stages 1–4) in the assessment of the abuse potential of GWP42003-P and completes a report.

Committee submits a report to GW.
10 WITHDRAWAL

In accordance with the Declaration of Helsinki\textsuperscript{56}, the ICH Tripartite Guideline for GCP Topic E6(R2)\textsuperscript{52}, the U.S. FDA regulations relating to good clinical practice and clinical trials\textsuperscript{57,58,59}, the European Union (EU) Clinical Trials Directive\textsuperscript{60}, the EU Good Clinical Practice (GCP) Directive\textsuperscript{61} and/or other applicable regulations, a patient has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

The patient must be withdrawn from the study if any of the following apply:

- Administrative decision by the investigator, GW, or a Regulatory Authority.
- Pregnancy.
- Protocol deviation that is considered to compromise potentially the safety of the patient.
- Withdrawal of patient consent/assent.
- Withdrawal of parent(s)/legal representative consent.
- ALT or AST $> 3 \times ULN$ with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($> 5\%$).
- ALT or AST $> 8 \times ULN$.
- ALT or AST $> 5 \times ULN$ for more than two weeks.
- ALT or AST $> 3 \times ULN$ and (TBL $> 2 \times ULN$ or INR $> 1.5$).
- Lost to follow-up.

Note: Prior to withdrawal for the transaminase elevations noted above, the investigator may choose to confirm the transaminase elevations by repeating the following laboratory tests within 24 to 48 hours: ALT, AST, TBL, INR, $%$eosinophils, gamma-glutamyl transferase and alkaline phosphatase. Should the above transaminase elevation criteria be confirmed, the patient must be withdrawn from the trial. In cases where the transaminase elevation withdrawal criteria are not met or confirmed, the dose of IMP or a concomitant AED with known hepatotoxicity should be reduced following discussion with the GW medical monitor.
Patients may also be withdrawn from the study for any of the following:

- Did not meet eligibility criteria.
- Patient non-compliance.
- AE (including clinically significant laboratory result) which, in the opinion of the investigator, would compromise the continued safe participation of the patient in the study.
- Suicidal ideation or behavior of type 4 or 5 during the treatment period, as evaluated with the C-SSRS.
- Any evidence of drug abuse or diversion.
- General anesthesia (blinded phase only).
- Addition of a new AED (blinded phase only).

Should a patient request or decide to withdraw from the study, all efforts must be made to complete all assessments of the End of Treatment/Withdrawal Visit (see Section 9.1.1.10 for withdrawals within the double-blind phase and Section 9.1.2.10 for withdrawals within the OLE phase). All observations should be reported as thoroughly as possible up to the date of withdrawal. Patients withdrawing due to an AE should be followed up according to Section 12.7. All information should be reported in the applicable CRF pages (refer to Section 9.2). Wherever possible, a post-study follow-up visit should take place 28-days after last dose of IMP (refer to Section 9.1.1.12 and Section 9.1.2.13). If withdrawing patients decline to give a reason for withdrawal of consent, the investigator must respect the patient’s wishes.
11 URGENT SAFETY MEASURES

The sponsor and investigator may take appropriate urgent safety measures in order to protect the patients of a clinical trial against any immediate hazard to their health or safety. If such measures are taken by the investigator they must notify GW immediately or at least within 24 hours of awareness. GW will report urgent safety measures to Regulatory Authorities by telephone within 24 hours of awareness, wherever possible, and will provide a written report to the Regulatory Authorities and EC/IRB within three days.
12 ADVERSE EVENT REPORTING

12.1 Definitions

12.1.1 Adverse Event

For the purposes of this study an AE is defined as:

Any new unfavorable/unintended signs/symptoms (including abnormal laboratory findings when relevant), or diagnosis or worsening of a pre-existing condition, which occurs following screening (Visit 1) and at any point up to the post-treatment, safety follow-up visit (Visit 12 and Visit OLE Follow-up), which may or may not be considered to be related to the IMP. Any event that is the result of a study procedure must be recorded as an AE.

Surgical/Investigational procedures are not AEs. The medical reason for the procedure is the AE. Elective hospitalizations for pre-study existing conditions or elective procedures are not AEs. The exception may be if the patient has an AE during hospitalization which prolongs their scheduled hospital stay in which case it would be considered a SAE (refer to Section 12.2).

If reporting a fatal event, the SAE term should be the underlying cause of the death (e.g., disease or medical condition leading to death).

12.1.2 Investigator

The term investigator refers to the study PI or a formally delegated study physician.

12.2 Serious Adverse Events

During clinical investigations, AEs may occur which, if suspected to be IMP-related, might be significant enough to lead to important changes in the way the IMP is developed (e.g., change in dose, population, monitoring need, consent/assent forms). This is particularly true for events that threaten life or function. Such SAEs will be reported promptly to Regulatory Authorities, applicable ECs/IRBs and investigators (expedited reporting) by GW.

An AE must only be classed as serious, i.e., a SAE, when the event falls into one of the following criteria:

- Results in death.
- Is life-threatening*.
Requires inpatient hospitalization or prolongation of existing hospitalization.

Results in persistent or significant disability/incapacity.

Is a congenital anomaly/birth defect.

Is medically significant**.

* The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which, hypothetically, might have caused death if it were more severe.

** Medical and scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. Important medical events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The sponsor considers all convulsive and non-convulsive status epilepticus events to be medically significant and should be reported to the Sponsor as medically significant SAEs.

12.3 Reporting Procedures for Serious Adverse Events

All SAEs occurring during the study must be reported to GW with any other supporting information and recorded in the AE section of the CRF. Any ongoing SAEs should be followed up until resolution wherever possible. For all deaths, the working diagnosis or cause of death as stated on a death certificate, available autopsy reports and relevant medical reports should be sent to GW promptly.

All SAEs must be reported directly to the GW PVD within 24 hours of discovery or notification of the event. All SAE information must be recorded in the SAE Report forms provided in the center files and faxed to the GW PVD. Additional information received for a case (follow-up or corrections to the original case) need to be detailed on a new SAE Report form, signed/dated and faxed to the GW PVD and the AE section of the CRF must be updated.

The investigator is not obliged to actively monitor for any new SAEs which occurred after the last formal follow-up observational period (Visit 12 or OLE Follow-up).
However, if the investigator becomes aware of any deaths or a new IMP-related SAE occurring within 28 days of the final dose of IMP, these should be reported to the GW PVD.

Any other problem discovered outside these time limits (Visit 12 or OLE Follow-up) which is deemed to be an unexpected safety issue and is likely to have an impact on patients who have taken part in the study must be treated as an SAE and reported to the GW PVD. Such post-study SAEs do not need to be recorded in the patient’s CRF if editing rights to the CRF have been removed due to final study data lock. GW PVD may request safety follow-up information after the final study visit in order to investigate a potential safety issue.

Contact details for the GW PVD are provided at the front of the center files for all study centers, and upon the GW SAE Report form.

12.4 Pregnancy

Any patient, or patient’s partner, who has become pregnant whilst receiving IMP, or within 90 days of last dose of IMP, must be reported to the GW PVD, using the GW Pregnancy Monitoring forms provided. Where possible the investigator should provide the outcome of the pregnancy.

Pregnancy reports must be sent to the GW PVD using the fax number for SAE reporting (see Appendix 3.2) within 24 hours of becoming aware.

The investigator is not obliged to actively monitor for any pregnancies that commence more than 90 days after the final dose of IMP. However, if the investigator becomes aware of a new pregnancy outside this time limit then they should report it as above. The GW PVD will follow up for all pregnancy outcomes.

12.5 Causality Assessment

Causality assessment is required for all AEs and SAEs. Causality assessment must only be assigned by the investigator. All cases judged as having a reasonable suspected causal relationship to the IMP must be reported as such. The expression “reasonable causal relationship” is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

The following question which must be answered by the investigator for all AEs is used to capture the reasonable causal relationship of an event to the IMP:

“In your opinion is there a plausible relationship to the IMP?” The answer is either “yes” or “no”.
Events that start before the first dose of IMP (pre-treatment) should be considered as not causally related. Where a pre-treatment event worsens in severity following the first dose of IMP, a new event record should be entered into the CRF.

Considering the explanation given above, investigators are strongly encouraged to express their opinion on what the cause of an AE might be. For individual patients, the investigator is usually in the best position to assess the underlying suspected cause of an AE. For all AEs, and especially SAEs, it is important that the investigator assess not only the possible role of the IMP but also other potential contributing factors. Factors for consideration of the underlying cause may include:

- Medical and disease history.
- Lack of efficacy/worsening of treated condition.
- Concomitant or previous treatment.
- Withdrawal of IMP.
- Protocol-related procedure.

12.6 Reporting Procedures for All Adverse Events

All AEs (including SAEs) occurring during the study will be reported on the running logs in the AE section of the CRF. This includes all events from the time following screening (Visit 1) up to and including the post-study follow-up visit (Visit 12 or OLE Follow-up), whether or not attributed to IMP and observed by the investigator or patient.

The following information will need to be provided for all AEs:

A) Adverse Event (Diagnosis or Syndrome if Known, or Signs and Symptoms)

Where the investigator cannot determine a diagnosis, signs or symptoms should be recorded in the AE section of the CRF. Once a diagnosis has been determined the AE section of CRF must be updated to reflect the diagnosis in replacement of the original symptoms. In circumstances where only a provisional diagnosis is possible (working diagnosis), the CRF must be updated to reflect the provisional diagnosis in replacement of the original symptoms. In some circumstances it may be relevant for the investigator to include the symptoms alongside the diagnosis in the verbatim event description. However, the diagnosis (full or provisional) should be clearly stated (e.g., headache and fever due to pneumonia).
B) Adverse Event Start Date and Stop Date

The start and stop dates of the event must be provided. All AEs require these fields to be completed in full. Partial dates or missing dates are not normally acceptable and significant effort must be undertaken to obtain any unknown information. If a precise date is not known an estimated date should be provided instead. When a complete date cannot be given then record as much information as possible (i.e., month and year or, in exceptional circumstances, just year). When the actual start date becomes known the CRF must be updated to replace the previously recorded date.

C) Outcome

The outcome of the event must be recorded accurately and classified into one for the following categories:

- Recovered.
- Recovered with sequelae.
- Continuing.
- Patient died.

D) Severity

When describing the severity of an AE the terms mild, moderate, or severe should be used. Clinical judgment should be used when determining which severity applies to any AE.

If the severity of an AE fluctuates day-to-day, e.g., a headache or constipation, the change in severity should not be recorded each time; instead, only the worst observed severity should be recorded with AE start and stop dates relating to the overall event duration, regardless of severity.

A severe AE is not the same as a SAE. For example, a patient may have severe vomiting but the event does not result in any of the SAE criteria above. Therefore, it should not be classed as serious.

E) Causality

See Section 12.5 above.

F) Action Taken with Study Medication

This question refers to the action taken with the IMP due to an AE. The action with the IMP must be classed as:
• None.
• Dose reduced temporarily.
• Dose reduced.
• Study medication interrupted.
• Study medication stopped.

12.7 Follow-up Procedures for Adverse Events

The investigator may be asked to provide follow-up information to the GW PVD for any AEs reported or during the investigation of potential safety issues. Such requests for additional safety information may occur post Visit 11 or OLE Follow-up after the study.

AEs considered related to the IMP by the investigator or the sponsor should be followed up until resolution or the event is considered stable.

It will be left to the investigator’s clinical judgment whether or not an AE is of sufficient severity to require the patient’s removal from treatment. A patient may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. Further details of withdrawal are presented in Section 10. If either of these occurs, the patient must undergo an end of treatment assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable. If a safety concern is identified following withdrawal of a participant, GW may contact the investigator for additional follow-up information.

12.8 Potential Cases of Drug-induced Liver Injury

All investigational centers are required to submit to the GW PVD the laboratory results for any patient after randomization that meet the criteria for the selected laboratory parameters as follows:

• ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).
• ALT or AST > 8 × ULN.
• ALT or AST > 5 × ULN for more than two weeks.
• ALT or AST > 3 × ULN and (TBL > 2 × ULN or INR > 1.5).
These reports must be sent to the GW PVD using the same fax number for SAE reporting within 24 hours of becoming aware of the results. In addition, please send a copy of the patient’s baseline laboratory results with all reports to the GW PVD.

Abnormal values in AST and/or ALT concurrent with abnormal elevations in TBL that meet the criteria outlined above are considered potential cases of drug-induced liver injury and will be considered as protocol defined criteria for withdrawal and important medical events. The investigator will arrange for the patient to return to the investigational site as soon as possible (within 24–48 hours of notice of abnormal results) for repeat assessment of ALT, AST, TBL, alkaline phosphatase and gamma-glutamyl transferase, detailed history and physical examination. Patients should be followed in this way until all abnormalities have normalized (in the investigator’s opinion) or returned to the baseline state; however, if the above transaminase elevation criteria are confirmed by the first set of follow-up laboratory tests, the patient must be withdrawn from the trial.

Elevations in ALT or AST > 3 × ULN or TBL > 2 × ULN alone are not considered potential cases of drug-induced liver injury, but will be followed as detailed above, within 72 hours’ notice of abnormal results. If the participant cannot return to the investigational center, repeat assessments may be done at a local laboratory and the results sent to GW PVD.

12.9 Notification of Safety Information to Investigators, Regulatory Authorities and Ethics Committees.

In accordance with the EU Clinical Trials Directive60, relevant parts of the FDA Code of Federal Regulations62 and any national regulations, GW will inform investigators, Regulatory Authorities and relevant ECs/IRBs of all relevant safety information. This will include the reporting of relevant SAEs and all Suspected Unexpected Serious Adverse Drug Reactions (SUSARs).

This information will be provided through three sources:

1) IB: a compilation of the clinical and non-clinical safety data available on the IMP that is relevant to the study. The IB is updated annually.

2) Development Core Safety Information: this document forms the safety section of the IB51, or is updated as an addendum to the IB51. This document is revised if necessary, when new important safety information becomes available (potentially up to a few times a year).
3) Council for International Organizations of Medical Sciences (CIOMS) reports: these reports are issued every time a SUSAR is reported to GW. They provide information on individual case reports and are sent to all the Regulatory Authorities, the relevant central ECs/IRBs which have approved the study and investigators. As required, the investigator should notify their regional ECs/IRBs of SAEs or SUSARs occurring at their center and other AE reports, i.e., CIOMS reports and any additional safety documentation received from GW, in accordance with local procedures.

In the USA, investigators are normally required to promptly report to their IRBs all unanticipated problems involving risks to human patients, or others, including AEs that should be considered unanticipated problems. Based on current FDA guidance the following clarification is provided in determining what constitutes an unanticipated problem:

In general, an AE observed during the conduct of a study should be considered an unanticipated problem involving risk to patients and reported to the IRB, only if it were unexpected, serious, and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent/assent, or IB). An individual AE occurrence ordinarily does not meet these criteria because, as an isolated event, its implications for the study cannot be understood.

In The Netherlands, all SAEs observed during the conduct of a study will be reported within the stipulated timelines to the De Medisch Ethische Toetsingscommissie/Centrale Commissie Mensgebonden Onderzoek only if it were considered an unanticipated problem involving risk to patients and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent/assent, or IB). All other SAEs will be reported in a cumulative summary as part of the Development Safety Update Report and updated on a yearly basis. This does not replace the ongoing obligation to report any SUSARs originating in The Netherlands, which do not meet the above criteria, to the accredited Medical Research Ethics Committee and competent authority.

The FDA guidance states that, accordingly, to satisfy the investigator’s obligation to notify the IRB of unanticipated problems, any investigators participating in a
multicenter study may rely on the sponsor’s assessment and provide to the IRB a report of the unanticipated problem prepared by the sponsor.

GW will inform investigators, Regulatory Authorities and relevant ECs/IRBs of any safety issues or case reports that are considered to be unanticipated and provide such reports as mentioned above. It should be noted that a single SUSAR report notified to investigators in the study does not necessarily constitute an unanticipated problem unless identified by GW in the submission cover letter.

As a minimum, the recipient will be sent all of the above and relevant updates between the period from ethical approval and final database lock.
13 STATISTICAL CONSIDERATIONS

A statistical analysis plan (SAP) will be produced prior to unblinding of the study. Any deviations from the original SAP will be described in the final clinical study report.

13.1 Sample Size, Power and Significance Levels

Blinded Phase:
A total of 210 patients will be enrolled. The 210 patients will be randomly allocated to one of four treatment groups (GWP42003-P 25 mg/kg/day, GWP42003-P 50 mg/kg/day, placebo 25 mg/kg/day dose volume equivalent, or placebo 50 mg/kg/day dose volume equivalent) at a 2:2:1:1 ratio. The placebo groups will be pooled for the analyses of efficacy.

If it is assumed that patients in the placebo group will experience a mean reduction in seizure frequency of 15% (from baseline), patients receiving GWP42003-P will experience at least a 50% reduction in seizures and a common standard deviation of 60%, then this sample size of 70 patients per group will be sufficient to detect a difference in response distributions with 90% power. This test is based on a two-sided non-parametric Wilcoxon-Mann-Whitney test for continuous response data with a 5% significance level.

Open-label Extension:
All patients who wish to continue on IMP following the blinded phase.

13.2 Interim Analysis

Blinded Phase:
No interim analysis is planned for this study. The blinded phase of this study will be locked and unblinded prior to completion of the OLE. The SAP covering the blinded phase will be finalized prior to unblinding the blinded phase.

Open-label Extension:
A cut of the OLE data will be used to support New Drug Application and Marketing Authorization Application filings. Further data cuts may be conducted as required.
13.3 Analysis Sets

Blinded Phase:

There will be up to three analysis sets in the blinded phase:

Intention to Treat (ITT)

- All patients who are randomized, receive IMP in the study and have post-baseline efficacy data will be included and analyzed according to their randomized treatment group.
- The ITT analysis set is the primary analysis set for all efficacy endpoints.

Per Protocol (PP)

If there are a sufficient number of significant protocol deviations in the study, a PP analysis set may also be presented.

- All patients who complete the study with no protocol deviations deemed to compromise the assessment of efficacy will be included and analyzed according to the treatment group they were randomized. The rules determining the PP analysis set will be fully defined prior to unblinding of the database.

Safety

All patients who received at least one dose of IMP in the study will be included and analyzed according to the treatment received. Only patients for whom it has been confirmed that they did not take any IMP will be excluded from this safety analysis set.

Open-label Extension:

There will be one analysis set in the open-label extension phase:

Safety

All patients who received at least one dose of IMP in the open-label extension phase of the study will be included. Only patients for whom it has been confirmed that they did not take any IMP in the OLE phase will be excluded from this safety analysis set.

13.3.1 Protocol Deviations

Protocol deviations will be listed and reasons for exclusion from the analysis populations will be summarized.
13.4 General Considerations

Unless stated otherwise, continuous variables will be summarized showing the number of non-missing values \(n\), mean, standard deviation, median, minimum and maximum and categorical variables will be summarized showing the number and percentage of patients falling in each category.

Unless otherwise specified, tables for the blinded phases will be summarized by randomized treatment group, and for the OLE phase will be summarized overall.

13.5 Accountability and Background Characteristics

13.5.1 Enrollment and Disposition

All patients (screened, enrolled/randomized, prematurely terminated IMP) will be accounted for in the enrollment and disposition summary tables.

13.5.2 Baseline and Demographic Characteristics

Age, sex, ethnic origin (as allowed per local regulations) and any other demographic or baseline characteristics, including history of epilepsy and epilepsy-specific genetic testing, will be summarized, using appropriate summary statistics.

13.5.3 Medical History

Previous and current medical conditions will be summarized by System Organ Class (SOC), including details of epilepsy.

13.5.4 Concomitant Medication

Concomitant medications (including standard AED and rescue medication) taken prior to and during the study will be summarized separately, by medication class and active ingredients.

13.6 Endpoints and Statistical Methods

Blinded Phase:

Statistical hypothesis testing will be performed on the primary endpoint and other endpoints as appropriate. Each endpoint, including the primary will have 2 comparisons against placebo (25 mg/kg/day GWP42003-P and 50 mg/kg/day GWP42003-P vs. placebo). Also, 3 key secondary endpoints have been defined.
The primary and key secondary endpoints will be tested with their Type I error controlled by use of a hierarchical gate-keeping procedure, in the sequence given in Table 13.6-1. One must reject the null hypothesis of an endpoint at the level of 0.05 (2-sided) to test the hypothesis of the subsequent endpoint in the sequence at the level of 0.05 (2-sided). If a null hypothesis is not rejected then testing will stop and all subsequent analyses will be declared not statistically significant.

<table>
<thead>
<tr>
<th>Test</th>
<th>Endpoint</th>
<th>Treatment Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Change from baseline in number of TSC-associated seizures</td>
<td>25 mg/kg/day GWP42003-P vs. Placebo</td>
</tr>
<tr>
<td>2</td>
<td>50% responder analysis</td>
<td>25 mg/kg/day GWP42003-P vs. Placebo</td>
</tr>
<tr>
<td>3</td>
<td>Change from baseline in number of TSC-associated seizures</td>
<td>50 mg/kg/day GWP42003-P vs. Placebo</td>
</tr>
<tr>
<td>4</td>
<td>50% responder analysis</td>
<td>50 mg/kg/day GWP42003-P vs. Placebo</td>
</tr>
<tr>
<td>5</td>
<td>Change in CGIC/SGIC</td>
<td>25 mg/kg/day GWP42003-P vs. Placebo</td>
</tr>
<tr>
<td>6</td>
<td>Change from baseline in total seizures</td>
<td>25 mg/kg/day GWP42003-P vs. Placebo</td>
</tr>
<tr>
<td>7</td>
<td>Change in CGIC/SGIC</td>
<td>50 mg/kg/day GWP42003-P vs. Placebo</td>
</tr>
<tr>
<td>8</td>
<td>Change from baseline in total seizures</td>
<td>50 mg/kg/day GWP42003-P vs. Placebo</td>
</tr>
</tbody>
</table>

### 13.6.1 Evaluable Period

**Blinded Phase:**

The start of the evaluable period of the study (Day 1) is defined as the first day the patient took IMP, as recorded on the CRF, or the day of randomization if this date is unknown.

The end of the evaluable period is defined as the earliest of:

- Day 113 of treatment for the IVRS reported efficacy data and the day of Visit 10 for the CRF-based efficacy data;
- The last day on which study IMP was taken (as stated on the study outcome CRF) for the IVRS reported efficacy data and the day after this for the CRF-based efficacy data;
- The day before a relevant change in prohibited or AED medications was made.

**Open-label Extension:**

All data collected during this phase will be summarized across time, using appropriate descriptive statistical methods. Changes from pre-randomization baseline will also be presented. Treatment compliance and exposure to treatment will also be summarized.
13.6.2 Primary Endpoint(s)

Blinded Phase:

The primary endpoint is the change in number of seizures* during the treatment period (maintenance and titration) compared to baseline in patients taking GWP42003-P compared with placebo.

*Seizures include: focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures (tonic–clonic, tonic, clonic or atonic) that are countable.

Data will be analyzed using negative binomial regression on the sum of the seizure counts during the treatment period. However, seizure frequency (average per 28 days) and percentage change in seizure frequency will be presented using summary statistics. A mixed effect model with repeated measures will be performed modelling the observed number of seizures in the baseline period and treatment period implemented within the framework of general linear models using the negative binomial response distribution. The model will include stratified age group (1–6 years, 7–11 years, 12–17 years and 18–65 years), time, treatment arm and treatment arm by time interaction as fixed effects and patient as a random effect. The log transformed number of days in which seizures were reported will be included as an offset. The time variable corresponds to an indicator for the baseline period and treatment period. The estimated ratio of least squares means for treatment period to baseline period and 95% confidence intervals (CIs) will be presented for each treatment arm. In addition, the estimated ratio of each GWP42003-P group to placebo and 95% CIs will be presented along with the p-value testing the null hypothesis that this ratio is 1.

The hypothesis testing approach for controlling the Type I error is described in Section 13.6 and Table 13.6-1.

If a patient withdraws from the study, then the primary analysis variable will be calculated from the available data, during the treatment period, prior to the patient withdrawing.

Open-label Extension:

The primary endpoint is the safety of GWP42003-P, evaluated by assessing the incidence, type and severity of AEs. Data will be presented as per Section 13.6.5.2.
13.6.2.1 Sensitivity Analysis for the Primary Endpoint

Blinded Phase:

The following sensitivity analyses will be conducted for the primary endpoint for the blinded phase:

- Wilcoxon rank-sum test on percentage change from baseline in seizure frequency during the treatment period. An estimate of the median differences between each GWP42003-P group and placebo, together with approximate 95% CIs, will be calculated using the Hodges–Lehmann approach.

- Primary endpoint analysis repeated using the PP analysis set.

- Primary endpoint analysis repeated using the maintenance period (Day 29 to the end of the evaluable period) rather than the treatment period.

- Primary endpoint analysis repeated using the worst case of last observation carried forward (LOCF), next observation carried backward (NOCB) and the mean from the non-missing data for each patient to impute missing data arising from unreported days in IVRS.
  
  - Any intermittent missing data for the number of seizures arising from unreported days in IVRS will be imputed using the worst (highest number of seizures) of the following for each patient: LOCF, NOCB and the mean daily number of seizures during the treatment period based on non-missing data:

    \[
    \text{Number of seizures} \div \text{Number of reported days in IVRS}.
    \]

- A rank ANCOVA on percentage change from baseline in number of seizures (average per 28 days) during the treatment period.
  
  - The ranks of the percentage change from baseline and the baseline number of seizures (average per 28 days) will be calculated. The rank of the percentage change from baseline will then be analyzed using an ANCOVA model with the rank of the baseline number of seizures (average per 28 days) and age group (1–6 years, 7–11 years, 12–17 years and 18–65 years) as covariates and treatment group as a fixed factor. The estimated least squares means, treatment differences, together with the 95% CIs and p-value will be presented.

- ANCOVA of log transformed number of seizures (average per 28 days) during the treatment period.
− The number of seizures (average per 28 days) during the treatment period and the baseline number of seizures (average per 28 days) will be log transformed prior to analysis. The log transformed number of seizures (average per 28 days) during the treatment period will then be analyzed using an ANCOVA model with the log transformed baseline number of seizures (average per 28 days) and age group as covariates and treatment group as a fixed factor. The back transformed estimated treatment ratios, together with the 95% CIs and p-value will be presented.

− If there are any patients with no seizures post-baseline, then 1 will be added to the number of seizures (average per 28 days) for all patients prior to log transformation.

• Primary endpoint analysis repeated using each 4 weeks of the maintenance period (Week 1 to 4, Week 5 to 8 and Week 9 to 12 of the 12-week maintenance period) rather than the treatment period.

− This analysis will include only patients who have at least 7 days of seizure data within each corresponding 4-week period.

• Wilcoxon rank-sum test on percentage change from baseline in number of seizures (average per 28 days) during the treatment period, using multiple imputation (MI) to impute data under the Missing Not at Random (MNAR) assumption.

− MNAR will be assumed for missing values resulting from two scenarios, discontinuation due to AEs, and discontinuation due to any reason in the GWP42003-P dose groups and missing at random (MAR) for others, including other patients discontinued in the GWP42003-P dose groups and patients in the placebo group.

− MI will be performed on the seizure frequency, based on time points corresponding to each 14 calendar days of the treatment period. Intermittent missing values for intermediate 14-day time points before the last 14-day time-point will be imputed using the MCMC method in SAS PROC MI with an IMPUTE=MONOTONE statement for 100 times for each treatment group separately. Then, monotone missing data assumed under the MAR assumption at time-point t (i.e., patients in the placebo group and patients in the GWP42003-P groups who did not discontinue due to AEs or for any reason) will be imputed using the MI procedure with the ‘MONOTONE REG’ option, for each treatment group separately. The
imputation model will include baseline seizure frequency and each 14-day time-point up to time-point $t$ (in chronological order). With the data imputed from above, monotone missing data of patients in the GWP42003-P groups under the MNAR assumption will be imputed. At each 14-day time-point $t$, the input dataset for the MI procedure will include all placebo patients and those patients from the GWP42003-P groups that have values missing under MNAR at that time-point. The imputation model will include seizure frequency at baseline and each 14-day time-point up to time-point $t$ (in chronological order) and will be performed for each GWP42003-P group separately.

Full details for this sensitivity analysis will be provided in the SAP.

### 13.6.3 Secondary Endpoint(s)

The following endpoints will be compared between treatment groups over the treatment period, for the blinded phase, and during the open-label extension phase relative to the pre-randomization baseline of the blinded phase:

**Antiepileptic Efficacy Measures:**

**Key:**

- Number of patients considered treatment responders defined as those with a $\geq 50\%$ reduction in seizure frequency (blinded phase only).
- Change in CGIC or SGIC score.
- Change in total seizures.

The hypothesis testing approach for controlling the Type I error for these endpoints are described in Section 13.6 and Table 13.6-1.

**Other:**

- Percentage change from baseline in number of seizures (average per 28 days; OLE phase only).
- Number of patients considered treatment responders defined as those with a $\geq 25\%, \geq 50\%$ (OLE phase only), $\geq 75\%$ or $100\%$ reduction in seizure frequency.
- Number of patients experiencing a $> 25\%$ worsening, $-25$ to $+25\%$ no change, $25$–$50\%$ improvement, $50$–$75\%$ improvement or $> 75\%$ improvement in seizure frequency.
• Change in number of seizure-free days.
• Change in number of ‘other’ seizures (absence, myoclonic, focal sensory and infantile/epileptic spasms).

Growth and Development (patients less than 18 years):
• Change in serum IGF-1 levels.
• Change in Tanner Staging score (for patients aged 10–17 [inclusive]).

Quality of Life:
• Changes in the QOLCE (patients 2–18 years) or QOLIE-31-P (patients 19+ years) score.
• Change in PGIC score.

Blinded Phase:

The number of patient responders (including the key secondary endpoint) and the number of patients seizure-free will be summarized and analyzed using a Cochran–Mantel–Haenszel test stratified by age group. In addition, the difference in proportions and the odds ratio, together with 95% CIs, comparing the treatment groups will be presented.

For number of seizure-free days, use of rescue medication, number of episodes of status epilepticus (only if there is a sufficient number of patients with data), Vineland-II, Wechsler scales, CBCL, ABCL, SCQ, QOLCE and QOLIE-31-P scores, the data will be summarized at baseline and over the treatment period, and at each time-point (or 28-day period, as appropriate) during the maintenance period. Changes from baseline to the average over the treatment period (or at end of study) will be analyzed using ANCOVA (or appropriate non-parametric methods if data are found to be not normally distributed). The models will include baseline and age group as covariates and treatment group as fixed factor. The treatment difference, together with the 95% CIs will be presented.

The changes in composite focal seizure score, change in total seizures, the number of seizures by subtype and the number of ‘other’ seizures will be analyzed using the same analysis as the primary endpoint.

SGIC-SD/CGIC-SD, SGIC/CGIC and PGIC assessments recorded at the end of treatment will be analyzed with ordinal logistic regression using the proportional odds model.
Changes from baseline for IGF-1 levels will be summarized by treatment group and plotted against the Tanner Stages, weight, and height.

Tanner Stages will be evaluated and summarized descriptively at each time-point in terms of frequency and proportions. Number (%) of patients with changes in Tanner Stages will be summarized by treatment group.

In order to explore the robustness of the primary analysis, further sensitivity analysis (in addition to that already detailed in Section 13.6.2.1) may be specified in the SAP.

**Open-label Extension:**

Secondary endpoints will be summarized across time, using appropriate statistical methods. Descriptive statistical methods will be used throughout. There will be no formal hypothesis testing.

**Exploratory Endpoints:**

**Antiepileptic Efficacy Measures:**

- Change in composite focal seizure score (frequency × severity).
- Change in number of seizures by subtype.
- Change in use of rescue medication.
- Change in the number of episodes of *status epilepticus* (convulsive and non-convulsive).
- Changes in duration of seizure subtypes as assessed by the Subject Global Impression of Change in Seizure Duration (SGIC-SD) or the Caregiver Global Impression of Change in Seizure Duration (CGIC-SD).

**TAND:**

**Cognitive and Behavioral Function:**

- Changes in Wechsler Scales (pre-school, primary, children, adult).
- Changes in Achenbach Child Behavior Checklist (CBCL) and Adult Behavior Checklist (ABCL).

**Autistic Features:**

- Change in Social Communication Questionnaire (SCQ) score.
PK (Blinded Phase Only):

- The plasma concentrations will be summarized by time window for CBD and its major metabolites following single and multiple doses of GWP42003-P. Where data allows, the area under the plasma concentration curve (AUC$_{0-t}$) from time zero to the last measurable time-point will be calculated.

- Plasma concentrations of concomitant AEDs before and after treatment with GWP42003-P, where available.

13.6.4 Pharmacokinetics

Plasma concentrations for CBD and its major metabolites, following single and multiple doses of GWP42003-P will be summarized by treatment group. Estimates of PK parameters will also be summarized using the appropriate statistics. Where available, plasma concentrations of concomitant AEDs will be summarized.

13.6.5 Safety

In the presentation of safety data for the blinded phase, data from the two cohorts of placebo patients (25 mg/kg/day and 50 mg/kg/day dosing volumes) will be presented separately and pooled together. This will allow the possibility to explore any effects of the volume of IMP on safety endpoints.

13.6.5.1 Treatment Compliance and Extent of Treatment Exposure

Treatment compliance and exposure to treatment will be summarized.

13.6.5.2 Adverse Events

AEs will be coded according to the Medical Dictionary for Regulatory Activities dictionary.

A treatment emergent AE is one that started, or worsened in severity or seriousness, following the first dose of IMP.

Descriptive presentations of treatment emergent AEs will be given by preferred term and SOC for the safety analysis. The number of patients reporting at least one AE will be provided.

The following summaries will be produced:

- All-causality AEs.
13.6.5.3 Clinical Laboratory Data

Clinical laboratory data at screening, during and at the end of treatment and the change from baseline to end of treatment will be summarized for the safety analysis set using appropriate summary statistics. Categorical shift tables will also be presented, showing the numbers of patients with values outside the normal range. Baseline for the open-label extension will be pre-randomization baseline.

13.6.5.4 Vital Signs, 12-Lead Electrocardiogram, Physical Examination and Other Safety Data

Vital signs, ECG, physical examination, number of inpatient hospitalizations and C-SSRS data will be summarized for the safety analysis set, at screening, baseline and at each time point during the treatment period using appropriate summary statistics. Changes in the vital signs and number of inpatient hospitalizations from baseline to end of treatment will also be summarized. Details of menstruation cycles (in females) will be summarized and listed as appropriate.
14 SAFETY MONITORING COMMITTEE

An independent Safety Monitoring Committee (SMC) will be used in this study. Details of the composition and standard operating procedures of the SMC will be detailed in a separate charter.

Furthermore, an independent ESC will be instated to verify the seizure types of screened patients on an ongoing basis. Investigators will submit a documented history of TSC directly to the ESC for verification of seizure types. The ESC will provide written documentation directly to the investigator and guidance on seizure types, if applicable, for inclusion in the patient file. Details of the composition and standard operating procedures of the ESC will be detailed in a separate charter.
15 REGULATORY AND ETHICAL OBLIGATIONS

15.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the current version and subsequent amendments of the Declaration of Helsinki, the ICH Tripartite Guideline for GCP Topic E6(R2), the EU Clinical Trials Directive, the EU GCP Directive and the clinical trial regulations adopting European Commission Directives into national legislation.

15.2 Informed Consent/Assent

An initial generic ICF consent and assent form will be prepared by GW and provided to the investigator, who will tailor these for their center by adding the center’s contact details and by using headed paper. The GW Clinical Manager will communicate updates to the template by letter. The written informed consent/assent documents should be prepared in the language(s) of the potential patient population.

Before a patient’s involvement in the trial, the investigator is responsible for obtaining written informed consent/assent (if allowed per local regulations) from the patient and/or along with written parent(s)/legal representative consent after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study and before any protocol specific screening procedures or any IMPs are administered. The patient and/or parent(s)/legal representative should have ample time for review to consider the information provided before giving written consent/assent, more specific definitions of ample time may be in force if required by ECs/IRBs or local regulations.

The acquisition of informed consent/assent should be documented in the patient’s medical records and the ICF should be signed and personally dated by the patient and/or parent(s)/legal representative (as applicable) and by the person who conducted the informed consent/assent discussion. GW also requires a physician to be present for consent/assent and to sign the consent/assent forms. The original signed ICF should be retained and a copy provided to the patient and/or parent(s)/legal representative.

15.3 Ethics Committee/Institutional Review Board

A copy of the protocol, proposed ICF, other patient information material, any proposed advertising material and any further documentation requested must be
submitted to the EC/IRB for written approval. GW must receive a copy of the written approval of the protocol and ICF before recruitment of patients into the study and shipment of IMP.

The investigator must submit and, where necessary, obtain approval from the EC/IRB for all subsequent protocol amendments and changes to the informed consent/assent documents. The investigator should notify the EC/IRB of deviations from the protocol, SAEs occurring at the center and other AE reports received from GW, in accordance with local procedures.

The investigator will be responsible for obtaining ongoing EC/IRB approval/renewal throughout the duration of the study. Copies of the investigator’s reports and the EC/IRB continuance of approval must be sent to GW.

### 15.4 Pre-study Documentation Requirements

The investigator is responsible for forwarding the following documents to GW for review before allowing any patients to consent/assent for entry into the study:

- Signed and dated protocol signature page.
- Copy of EC/IRB-approved ICF and other patient information material.
- Copy of the EC/IRB approval of the protocol, ICF and other patient information material.
- Up to date curricula vitae and medical licenses (as per local regulations) of the PI and all sub-investigators.
- The EC/IRB composition and/or written statement of the EC/IRB in compliance with the FDA regulations relating to GCP and clinical trials\(^{57,58,59,68}\), the EU Clinical Trials Directive\(^{60}\), the EU GCP Directive\(^{61}\), or the ICH Tripartite Guidelines for GCP Topic E6(R2)\(^{52}\) where the EU Clinical Trials and GCP Directives do not apply.
- Signed laboratory normal ranges and documentation of laboratory certification (or equivalent) unless using central laboratory arranged by GW.
- Signed clinical trial agreement (including patient/investigator indemnity insurance and financial agreement).
- Form FDA 1572, if required.
- Drug Enforcement Administration license (where applicable).
15.5 **Patient Confidentiality**

The investigator must ensure that the patient’s anonymity is maintained. In the CRFs and within the IVRS databases used to collect the trial data or other documents submitted to GW, patients should be identified by their initials and ethnic origin (if allowed per local regulations) and their study screening number only. Documents that are not for submission to GW, e.g., signed ICFs, should be kept in strict confidence by the investigator.

In compliance with the FDA regulations relating to good clinical practice and clinical trials\(^57,58,59,68\), and the EU Clinical Trials Directive\(^60\)/ICH Tripartite Guidelines for GCP Topic E6(R2)\(^52\), it is required that the investigator and institution permit authorized representatives of the company, the Regulatory Authorities and the EC/IRB have direct access to review the patient’s original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform the patient that his/her study-related records will be reviewed by the above-named representatives without violating the confidentiality of the patient.

All information concerning the IMP and operations of GW such as patent applications, formulae, manufacturing processes, basic scientific data or formulation information supplied to the investigator by the company and not previously published is considered confidential by the company and shall remain the sole property of the company. The investigator will agree to use this information only in accomplishing the study and will not use it for any other purposes without the written consent of the company.
16 ADMINISTRATIVE AND LEGAL OBLIGATIONS

16.1 Protocol Amendments and End of Study or Termination

Protocol amendments must be made only with the prior approval of GW. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent/assent documents. The EC/IRB and Regulatory Authorities must be informed of all amendments and give approval for any substantial amendments. Amendments for administrative changes can be submitted to the EC/IRB for information only. The investigator must send a copy of the approval letter from the EC/IRB to GW.

Both GW and the investigator reserve the right to terminate the study, according to the clinical trial agreement. The investigator should notify the EC/IRB in writing of the study’s completion or early termination and send a copy of the notification to GW.

16.2 Study Documentation and Storage

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections in CRFs will be included on the GW Delegation of Authority and Signature form.

Source documents are original documents, data and records from which the patient’s CRF data are obtained. These include, but are not limited to, hospital records, clinical and office charts, laboratory and pharmacy records, diaries, electronic data captured by IVRS, microfiches, radiographs and correspondence. CRF entries may be considered source data if the CRF is the site of the original recording; that is, there is no other written or electronic record of data. A source data verification plan, identifying the source for each data point at each center, will be agreed with each center prior to patient recruitment. In the rare situations of data being recorded directly into the CRF in error, then the source data from the CRF should be transcribed into the patient’s notes with appropriate signature and date to provide a full audit trail.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related, essential documentation (as outlined in the ICH Tripartite Guidelines for GCP Topic E6(R2)\(^52\), section 8.2), suitable for inspection at any time by representatives from GW and/or applicable Regulatory Authorities. Elements should include:
- Patient files containing completed CRFs, ICFs and supporting copies of source documentation.

- Study files containing the protocol with all amendments, IB, copies of pre-study documentation (see Section 15.4) and all correspondence to and from the EC/IRB and GW.

- Proof of receipt, IMP accountability record, return of IMP for destruction, final IMP reconciliation statement and all drug-related correspondence.

In addition, all original source documents supporting entries in the CRFs, diary data and electronic data captured by IVRS must be maintained and be readily available.

Following completion or termination of a clinical study, GW will initiate proper archive of clinical study-related documentation and electronic records generated by the investigator and/or GW. All clinical trial-related documents and electronic records will be retained within an archiving system for a period dependent upon need and for a minimum of 25 years. Essential documents should be retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least two years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or if needed by GW.

GW will inform the investigators for each center in writing of the need for record retention. No study document should be destroyed without prior written agreement between GW and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify GW in writing of the new responsible person and/or the new location.

### 16.3 Study Monitoring and Data Collection

The GW representative and Regulatory Authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study, e.g., CRFs and other pertinent data, provided that patient confidentiality is respected.

The GW study monitor, or designee, is responsible for inspecting the CRFs and available IVRS/diary data at regular intervals throughout the study to verify adherence to the protocol, completeness, accuracy and consistency of the data and adherence to local regulations on the conduct of clinical research. The study monitor
should have access to patient medical records and other study-related records needed to verify the entries in the CRFs.

The investigator agrees to co-operate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

To ensure the quality of clinical data across all patients and centers, a clinical data management review will be performed on patient data received at GW or a contract research organization (CRO). During this review, patient data will be checked for consistency, omissions and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and FDA regulations\textsuperscript{57,58,59,68}, ICH Tripartite Guidelines for GCP Topic E6(R2)\textsuperscript{52} and all other applicable regulatory requirements. To resolve any questions arising from the clinical data management review process, data queries and/or center notifications will be sent to the center for completion and then returned to GW or the CRO, as applicable.

16.4 Electronic Data collected by Interactive Voice Response System

Source data for the assessments collected via IVRS will be managed by the service provider in accordance with ICH Tripartite Guidelines for GCP Topic E6(R2)\textsuperscript{52} and in adherence to a quality management system. All data will be stored in a secure (e.g., redundant hardware, password control, limited physical access to servers), fully audit trailed environment with appropriate industry standard back-up and off-site storage practices.

Access for patients providing assessments and investigators will be authenticated and meet industry standards and comply with the requirements outlined in the FDA Code of Federal Regulations Title 21, Part 11, Subpart B (Electronic Records)\textsuperscript{68}.

After database lock, all investigators will receive a certified copy of all IVRS assessment data. These data will be in an agreed, read-only format with a covering letter explaining the content of the data, a quality statement from the IVRS provider and the investigator’s responsibilities.

Regulatory and sponsor auditors will have the ability to review, but not modify, IVRS data via an agreed means of access.

16.5 Quality Assurance

In accordance with the FDA regulations\textsuperscript{57,58,59,68}, EU Clinical Trials Directive\textsuperscript{60}/ICH Tripartite Guidelines for GCP Topic E6(R2)\textsuperscript{52} and the sponsor’s audit plans,
representatives from GW’s Clinical Quality Assurance Department may select this study for audit. Inspection of center facilities, e.g., pharmacy, drug storage areas, laboratories, and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, the EU Clinical Trials Directive\textsuperscript{60}/ICH Tripartite Guidelines for GCP Topic E6 (R2)\textsuperscript{52} and applicable regulatory requirements.

**16.6 Compensation**

GW will indemnify the investigator and the study center in the event of any claim in respect of personal injury arising due to a patient’s involvement in the study, providing that the study protocol has been adhered to. This would include claims arising out of or relating to the administration of the IMP or any clinical intervention or procedure provided for or required by the protocol to which the clinical study patient would not otherwise have been exposed, providing there is no evidence of negligence on behalf of the investigator or their team. GW will not be liable for any claims arising from negligence on the part of the investigator or their team.

**16.7 Publication Policy**

GW recognizes that there is a responsibility under the regulatory guidelines to ensure that results of scientific interest arising from this clinical study are appropriately published and disseminated. They will co-ordinate this dissemination and may solicit input and assistance from the chief/principal investigators. A summary of the results of this study will be made available on [http://www.clinicaltrials.gov](http://www.clinicaltrials.gov), as required by U.S. Law.

The raw data from this study may be obtained by the PIs or by their steering committee representatives on request. Should they wish, PIs are allowed to conduct their own analyzes and are permitted to present such information along with methods and results of the clinical study at symposia, national or regional professional meetings and to publish it in theses or dissertations.

All publications, e.g., manuscripts, abstracts, oral/slide presentations or book chapters based on this study, must be submitted to the GW Medical Writing Department and, as applicable, GW Publication Committee for corporate review before release. To ensure adequate time for GW to make comments and suggestions where pertinent, all such material should be submitted to them at least 60 days prior to the date for submission for publication, public dissemination, or review by a publication
committee. The PIs must then incorporate all reasonable comments made by GW into the publication.

GW also reserves the right to delay the submission of such information by a period of up to six months from the date of first submission to them in order to allow them to take steps to protect proprietary information where applicable.

16.8 Intellectual Property Rights

All Intellectual Property Rights owned by or licensed to either GW or the PIs, other than those arising from the clinical study, will remain their property. All Intellectual Property Rights arising out of the clinical study will vest in or be exclusively licensed to GW and, as such, the PI should promptly disclose all knowledge to GW and refrain from using such knowledge without the prior written consent of GW.

16.9 Confidential Information

GW and the PI should ensure that only personnel directly concerned with the study should be party to confidential information and that any information coming to either party about the other during the course of the study should be kept strictly confidential and should not be disclosed to any third party or made use of without the prior written consent of the other.
17 REFERENCES


11. The Tuberous Sclerosis Alliance [Internet]. [cited 2015 Apr 01];Available from: http://www.tsalliance.org/


48 GWMD09112 Clinical Study Report. A randomized, partially-blind, placebo-controlled, pilot, dose-ranging study to assess the effect of Cannabidiol (CBD) on liver fat levels in subjects with fatty liver disease. 28 November 2013.
54 Clinical Trial Facilitation Group recommendations related to contraception and pregnancy testing in clinical trials. September 2014.


### APPENDIX 1  SCHEDULE OF ASSESSMENTS

#### Blinded Phase

<table>
<thead>
<tr>
<th>Visit Number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12 (Tel.)</th>
<th>Safety Calls*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>-35</td>
<td>-28</td>
<td>1</td>
<td>15</td>
<td>29</td>
<td>43</td>
<td>57</td>
<td>71</td>
<td>85</td>
<td>113</td>
<td>123</td>
<td>151</td>
<td></td>
</tr>
<tr>
<td>Visit Window</td>
<td></td>
<td>+3</td>
<td>+3</td>
<td>+3</td>
<td>+3</td>
<td>+3</td>
<td>+3</td>
<td>+3</td>
<td>+3</td>
<td>+3</td>
<td>+3</td>
<td>+3</td>
<td>+3</td>
</tr>
<tr>
<td>Informed consent/assent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eligibility Criteria</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital signs and BP</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postural BP</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination (including height and body weight)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>X</td>
<td>X$^5$</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical laboratory blood sampling</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical laboratory IGF-1 testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Clinical laboratory urine sampling (dipstick urinalysis)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine/serum THC screen</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy tests (if appropriate)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit Number</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>12 (Tel.)</td>
<td>Safety Calls*</td>
</tr>
<tr>
<td>--------------</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Day</td>
<td>-35</td>
<td>-28</td>
<td>15</td>
<td>29</td>
<td>43</td>
<td>57</td>
<td>71</td>
<td>85</td>
<td>113</td>
<td>123</td>
<td>151</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit Window</td>
<td>±7</td>
<td>+3</td>
<td>±3</td>
<td>±3</td>
<td>±3</td>
<td>±3</td>
<td>±3</td>
<td>±3</td>
<td>±3</td>
<td>±3</td>
<td>+3</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>Pharmacokinetic blood sampling</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AED concentration</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSC1 and TSC2 mutation status (if unknown and consent is given)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Concomitant medications</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Inpatient epilepsy-related hospitalizations</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Suicidality/C-SSRS/Children’s C-SSRS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Vineland-II</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGIC/CGIC</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGIC</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGIC-SD/CGIC-SD</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QOLCE/QOLIE-31-P</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wechsler Tests</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBCL/ABCL</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCQ</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanner Staging (where appropriate)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstruation question (where appropriate)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit Number</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>12 (Tel.)</td>
<td>Safety Calls*</td>
</tr>
<tr>
<td>--------------</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>----</td>
<td>----</td>
<td>----------</td>
<td>---------------</td>
</tr>
<tr>
<td>Day</td>
<td>-35</td>
<td>-28</td>
<td>1</td>
<td>15</td>
<td>29</td>
<td>43</td>
<td>57</td>
<td>71</td>
<td>85</td>
<td>113</td>
<td>123</td>
<td>151</td>
<td></td>
</tr>
<tr>
<td>Visit Window</td>
<td>±7</td>
<td>+3</td>
<td>±3</td>
<td>±3</td>
<td>±3</td>
<td>±3</td>
<td>±3</td>
<td>±3</td>
<td>±3</td>
<td>+3</td>
<td>+3</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>Patient IVRS and paper diary review (seizures, AE information, concomitant AEDs, rescue medication, IMP dosing)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>IVRS and diary training</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>IMP dispensing</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Collection of IMP</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>IMP compliance review</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Study Medication Use and Behavior Survey</td>
<td>X†</td>
<td>X†</td>
<td>X†</td>
<td>X†</td>
<td>X†</td>
<td>X†</td>
<td>X†</td>
<td>X†</td>
<td>X†</td>
<td>X†</td>
<td>X†</td>
<td>X†</td>
<td></td>
</tr>
</tbody>
</table>

*Telephone safety calls will be completed every two days during titration, one week after the end of titration and, for patients not entering the OLE, weekly from Visit 10 to Visit 12. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead.

‡ ECG must be re-assessed four hours (±30 minutes) post-dose.

♦ Only for patients weighing > 20 kg.

† Performed at final dosing visit (End of Treatment/Withdrawal visit or End of Taper visit, as applicable) for patients 12 years of age and older only.
## Open-label Extension

<table>
<thead>
<tr>
<th>Visit Number</th>
<th>B1</th>
<th>B2</th>
<th>B3</th>
<th>B4</th>
<th>B5</th>
<th>B6</th>
<th>B7</th>
<th>B8</th>
<th>B9</th>
<th>B10</th>
<th>B11</th>
<th>B12</th>
<th>Follow up (Tel)</th>
<th>Safety Calls*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>1</td>
<td>15</td>
<td>36</td>
<td>92</td>
<td>141</td>
<td>183</td>
<td>232</td>
<td>274</td>
<td>323</td>
<td>365</td>
<td>375</td>
<td>389</td>
<td>403</td>
<td></td>
</tr>
<tr>
<td>Visit Window</td>
<td>±3</td>
<td>±3</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>+3</td>
<td>±3</td>
<td>+3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed consent/assent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital signs and BP</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postural blood pressure</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination (including height and body weight)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical laboratory blood sampling</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical laboratory IGF-1 testing</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical laboratory urine sampling (dipstick urinalysis)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy tests (if appropriate)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AED concentration</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant medications</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatient epilepsy-related</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit Number</td>
<td>B1</td>
<td>B2</td>
<td>B3</td>
<td>B4</td>
<td>B5</td>
<td>B6</td>
<td>B7</td>
<td>B8</td>
<td>B9</td>
<td>B10</td>
<td>B11</td>
<td>B12</td>
<td>Follow up (Tel)</td>
<td>Safety Calls</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Day</td>
<td>1</td>
<td>15</td>
<td>36</td>
<td>92</td>
<td>141</td>
<td>183</td>
<td>232</td>
<td>274</td>
<td>323</td>
<td>365</td>
<td>375</td>
<td>389</td>
<td>403</td>
<td></td>
</tr>
<tr>
<td>Visit Window</td>
<td>±3</td>
<td>±3</td>
<td>±3</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±3</td>
<td>±3</td>
<td>±3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hospitalizations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicidality/C-SSRS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children’s C-SSRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vineland-II</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGIC/CGIC</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGIC</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGIC-SD/CGIC-SD</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QOLCE/QOLIE-31-P</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wechsler Tests</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBCL/ABCL</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCQ</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanner Staging (where</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>appropriate)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstruation question (</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>where appropriate)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient IVRS and paper</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diary review (seizures, AE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>information, concomitant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEDs, rescue medication,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMP dosing)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Visit Schedule

<table>
<thead>
<tr>
<th>Visit Number</th>
<th>B1</th>
<th>B2</th>
<th>B3</th>
<th>B4</th>
<th>Re-supply Visit</th>
<th>B5</th>
<th>B6</th>
<th>Re-supply Visit</th>
<th>B7</th>
<th>B8</th>
<th>Re-supply Visit</th>
<th>B9</th>
<th>End of Treatment</th>
<th>B10</th>
<th>End of Taper</th>
<th>B11</th>
<th>Post-taper Safety Telephone Call</th>
<th>B12</th>
<th>Follow up</th>
<th>Safety Calls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td></td>
<td>15</td>
<td>36</td>
<td>92</td>
<td>141</td>
<td>183</td>
<td>232</td>
<td>274</td>
<td>323</td>
<td>365</td>
<td>375</td>
<td>389</td>
<td>403</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit Window</td>
<td>±3</td>
<td>±3</td>
<td>±3</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>+3</td>
<td>±3</td>
<td>±3</td>
<td>+3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVRS and diary training</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMP dispensing</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collection of IMP</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMP compliance review</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Medication Use and Behavior Survey</td>
<td>X†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Telephone safety calls will be completed every two days during the blinded transition, titration and one week after the end of titration. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead.

†Performed at final dosing visit (End of Treatment/Withdrawal visit or End of Taper visit, as applicable) for patients 12 years of age and older only.
APPENDIX 2  TANNER STAGING

(Reproduced with permission from the New England Journal of Medicine)55.

The following is to be completed for all female adolescent patients (i.e., 10 to less than 18 years of age at the time of signing the informed consent/assent form, or earlier if clinically indicated by onset of menarche or other signs of precocious puberty).

Female Development & Pubic Hair

Please check the box next to the most appropriate stage; in the event that qualifying characteristics are not within the same stage, defer to the lesser stage as the overall Tanner Score.

Tanner Stage 1 (Prepubertal, typically 10 years and younger)

- No glandular tissue; areola follows the skin contours of the chest.
- No pubic hair at all.

Tanner Stage 2 (10–11.5 years)

- Breast bud forms, with small area of surrounding glandular tissue; areola begins to widen. †
• Small amount of long, downy hair with slight pigmentation on the labia
  majora.

**Tanner Stage 3 (11.5–13 years)**

• Breast begins to become more elevated, and extends beyond the borders of the
  areola, which continues to widen but remains in contour with surrounding
  breast.

• Hair becomes more coarse and curly and begins to extend laterally.

**Tanner Stage 4 (13–15 years)**

• Increased breast size and elevation; areola and papilla form a secondary
  mound projecting from the contour of the surrounding breast.

• Adult-like hair quality, extending across pubis but sparing medial thighs.

**Tanner Stage 5 (15+ years)**

• Breast reaches final adult size; areola returns to contour of the surrounding
  breast, with a projecting central papilla.

• Hair extends to medial surface of the thighs.

The following is to be completed for all male adolescent patients (i.e., 12 to less than
18 years of age at the time of signing the informed consent/assent form).

**Male Genital Development & Pubic Hair**

Please check the box next to the most appropriate stage.

**Tanner Stage 1 (Prepubertal, typically 9 years and younger)**

• Testicular volume less than 1.5 mL; small penis of 3 cm or less.

• No pubic hair at all.

**Tanner Stage 2 (9–11 years)**
• Testicular volume between 1.6 and 6 mL; skin on scrotum thins, reddens and enlarges; penis length unchanged.

• Small amount of long, downy hair with slight pigmentation at the base of the penis and scrotum.

**Tanner Stage 3 (11–12.5 years)**

• Testicular volume between 6 and 12 mL; scrotum enlarges further; penis begins to lengthen to about 6 cm.

• Hair becomes more coarse and curly and begins to extend laterally.

**Tanner Stage 4 (12.5–14 years)**

• Testicular volume between 12 and 20 mL; scrotum enlarges further and darkens; penis increases in length to 10 cm and circumference.

• Adult-like hair quality, extending across pubis but sparing medial thighs.

**Tanner Stage 5 (14+ years)**

• Testicular volume greater than 20 mL; adult scrotum and penis of 15 cm in length.

• Hair extends to medial surface of the thighs.
APPENDIX 3  STUDY PERSONNEL

Appendix 3.1  Investigator Details

At the time of protocol production, the participating investigators had not been confirmed. A list of all investigators will be maintained within the GW Master Files (electronically and added to the Trial Master File at the end of the study).

Appendix 3.2  Sponsor Contact Details

Pharmacovigilance Department — SAE Reporting:  
Fax: PPD  
USA Toll Free Fax: PPD  
Tel: PPD

Sponsor:  
GW Research Ltd  
Sovereign House  
Vision Park  
Chivers Way  
Histon  
Cambridge CB24 9BZ  
United Kingdom  
Tel: PPD  
Fax: PPD

Medical Monitor:  
Refer to Study Contact List in the site file.

Clinical Project Manager/Clinical Operations Director:  
GW Research Ltd  
Sovereign House  
Vision Park  
Chivers Way  
Histon  
Cambridge CB24 9BZ  
United Kingdom  
Tel: PPD  
Fax: PPD

Clinical Trial Supplies:  
G-Pharm Ltd  
Tel: PPD  
Fax: PPD
APPENDIX 4  IVRS CALLS FOLLOWING END OF TREATMENT/Withdrawal

Timings of IVRS calls to be made by the patient/caregiver following the date of End of Treatment/Withdrawal in the blinded or OLE phase are summarized overleaf.
<table>
<thead>
<tr>
<th>Relative Day</th>
<th>Blinded Phase(^a)</th>
<th>OLE Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of End of Treatment/Withdrawal(^b)</td>
<td>IMP Not Tapered</td>
<td>IMP Tapered</td>
</tr>
<tr>
<td>+1</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>+2</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>+3</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>+4</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>+5</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>+6</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>+7</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>+8</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>+9</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>+10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+27</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>+28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+37</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>+38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Gray shading denotes visit windows.

\(^a\) Only for patients who do not enter the OLE on the day of Visit 10 or for those who withdraw early from the blinded phase.

\(^b\) Date of End of Treatment/Withdrawal should match the date reported in interactive web/voice response system.
A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled seizures

Study Code: GWEP1521

EudraCT Number: 2015-002154-12

CLINICAL PROTOCOL AMENDMENT NUMBER: 7
to be incorporated into the Protocol, creating
CLINICAL PROTOCOL VERSION 8
DATE 23 APR 2019

GW Research Ltd
Sovereign House
Vision Park
Chivers Way
Histon
Cambridge CB24 9BZ
United Kingdom
Tel: PPD
Fax: PPD

Confidentiality Statement

This document contains confidential information of GW Research Ltd (GW) that must not be disclosed to anyone other than the recipient study staff and members of the institutional review board or independent ethics committee. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW.
2 RATIONALE

This clinical protocol amendment 7 (will be incorporated into the Protocol creating Clinical Protocol Version 8 Date 23 April 2019) addresses the following issue(s):

2.1 Change in Hierarchy for Analysis

Following review of the original hierarchy for analysis, the Global Impression of Change (GIC) and total seizure endpoints were deemed of lower critical importance compared with the TSC-associated seizure endpoints. Therefore, the GIC and total seizure endpoints were moved down in the hierarchy so that all TSC-associated seizure endpoints are tested first.

2.2 Minor Corrections and Clarifications

3 IMPLEMENTATION OF THE AMENDMENT

The changes detailed in this amendment will be issued as Clinical Protocol Version 8, Date 23 April 2019. It will be kept in the trial master file at GW as well as in each investigational center file and, if applicable, pharmacy site file.
A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled seizures

Study Code: GWEP1521

EudraCT Number: 2015-002154-12

CLINICAL PROTOCOL AMENDMENT NUMBER: 6
to be incorporated into the Protocol, creating CLINICAL PROTOCOL VERSION 7
DATE 06 SEPTEMBER 2018

GW Research Ltd
Sovereign House
Vision Park
Chivers Way
Histon
Cambridge CB24 9BZ
United Kingdom

Confidentiality Statement
This document contains confidential information of GW Research Ltd (GW) that must not be disclosed to anyone other than the recipient study staff and members of the institutional review board or independent ethics committee. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW.
2 RATIONALE

This clinical protocol amendment 6 (will be incorporated into the Protocol creating Clinical Protocol Version 7, Date 06 September 2018) addresses the following issue(s): Change in Primary Endpoint Analysis Method and Wording

A suitable modelling approach to seizure count data would be superior to the non-parametric Wilcoxon rank-sum test as it allows estimates of effect size that are meaningful and can easily be interpreted, can incorporate the stratification variable, can be used to explore potential effect modifying variables, and might be expected to provide more power. Exploration of data from previous epilepsy trials in Dravet syndrome and Lennox–Gastaut syndrome indicate that modelling of seizure counts implemented within the framework of general linear models, using the negative binomial response distribution, provides an optimal fit to the data. Additionally, this modelling approach also has advantages such as being able to model the exact seizure count during the treatment period, incorporating the number of days with data as an offset within the model, without requiring the seizure count to be transformed into a frequency prior to analysis. For example, if there are patients who withdraw early in the trial prior to experiencing a seizure, calculating a seizure frequency and percentage change could lead one to assume a patient had a 100% reduction in seizure frequency when in fact they might not have been evaluated for a sufficient amount of time. The negative binomial model accounts for the number of days each patient is evaluated for and so is not impacted. Accordingly, the proposed primary analysis method has been updated from the Wilcoxon rank-sum test to a negative binomial regression analysis.

As percentage change does not apply to negative binomial regression, the primary endpoint wording has been changed throughout the protocol to remove the words ‘percentage change’ as follows:

‘Percentage change from baseline in number of TSC-associated seizures* (average per 28 days) during the treatment period (maintenance and titration) in patients taking GWP42003-P compared with placebo.’

has been amended to:

‘Change in number of TSC-associated seizures* during the treatment period (maintenance and titration) compared to baseline in patients taking GWP42003-P compared with placebo.’
Similar changes have been made for percentage change in other seizure types under key secondary, other secondary, and exploratory endpoints.

2.2 Changes to the Proposed Sensitivity Analyses

The proposed sensitivity analyses have been changed as follows:

- Addition of the replaced primary analysis of Wilcoxon rank-sum test as a sensitivity analysis;
- Where appropriate, other sensitivity analyses using the Wilcoxon rank-sum test will now use the same method as the primary analysis (i.e., negative binomial regression).

3 IMPLEMENTATION OF THE AMENDMENT

The changes detailed in this amendment will be issued as Clinical Protocol Version 7, Date 06 September 2018. It will be kept in the trial master file at GW as well as in each investigational site file and, if applicable, pharmacy site file.
A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled seizures

Study Code: GWEP1521

EudraCT Number: 2015-002154-12

CLINICAL PROTOCOL AMENDMENT NUMBER: 5
to be incorporated into the Protocol, creating
CLINICAL PROTOCOL VERSION 6,
DATE 07 AUGUST 2018

GW Research Ltd
Sovereign House
Vision Park
Chivers Way
Histon
Cambridge CB24 9BZ
United Kingdom

Tel: PPD
Fax: PPD

Confidentiality Statement

This document contains confidential information of GW Research Ltd (GW) that must not be disclosed to anyone other than the recipient study staff and members of the institutional review board or independent ethics committee. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW.
2 RATIONALE

This clinical protocol amendment 5 (will be incorporated into the Protocol creating Clinical Protocol Version 6, Date 07 August 2018) addresses the following issue(s): Clarification of Eligibility Criteria

The primary objective of the trial is to evaluate the efficacy of GWP42003-P as add-on therapy in reducing the frequency of seizures when compared with placebo in patients with tuberous sclerosis complex (TSC). To comply with this, an inclusion criterion has been added to ensure that eligible patients must be taking one or more antiepileptic drugs (AEDs) at a dose which had been stable for at least four weeks prior to screening. In addition, as eligible patients must experience at least eight seizures during baseline, the inclusion criteria have been amended to clarify that eligible patients must have a well-documented clinical history of epilepsy which is not completely controlled by their current AEDs.

2.2 Correction of the Treatment Allocation Ratio

The treatment allocation ratio has been amended to clarify that patients will be allocated to one of four treatment groups (GWP42003-P 25 mg/kg/day, GWP42003-P 50 mg/kg/day, placebo 25 mg/kg/day dose volume equivalent, or placebo 50 mg/kg/day dose volume equivalent) at a 2:2:1:1 ratio, and that the two placebo groups will be pooled for the analyses of efficacy. The planned sample size has not changed.

2.3 Use of mTOR Inhibitors and General Anesthesia in the OLE

As everolimus (a mammalian target of rapamycin [mTOR] inhibitor) is approved in the European Union (and now also in the United States) for the treatment of refractory partial-onset seizures associated with TSC, oral mTOR inhibitors are excluded from use in the blinded phase of the trial. Similarly, due to its effects on seizure control, general anesthesia is excluded from use in the blinded phase.

As it would not be medically ethical to exclude on-label use of mTOR inhibitors (for the treatment of seizures or tumors) or general anesthesia following completion of the blinded phase, the protocol has been amended to clarify that their use is permitted in the open-label extension (OLE) in accordance with local licensing and after discussion and approval by the GW medical advisor(s).
2.4 Minor Corrections and Clarifications

The following minor corrections/clarifications have been made to the protocol:

- Removal of wording for investigational medicinal product (IMP) dispensing in countries where controlled drugs can only be prescribed for a maximum of 28 days’ treatment as this is not applicable to any of the countries in which the trial is being conducted.

- As there is now a 1 mL accuracy for measuring IMP instead of the quarter bottle estimate/range within interactive voice response system (IVRS), the dosing calculator is now the only accurate measure of expected IMP usage. Further details for determining expected usage will therefore be provided in the Pharmacy Manual rather than the protocol, where the text has been simplified.

- Clarification that the exploratory objective for the OLE phase does not involve comparison of GWP42003-P with placebo.

- Clarification that for all pregnancy tests, both serum and urine tests will be performed.

- Clarification that the blood draw for testing TSC1 and TSC2 mutation status can be performed only if the patient/parent(s)/legal representative provide consent.

- Clarification that the 4-hour post-dose 12-lead electrocardiogram (ECG) performed at Visit 3 (Randomization) has a ±30-minute time window.

- Clarification that pharmacokinetic (PK) blood samples must be taken at Visits 3 and 10 for patients weighing > 20 kg as follows: One sample pre-dose (i.e., prior to administration of IMP); one sample between 2 and 3 hours post-dose; one sample between 4 and 6 hours post-dose; and for patients 18 years and above only: one sample between 8 and 10 hours post-dose. There must be a minimum period of at least 2 hours between each of the blood sampling time points.

- Clarification that dose selection was based on the data available at the time of trial initiation.

- Clarification that if the maintenance dose of IMP becomes poorly tolerated or an adverse event (AE) occurs (e.g., somnolence, transaminase elevation not meeting withdrawal criteria specified in Sections 10 and 12.8 of the protocol), the investigator may consider temporarily or permanently reducing the dosage for the remainder of the maintenance period following discussion with the GW medical
advisor(s). In addition, in cases where the transaminase elevation withdrawal criteria are not met or confirmed, the dose of IMP or a concomitant AED with known hepatotoxicity should be reduced following discussion with the GW medical advisor(s).

- A footnote to Table 8.1.2-3 explains how the OLE Day 15 dose is derived.

- Clarification that the investigator must contact the GW medical monitor to discuss best management of potential drug-drug interactions arising during the blinded and OLE phases of the study, with decisions based on clinical symptoms and not plasma levels of AEDs. In addition, clarification that concomitant AED dose reductions are permitted on clinical grounds (e.g., due to AEs or transaminase elevations not meeting withdrawal criteria specified in Sections 10 and 12.8 of the protocol) following discussion with the GW medical advisor(s).

- For consistency with the Schedule of Assessments, the protocol has been amended to clarify that eligibility must be assessed at Visit 1 (Screening) and Visit 3 (Randomization) according to the criteria specified in Section 6 of the protocol.

- Clarification that although the attendance of the patient is preferred, it is not required for Visit 2 (Baseline) provided the primary caregiver is able to attend, and that this caregiver (not the patient) will be responsible for seizure identification, IVRS use, and paper diary completion.

- Clarification that the investigator must retain oversight of all safety telephone calls.

- Clarification of timings of IVRS calls to be made by the patient/caregiver following the date of End of Treatment/Withdrawal in the blinded and OLE phases.

- Clarification that only patients who successfully complete the blinded phase of the study will be invited to participate in the OLE.

- Clarification that patients in the US and Poland may have the opportunity to continue in the OLE beyond 1 year.

- Text in Section 9.1.2.2 has been corrected to state that patients will receive sufficient open-label IMP for three weeks' home dosing.
• Clarification that continued use of GWP42003-P following the ‘End of Treatment’ visit of the OLE refers to use of GWP42003-P outside of the GWEP1521 study.

• Simplification of language regarding provision of instructions for tapering the dose at Visit B10.

• Clarification that postural blood pressure assessments should be performed if it is possible for the patient to stand, and that the ECG will be performed after 5 minutes in a supine position, if this is possible.

• Clarification in Table 9.2.9-1 that international normalized ratio (INR) is derived from prothrombin time (PT).

• Clarification that meal times are to be recorded only for patients who undergo PK blood sampling.

• Clarification that in patients with profound cognitive impairment aged 6 years or older, where completion of the Columbia-Suicide Severity Rating Scale (C-SSRS) is not appropriate, suicidality is assessed by the investigator’s clinical judgment following interview of the patient. In addition, the text has been amended to clarify that for C-SSRS assessments, “qualified delegate” is defined as anyone who has completed the C-SSRS training within the past two years or has continually administered the C-SSRS assessments throughout the trial since obtaining the training certificate.

• The references section has been updated to cite the most recent versions of the regulatory guidelines and the CBD Investigator’s Brochure.

• Clarification that the Study Medication Use and Behavior Survey should be administered at the final dosing visit of the blinded phase and again at the final dosing visit of the OLE.

• Additional assessments for patients who withdraw early and taper IMP were listed in the Visit B11 section of the protocol but these apply to all patients who taper IMP.

• Clarification that the blinded phase of this study will be locked and unblinded prior to completion of the OLE and that the statistical analysis plan (SAP) covering the blinded phase will be finalized prior to unblinding the blinded phase. Cuts of the OLE data will be conducted as required.
• Clarification in the schedules of assessment that patient diary review includes review of both the patient’s IVRS data and paper diary.

• Clarification in the open-label phase schedule of assessments that vital signs assessments include measurement of blood pressure.

• For consistency within the protocol it has been clarified that informed assent is sought alongside informed consent.

• Correction, per Section 9.2.10, that IMP dispensing information for Visit B1 (Section 9.1.2.1) will not be provided by IVRS.

• Minor formatting/spelling/punctuation/grammatical corrections have been made to improve consistency and readability; however, in the interest of brevity, not all of these changes are captured in Section 4 of this amendment document.

3 IMPLEMENTATION OF THE AMENDMENT

The changes detailed in this amendment will be issued as Clinical Protocol Version 6, Date 07 August 2018. It will be kept in the trial master file at GW as well as in each investigational site file and, if applicable, pharmacy site file.
Study Title: A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled seizures

Study Code: GWEP1521

EudraCT Number: 2015-002154-12

CLINICAL PROTOCOL AMENDMENT NUMBER: 4

to be incorporated into the Protocol, creating
CLINICAL PROTOCOL VERSION 5, DATE 27 June 2017

GW Research Ltd
Sovereign House
Vision Park
Chivers Way
Histon
Cambridge CB24 9BZ
United Kingdom

Tel: PPD
Fax: PPD

Confidentiality Statement
This document contains confidential information of GW Research Ltd (GW) that must not be disclosed to anyone other than the recipient study staff and members of the institutional review board or independent ethics committee. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW.
2 RATIONALE

This clinical protocol amendment 4 (will be incorporated into the Protocol creating Clinical Protocol Version 5, Date 27 June 2017) addresses the following issue(s):

2.1 Amendments to Trial Design

- Secondary endpoints have been sub divided into three categories: key, other and exploratory, in order to better reflect the importance of each in the overall trial design and to enable prioritization during data analysis.

- The statistical analysis has been amended to reflect the re categorization of secondary endpoints. The hierarchy of analysis of key secondary endpoints has been clearly defined.

- Clarification of exclusion criteria relating to mTOR inhibitors to reflect their changing regulatory approval status.

- Provision has been made to extend the open-label extension for patients in the US and Poland. Patients in other countries will be able to access continued supply of investigational medicinal product (IMP) by alternative schemes.

- Administration of cannabidiol through a gastrostomy (G)/nasogastric (NG) feeding tube has been added as an option after consultation with the medical monitor. This will allow certain patients who are unable to swallow to possibly use the G/NG tube, since in vitro experiments demonstrated this route of feeding to be acceptable with medical guidance.

2.2 Minor Corrections and Clarifications

- Administrative updates have been made throughout for consistency (NB. in the interest of brevity, minor changes to grammar, punctuation or formatting are not all captured in this amendment document).

- The reference list has been updated to include the current version of the investigator brochure (IB) and safety information. The IMP background section of the protocol has also been updated to reflect the current version of the IB.
3  IMPLEMENTATION OF THE AMENDMENT

The changes detailed in this amendment will be issued as Clinical Protocol Version 5, Date 27 June 2017. It will be kept in the trial master file at GW as well as in each investigational center file and, if applicable, pharmacy site file.
Study Title: A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled seizures

Study Code: GWEP1521

EudraCT Number: 2015-002154-12

CLINICAL PROTOCOL AMENDMENT NUMBER: 3

to be incorporated into the Protocol, creating

CLINICAL PROTOCOL V4 05Dec16

GW Research Ltd
Sovereign House
Vision Park
Chivers Way
Histon
Cambridge CB24 9BZ
United Kingdom

Tel: PPD
Fax: PPD

Confidentiality Statement

This document contains confidential information of GW Research Ltd (GW) that must not be disclosed to anyone other than the recipient study staff and members of the institutional review board or independent ethics committee. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW.
2 RATIONALE

This Clinical Protocol Amendment 3 (will be incorporated into the Protocol creating Clinical Protocol V4 05Dec16) addresses the following issue(s):

2.1 Exclusion and Withdrawal Criteria

- The exclusion criterion wording in section 6 of the protocol pertaining to liver enzyme monitoring has been updated to not repeat two conflicting exclusions.

- The withdrawal criteria wording in section 10 of the protocol pertaining to liver enzyme monitoring now stipulates that patients with “Serum ALT or AST ≥ 3 × ULN and (TBL [serum total bilirubin] ≥ 2 × ULN or international normalized ratio [INR] > 1.5)” should be withdrawn from the trial. This amendment brings the protocol back in line with the current FDA guidance on liver enzyme related withdrawal criteria.

2.2 Minor Corrections and Clarifications

The following minor corrections/clarifications have been made to the protocol:

- Minor corrections made throughout – see table below and tracked changes

- Updated wording for the Clinical Hypothesis

- Additional wording regarding the different colored labels on the double-blind and open-label IMP

- Further clarification of the mechanism for simultaneous tapering down blinded IMP and titrating up OLE IMP.

- Deletion of the Tanner staging examination at Visit B6

- Addition of Creatine Kinase to the laboratory assessments
3 IMPLEMENTATION OF THE AMENDMENT

The changes detailed in this amendment will be issued as Clinical Protocol V4 05Dec16. It will be kept in the trial master file at GW as well as in each investigational center file and, if applicable, pharmacy site file.
Study Title: A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled seizures

Study Code: GWEP1521

EudraCT Number: 2015-002154-12

CLINICAL PROTOCOL AMENDMENT NUMBER: 2

to be incorporated into the Protocol, creating
CLINICAL PROTOCOL V3 25Aug16

GW Research Ltd
Sovereign House
Vision Park
Chivers Way
Histon
Cambridge CB24 9BZ
United Kingdom
Tel: PPD
Fax: PPD

Confidentiality Statement

This document contains confidential information of GW Research Ltd (GW) that must not be disclosed to anyone other than the recipient study staff and members of the institutional review board or independent ethics committee. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW.
2 RATIONALE

This Clinical Protocol Amendment 2 (will be incorporated into the Protocol creating Clinical Protocol V3 25Aug16) addresses the following issue(s): **Duration of Open-label Extension Phase**

The open-label extension (OLE) phase of the trial will last for a maximum of 1 year in all cases as GWP42003-P will continue to be supplied irrespective of marketing authorization.

2.2 Change to Frequency of Assessment Measures

- In order to reduce the overall burden of the study, the frequency of assessments (QOLCE/QOLIE-31P, PGIC, SGIC/CGIC, Weshler Tests, CBCL/ABCL, SCQ and the Vineland II) have been reduced.

- The Physician Global Impression of Change (PGIC) scale has now been described, which was omitted in the original protocol.

2.3 Change to Statistical Considerations

Each of the primary and secondary endpoints will be described and compared between treatment groups, using appropriate statistical methods, over the 16-week, double-blind maintenance and titration period.

- The primary analysis has been updated from an analysis of covariance to a Wilcoxon rank-sum test and the assumptions for this test require more patients. The target sample size has therefore increased to 210.

- A modified description has been included to describe how type I error will be controlled. Equal standing is to be given to 25 mg and 50 mg groups. An adjusted p value for significance (p<0.025) will be required if one of the comparisons is >0.05.

2.4 Pharmacokinetics Analysis

The timings for the PK blood samplings have been changed to try to capture the C\text{max} time point within the time/concentration curve. In addition, the description of the pharmacokinetic parameters that will be described has been changed to better reflect the low number of blood samples that are likely to be available.

THC will no longer be included, since the PK parameters of this minor constituent of GWP42003-P have been investigated thoroughly in previous GW sponsored studies.
2.5 Withdrawal Criteria

The “Did not meet eligibility criteria” bullet has been moved from must to may be withdrawn from the study, providing clarification that once a patient has been enrolled onto the study, they are in the intention to treat group and will stay in the study unless there is a safety concern.

2.6 Endpoint Definitions

The primary and secondary endpoints have been more clearly defined:

- Confirmation that the primary endpoint is focused on TSC-associated seizures.
- Confirmation that secondary endpoints are divided into “Key” and “other” and clarity in their definitions.
- Confirmation that change in total seizures will be included in the other secondary endpoints.

2.7 Concomitant Medications

It is theoretically possible that GWP42003-P may modify the metabolism of other drugs (including AEDs) administered concurrently and there remains the possibility of pharmacological interactions between GWP42003-P and other concurrently administered drugs. Therefore, the following clarifications have been made for management of possible drug-drug interactions:

- For entry to the study, if patients are taking felbamate then they must have been taking it for at least one year.
- Management of possible interactions must be on emerging clinical symptoms with discussion with the GW medical advisor.
- Care should be taken with drugs, or their metabolite, that are cytochrome P450 (CYP) 2C19 substrates or those solely or primarily metabolized by UDP-glucuronosyltransferase 1A9 and 2B7.

2.8 THC screening

A THC test is carried out at screening to assess eligibility for the study. It will no longer be used as a measure of study compliance, since:

- The urine THC test may cross-react with other (i.e., non-THC) cannabinoids meaning it could yield ‘false positive’ results in patients receiving CBD and therefore would not provide any useable study information.
• THC serum test has been added in, since this was always supposed to be included but was omitted in error from the original protocol.

2.9 Changes requested by the Medicines and Healthcare Products Regulatory Agency

In response to a number comments from the Medicines and Healthcare Products Regulatory Agency, the following changes have been included within this amendment:

• Amend the wording included in the exclusion and withdrawal criteria involving liver enzyme monitoring to stipulate that patients with “Serum ALT or AST ≥ 3 × ULN or (TBL [serum total bilirubin] ≥ 2 × ULN or international normalized ratio [INR] > 1.5)” should be excluded from the trial and that patients with “ALT or AST > 3 × ULN or (TBL* > 2 × ULN or INR > 1.5)” should be withdrawn from the trial.

• For patients with Gilbert’s disease, a raised TBL would be considered normal and not a cause of exclusion or withdrawal unless ALT or AST were also elevated.

• In the UK, in order to demonstrate safety before exposing the younger patients to treatment, enrolment of patients between the ages of 12 and 23 months will only commence once 15 patients over the age of 23 months have been dosed for a minimum of 4 weeks and no new safety issues have been observed.

• Monthly pregnancy tests will be included.

2.10 Minor Corrections and Clarifications

The following minor corrections/clarifications have been made to the protocol:

• Aligning language in the exclusion and withdrawal criteria to that of other protocols, taking into account recommendations from the FDA.

• Wording has been added to cover countries where local law requires controlled drugs to be dispensed for a maximum of 28 days. This is to ensure this is covered if the study is introduced to countries where this is the legislation.

• The physical description of the IMP has been updated to ‘clear, colorless to yellow’.
• In the OLE phase, all scheduled visits are clarified and amended to be represented in days or weeks as per the interactive voice response system (IVRS) diary.

• Clarification of safety telephone calls to take place during OLE titration.

• Clarification that if a safety telephone call falls at a weekend then the call may be scheduled for the Friday before or the Monday after the weekend instead. This prevents the need for center staff and patients to be available for such calls at the weekend.

• Clarification of the mechanism for simultaneous taper down of blinded IMP and titration of OLE IMP.

• Clarification that a well-documented clinical history of epilepsy is sufficient without the requirement for an EEG, since EEG recordings do not always reflect the patient’s seizures.

• Clarification of the definition of history of suicidal behavior or suicidal ideation.

• Clarification that any recreational or medicinal cannabis use or any other IMP are prohibited during the study, since they may confound the interpretation of study results.

• Clarification that the patient and/or their caregiver will receive training in seizure type identification.

• Clarification of bullet points and subheading in Section 4.1.2.

• Since a separate consent form is signed by the patient to allow genetic testing, the wording within the Visit 1 (screening) visit has been amended.

• Updated information on safety from the Expanded Access IND Program and clarification of the rationale for the 25 to 50 mg/kg doses within this study.

• Update on projected number of centers based on current data.

• Correction of reference to randomization visit as Visit 3.

• Clarification that patient number is only assigned at Visit 1.

• Clarification of SAE reporting in the Netherlands.

• In Section 9.1.1.3, description of when PK samples will be taken has been cross-referenced to Section 9.2.9.1 for brevity.
• Clarification of visits at which IMP should be returned and clarification of use of dose calculator.

• All visits (assessment and resupply) are now described in detail for clarity.

• Clarification of GW’s expectation of status epilepticus reporting.

• Changes to enable more flexibility in the timing of IVRS diary calls during the period from completion/withdrawal to follow up.

• Text relating to TSC1 and TSC2 genetic screening has been moved from 9.2.4 to 9.2.9.3.

• Clarification that vital signs includes blood pressure since there is a different definition for vital signs between the US and Europe.

• Amend partial sensory seizures to focal sensory seizures to reflect accepted seizure nomenclature.

• Section numbering amended due to the addition and deletion of sections.

• Deletion of near duplicated text in sections 1, 4.1.2, 9.1.1.3, 9.1.2.2 and 9.2.12.

• Amending text to ensure that the synopsis and main body language align.

• References renumbered sequentially after number 52.

• Minor changes to the text relating to improved brevity.

• Removal of exact numbers of studies from EAP information, as these change frequently.

• Minor spelling/grammatical corrections have been made to improve consistency but these are not captured within this amendment document.
3 IMPLEMENTATION OF THE AMENDMENT

The changes detailed in this amendment will be issued as Clinical Protocol V3 25Aug16. It will be kept in the trial master file at GW as well as in each investigational center file and, if applicable, pharmacy site file.
A Double-blind, Randomized, Placebo-controlled Study to Investigate the Efficacy and Safety of Cannabidiol (GWP42003-P, CBD) as Add-on Therapy in Patients with Tuberous Sclerosis Complex who Experience Inadequately-controlled Seizures

Study Code: GWEP1521

EudraCT Number: 2015-002154-12

CLINICAL PROTOCOL AMENDMENT NUMBER: 1

to be incorporated into the Protocol, creating

CLINICAL PROTOCOL VERSION 2,
DATE 21 OCT 15

GW Research Ltd
Sovereign House
Vision Park
Chivers Way
Histon
Cambridge CB24 9BZ
United Kingdom

Tel: [redacted]
Fax: [redacted]

Confidentiality Statement
This document contains confidential information of GW Research Ltd (GW) that must not be disclosed to anyone other than the recipient study staff and members of the institutional review board or independent ethics committee. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW.
2 RATIONALE

This clinical protocol amendment 1 (will be incorporated into the Protocol creating Clinical Protocol Version 2, Date 21 Oct 15) addresses the following issue(s):

2.1 Compliance with U.S. Regulatory Requirements

In accordance with feedback received from the United States Food and Drug Administration, the protocol has been amended as follows:

2.1.1 Amendment to Study Title

The study title has been amended to reflect the change to indication described below.

2.1.2 Amendment to Indication

The indication has been amended to include generalized seizures where previously only focal seizures were considered. This will enable more accurate classification of seizures according to pre-defined seizure subtypes. The indication of seizures in tuberous sclerosis complex (TSC) now includes focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures (tonic–clonic, tonic, clonic or atonic) that are countable. Objectives have been amended to this affect.

2.1.3 Amendment to the Blinded Phase Primary Endpoint

The primary endpoint of the blinded phase of the study has been amended in parallel to reflect the change in indication. Seizures counted towards the primary endpoint now include focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures (tonic–clonic, tonic, clonic or atonic) that are countable. Each seizure subtype will also be counted and assessed separately as secondary endpoints.

2.1.4 Insertion of New Secondary Endpoint to Blinded Phase and Open Label Extension

Absence seizures, myoclonic seizures, partial sensory seizures and infantile/epileptic spasms will now be counted towards a composite secondary endpoint measuring the change from baseline in number of ‘other’ seizures. Each seizure subtype will also be counted and assessed separately. The classification of these seizure subtypes as secondary endpoints reflects the difficulty in obtaining accurate and consistent counts.
2.1.5 Amendment to Open-label Extension Secondary Endpoint

The antiepileptic secondary endpoints of the open-label extension (OLE) phase have been amended to maintain consistency with the blinded phase indication and endpoints. Seizures counted towards this endpoint now include focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures (tonic–clonic, tonic, clonic or atonic) that are countable. Each seizure subtype will also be counted and assessed separately.

2.1.6 Amendment to Inclusion Criteria

Inclusion criteria have been amended to remain consistent with the change to indication and endpoints. The seizure types counted towards eligibility in the baseline period have been extended and now include focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures (tonic–clonic, tonic, clonic or atonic) that are countable.

2.1.7 Guidance on Dose Reductions

Further guidance on dose reductions in the event a patient experiences poor tolerability has been introduced. It is recommended that patients with poor tolerability have their dose reduced by 10 mg/kg/day every seven days unless, in the Investigator’s opinion, smaller or larger dose reductions are clinically indicated. Where possible, the patient should be encouraged to return to the target Dose Level.

2.2 Clarification of Epilepsy Study Consortium Role and Responsibilities

The independent Epilepsy Study Consortium (ESC) will verify the seizure types of screened patients on an ongoing basis. The ESC will provide written documentation directly to the investigator and guidance on seizure types, if applicable, for inclusion in the patient file. The ESC will not review or verify TSC diagnosis. TSC diagnosis will be documented according to criteria agreed by the 2012 International Tuberous Sclerosis Complex Consensus Conference and independent verification is not required.

2.3 Extension of Screening Period and Introduction of the ‘Baseline’ Visit

The screening period has been extended to ensure seizure classification has been verified and documented before baseline seizure recording begins. Investigators will
submit a documented history of TSC directly to the ESC for verification of seizure types. The ESC will provide written documentation directly to the investigator and guidance on seizure types, if applicable, for inclusion in the patient file. Upon completion of this process patients will return to the clinic for the Baseline Visit to be trained on the use of the daily interactive voice response system (IVRS) diary. The 28 day baseline period will commence at this visit. This screening extension and extra visit will ensure that accurate seizure classifications and counts are recorded in the IVRS system and that seizure re-classifications do not cause discrepancies in source data. The numbering of subsequent visits has been amended as applicable.

2.4 Amendment to Secondary Objectives for Blinded and Open-label Extension Phases

The wording of secondary objectives have been amended to better reflect accepted terminology used in the treatment and care of patients with TSC and in the research community. Two existing secondary objectives have been combined to produce the following objective: To evaluate the effect of GWP42003-P on TSC Associated Neuropsychiatric Disorders (TAND), including cognitive and behavioral function and autistic features compared with placebo. The following secondary objective has been removed: To evaluate the effect of GWP42003-P on autistic features compared with placebo. Endpoints relating to TAND have not been amended.

2.5 Amendment to Inclusion Criterion to Include One Year Old Patients

The age range for this study has been amended from 2–65 years to 1–65 years. This will ensure that the study population remains representative of the wider TSC patient population. One retrospective study of TSC patients showed that > 60% had the onset of seizures in the first year of life. It also ensures consistency with the Pediatric Investigation Plan for Epidiolex.

2.6 Increase in Patient Numbers

The number of patients per treatment group has been increased from 48 to 64 (a total increase from 144 to 192 patients). The increase in patient numbers reflects an increase in power from 80% to 90% which is deemed more appropriate for a Phase Three study.
2.7 Clarification of Inclusion Criterion Relating to IVRS Diary Call Compliance

Patients are required to complete at least 90% of the daily diary calls during baseline to be considered eligible for randomization. The inclusion criterion wording has been clarified to confirm that a minimum of 25 completed daily calls out of 28 is required.

2.8 Dose Administration and Investigational Medicinal Product Description

Specific details regarding oral dosing has been removed from the protocol to allow for possible future gastrostomy tube (G-tube) administration. Specific dosing instructions will be provided to patients/caregivers.

2.9 Pharmacokinetic Blood Sampling

The timings of blood samples for pharmacokinetic (PK) blood sampling of cannabidiol (CBD), Δ9-tetrahydrocannabinol (THC) and their major metabolites have been amended. This is in accordance with emerging data from a single ascending dose PK study in healthy volunteers which showed t\text{max} to occur at approximately five hours post-dose.

Text has been amended in order to clarify that PK samples will only be taken from patients who weigh ≥ 20 kg in order to avoid multiple blood sampling (and associated risks thereof) in younger children.

2.10 Vineland Adaptive Behavior Scales

The frequency of Vineland-II assessments has been reduced during the blinded phase of the study. This assessment will be completed at the Randomization (Visit 3) and End of Treatment Visits (Visit 11) only. The relatively proximity of visits during this phase of the study means significant changes would be unlikely at interim visits. This change will also reduce the patient burden.

2.11 Administrative Changes

Minor spelling/formatting/consistency/administrative issues have been corrected. (NB. In the interest of brevity, minor changes to grammar and punctuation are not captured in this amendment document).
3 IMPLEMENTATION OF THE AMENDMENT

The changes detailed in this amendment will be issued as Clinical Protocol Version 2, Date 21 Oct 15. It will be kept in the trial master file at GW as well as in each investigator site file and, if applicable, pharmacy site file.
A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled seizures

Study Code: GWEP1521

EudraCT Number: 2015-002154-12

CLINICAL PROTOCOL ANNEX 1

(US ONLY)

This annex outlines the assessments and procedures for years 2–4 of the open-label extension. This annex will be implemented at US sites only.

GW Research Ltd
Sovereign House
Vision Park
Chivers Way
Histon
Cambridge CB24 9BZ
United Kingdom
Tel: PPD
Fax: PPD

Confidentiality Statement

This document contains confidential information of GW Research Ltd (GW) that must not be disclosed to anyone other than the recipient study staff and members of the institutional review board or independent ethics committee. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW.
Investigator Agreement

I have read the attached clinical protocol annex 1 entitled ‘A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled seizures’, dated 15 Apr 2019 and agree to abide by all provisions set forth therein.

I agree to comply with applicable regulatory requirement(s) the US Food and Drug Administration (FDA) regulations relating to good clinical practice (GCP) and clinical trials, the European Union (EU) Clinical Trials Directive (2001/20/EC), the EU Good Clinical Practice / GCP Directive (2005/28/EC) and subsequent applicable regulatory/statutory instruments, or the International Conference for Harmonisation Tripartite Guidelines for GCP where the EU Clinical Trials and GCP Directives do not apply, and to complete Form FDA 1572, if required. I accept responsibility for the overall medical care of patients during the trial and for all trial-related medical decisions.

I am not aware that any conflicts of interest, financial or otherwise, exist for myself, my spouse [or legal partner] and dependent children and agree to confirm this in writing if required and update as necessary.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW.

Centre No: ___________________________

Print name: ___________________________ Date: ___________________________

Principal Investigator

Signature: _____________________________

GW Authorization

Print name: ___________________________ Date: _______ 23- apr - 2019 _______

Senior Clinical Manager

Signature: _____________________________

Confidential

Clinical Protocol Annex Template

Page 2 of 17

V1, 24Sep13
Table of Contents

Title Page ........................................................................................................ 1
Table of Contents ........................................................................................... 3
List of Abbreviations ..................................................................................... 4
Definition of Terms ........................................................................................ 5
1 RATIONALE ........................................................................................ 6
2 SUMMARY OF THE ANNEX ........................................................... 6
3 TREATMENT SCHEMATIC DIAGRAM ....................................... 7
4 DESIGN AND PROCEDURES .......................................................... 8
  4.1 Visit B10 (Week 52) ........................................................................................... 8
  4.2 Resupply Visits B13 (Week 61), B14 (Week 70), B16 (Week 87),
      B17 (Week 96), B19 (Week 113), B20 (Week 122), B22 (Week 139),
      B23 (Week 148), B25 (Week 165), B26 (Week 174), B28 (Week 191),
      and B29 (Week 200) ................................................................................... 8
  4.3 Assessment Visits B15 (Week 78), B18 (Week 104), B21 (Week 130),
      B24 (Week 156), and B27 (Week 182) .......................................................... 9
  4.4 End of Treatment/Withdrawal Visit............................................................ 10
  4.5 End of Taper Visit .......................................................................................... 12
  4.6 Safety Telephone Call ................................................................................ 13
  4.7 Follow-up Visit ............................................................................................ 13
5 INFORMED CONSENT/ASSENT ................................................... 14
6 DATA ANALYSIS ............................................................................. 14
  6.1 Patients to Analyze .................................................................................... 14
7 IMPLEMENTATION OF THE ANNEX ........................................ 14
APPENDIX 1 SCHEDULE OF ASSESSMENTS ................................. 15
List of Abbreviations

ABCL  
Adult Behavior Checklist

AE  
Adverse event

AED  
Antiepileptic drug

CBCL  
Child Behavior Checklist

CBD  
Cannabidiol

CGIC  
Caregiver Global Impression of Change

CGIC-SD  
Caregiver Global Impression of Change in Seizure Duration

C-SSRS  
Columbia-Suicide Severity Rating Scale

ECG  
12-lead electrocardiogram

EU  
European Union

FDA  
US Food and Drug Administration

GCP  
Good clinical practice

GW  
GW Research Ltd

IGF-1  
Insulin-like growth factor-1

IMP  
Investigational medicinal product

IVRS  
Interactive voice response system

OLE  
Open-label extension

PGIC  
Physician Global Impression of Change

QOLCE  
Quality of Life in Childhood Epilepsy

QOLIE  
Quality of Life in Epilepsy

SCQ  
Social Communication Questionnaire

SGIC  
Subject Global Impression of Change

SGIC-SD  
Subject Global Impression of Change in Seizure Duration

TSC  
Tuberous sclerosis complex

(continued)
US United States
Vineland-II Vineland Adaptive Behavior Scales, Second Edition

**Definition of Terms**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of trial</td>
<td>Last patient last visit or last contact, whichever occurs last.</td>
</tr>
<tr>
<td>Enrolled patient</td>
<td>Any patient who has provided written informed consent/assent to take part in the trial.</td>
</tr>
<tr>
<td>Investigational medicinal product</td>
<td>Term used to describe both investigational active product and reference therapy (placebo).</td>
</tr>
<tr>
<td>Investigator</td>
<td>Trial principal investigator or a formally delegated study physician.</td>
</tr>
</tbody>
</table>
1 RATIONALE

Trial GWEP1521 consists of a randomized, parallel-group, 16-week double-blind-phase comparing 2 doses of GWP42003-P with placebo, followed by a 1-year open-label extension (OLE) phase. To ensure continued access to GWP42003-P prior to approval, the OLE phase will be extended to a total of 4 years in duration in the United States (US). Patients will complete the OLE phase when GWP42003-P is approved in tuberous sclerosis complex (TSC) and is commercially available to the patient, or after a maximum of 4 years of OLE treatment, whichever occurs first.

2 SUMMARY OF THE ANNEX

Patients will complete the first year of the OLE at Visit B10 and enter a second year of OLE treatment. Patients completing a second year of OLE treatment will enter a third year of OLE treatment. Patients who complete OLE year 3 may enter a fourth year of OLE treatment. Dosing will remain consistent and there is no requirement for dose adjustment or further titration upon entry into years 2, 3, or 4.

Assessment visits have been added at Week 78, Week 104, Week 130, Week 156, and Week 182 (relative to Visit B1). Investigational medicinal product (IMP) dispensing visits have also been added between assessment visits in years 2, 3, and 4 to ensure resupply volumes are manageable for both patients and dispensing staff. Attendance of the patient is not required for the dispensing visits provided the primary caregiver is able to attend. However, it is preferred that the patient attend where possible.

Patients will complete the OLE phase when GWP42003-P is approved in TSC and is commercially available to the patient, or after a maximum of 4 years of OLE treatment, whichever occurs first. Following completion of the OLE, patients who do not immediately continue to use commercial GWP42003-P will commence a 10-day taper period (tapering 10% per day) before attending an End of Taper visit. A safety follow-up telephone call will be completed 2 weeks after the End of Taper visit and a safety Follow-up visit will be completed 4 weeks after the End of Taper visit.
3 TREATMENT SCHEMATIC DIAGRAM

End of Treatment/Withdrawal Visit will occur: 1) following early withdrawal from the trial; 2) in place of the next scheduled clinic visit (assessment or resupply) when GWP42003-P is approved in TSC and is commercially available to the patient; or 3) after a maximum of 4 years of OLE treatment (i.e., 208 weeks [±7 days] from Visit B1); whichever occurs first.

b Only required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P.

c Safety Telephone Call must be made 2 weeks (+3 days) after the patient’s last dose of IMP.

d This must be made 4 weeks (+3 days) after the patient’s last dose of IMP and can be conducted by telephone.

e Visits B13, B14, B16, B17, B19, B20, B22, B23, B25, B26, B28, and B29 – Resupply visits (±7 days).
4 DESIGN AND PROCEDURES

Patients and their parent(s)/legal representative will be invited to participate in years 2, 3, and 4 of the OLE when they reach Visit B10 of the OLE phase. They will be issued with additional OLE patient information and informed assent or the patient/parent(s)/legal representative information and informed consent (as applicable). Following adequate time to discuss the additional visits with the investigator, nurse, relatives or caregiver, patients/parent(s)/legal representatives who provide written informed consent/assent at Visit B10 will continue in the OLE.

Patients will continue to make weekly interactive voice response system (IVRS) diary calls throughout their second, third, and fourth years of OLE participation.

4.1 Visit B10 (Week 52)

In addition to the visit schedule outlined in Section 9.1.2.10 of the main protocol, patients treated in the US who provide written informed consent/assent (see Section 5) will receive sufficient open-label IMP for 9 weeks’ home dosing and will be instructed to maintain consistent dosing. An additional dose calculator and paper diary will be issued, and patients will be trained on their appropriate use.

The Study Medication Use and Behavior Survey should not be administered at Visit B10 for patients entering the second year of the OLE. The investigator must record the patient’s attendance at the visit and confirm their continued participation.

4.2 Resupply Visits B13 (Week 61), B14 (Week 70), B16 (Week 87), B17 (Week 96), B19 (Week 113), B20 (Week 122), B22 (Week 139), B23 (Week 148), B25 (Week 165), B26 (Week 174), B28 (Week 191), and B29 (Week 200)

Visits B13, B14, B16, B17, B19, B20, B22, B23, B25, B26, B28, and B29 will occur 61, 70, 87, 96, 113, 122, 139, 148, 165, 174, 191, and 200 weeks after Visit B1, respectively. A visit window of ±7 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

Attendance of the patient is not required for resupply visits provided the primary caregiver is able to attend. However, it is preferred that the patient attend where possible.

Each visit will comprise a review of concomitant medications (including antiepileptic drugs [AEDs]), epilepsy-related hospitalizations and adverse events (AEs).
The investigator must assess adherence to the dosing regimen by reviewing the patient’s diary and IVRS data, record the patient’s/caregiver’s attendance at the visit, and confirm the outcome of the visit.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients/caregivers will then receive sufficient IMP until the next scheduled visit.

4.3 Assessment Visits B15 (Week 78), B18 (Week 104), B21 (Week 130), B24 (Week 156), and B27 (Week 182)

Visits B15, B18, B21, B24, and B27 will occur 78, 104, 130, 156, and 182 weeks after Visit B1, respectively. A visit window of ±7 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

The following assessments will be made at each visit:

- Concomitant medications (including AEDs)
- Physical examination (including height and body weight)
- 12-lead electrocardiogram (ECG)
- Vital signs
- Epilepsy-related hospitalizations
- AEs
- Subject Global Impression of Change in Seizure Duration (SGIC-SD)/Caregiver Global Impression of Change in Seizure Duration (CGIC-SD)
- Suicidality, assessed in accordance with Section 9.2.12.8 of the main protocol

At each assessment visit, clinical laboratory samples (blood and urine [where possible]), including a pregnancy test if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry, urinalysis, and determination of serum insulin-like growth factor-1 (IGF-1) levels (for patients less than 18 years of age) to be performed by the central laboratory. Provided that the risk/benefit outcome is favorable in the investigator’s opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs.
The investigator must assess adherence to the dosing regimen by reviewing the patient’s diary and IVRS data, record the patient’s attendance at the visit, and confirm the outcome of the visit.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients/caregivers will then receive sufficient IMP until the next scheduled visit.

**In addition to the above, the following assessments will be made at Visit B18 and Visit B24:**

- Details of menstruation (for females)
- Tanner staging (patients aged 10–17 [inclusive] only)
- Quality of Life in Childhood Epilepsy (QOLCE)/Quality of Life in Epilepsy (QOLIE-31-P)
- Subject Global Impression of Change (SGIC)/Caregiver Global Impression of Change (CGIC)
- Physician Global Impression of Change (PGIC)
- Wechsler Tests
- Child Behavior Checklist (CBCL)/Adult Behavior Checklist (ABCL)
- Social Communication Questionnaire (SCQ)
- Vineland Adaptive Behavior Scales, Second Edition (Vineland-II)

**4.4 End of Treatment/Withdrawal Visit**

This visit will occur: 1) following early withdrawal from the trial; 2) in place of the next scheduled clinic visit (assessment or resupply) when GWP42003-P is approved in TSC and is commercially available to the patient; or 3) after a maximum of 4 years of OLE treatment (i.e., 208 weeks [±7 days] from Visit B1); whichever occurs first.

The following assessments will be made at the End of Treatment/Withdrawal visit:

- Vital signs
- Physical examination (including height and body weight)
- Details of menstruation (for females)
• Tanner staging (patients aged 10–17 [inclusive] only)
• ECG
• IVRS and paper diary information (including information regarding seizures, AEs, usage of rescue medication, concomitant AEDs, and IMP dosing)
• Epilepsy-related hospitalizations
• Concomitant medications and/or changes to medication
• AEs
• QOLCE/QOLIE-31-P
• SGIC/CGIC
• PGIC
• SGIC-SD/CGIC-SD
• Wechsler Tests
• CBCL/ABCL
• SCQ
• Vineland-II
• Suicidality, assessed in accordance with Section 9.2.12.8 of the main protocol

Clinical laboratory samples (blood and urine [where possible]), including a pregnancy test if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry, urinalysis and determination of serum IGF-1 levels (for patients less than 18 years of age) to be performed by the central laboratory. Provided that the risk/benefit outcome is favorable in the investigator’s opinion, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs. The investigator must assess adherence to the dosing regimen.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. For patients who withdraw early, the IVRS will be contacted to confirm withdrawal from the trial. For patients who immediately continue to use commercial GWP42003-P following the End of Treatment visit, the IVRS will be contacted to confirm the patient’s completion of this trial and the paper diaries will be collected. For patients 12 years of age and older who complete treatment and
immediately continue to use commercial GWP42003-P, or for patients 12 years of age and older who withdraw early and do not taper IMP, the trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.

For patients who complete treatment but do not immediately continue to use commercial GWP42003-P following the End of Treatment visit, IMP will be tapered at home (10% per day for 10 days). Additional IMP will be dispensed, if required, and instructions for tapering the dose will be provided. Patients who withdraw early should also begin the taper period following the Withdrawal visit unless continued dosing is not possible due to an AE. Information will continue to be recorded in the paper diary during the taper period.

Following the End of Treatment/Withdrawal visit, the IVRS seizure reporting diary should be completed up to the Follow-up visit.

4.5 End of Taper Visit

This visit is required for patients who: 1) withdraw from the trial and taper IMP; or 2) complete treatment but do not immediately continue to use commercial GWP42003-P. The End of Taper visit will take place 10 (+3) days after the End of Treatment/Withdrawal visit. For patients who begin to taper IMP but subsequently withdraw/do not complete the full taper period, this visit should occur on the final day of dosing or as soon as possible after this date.

The following assessments will be made:

- Vital signs
- Physical examination (including height and body weight)
- IVRS and paper diary information (including information regarding seizures, AEs, usage of rescue medication, concomitant AEDs, and IMP dosing)
- Epilepsy-related hospitalizations
- Concomitant medications and/or changes to medication
- AEs
- Suicidality, assessed in accordance with Section 9.2.12.8 of the main protocol
- ECG
• Clinical laboratory samples (blood and urine for hematology, biochemistry and urinalysis)

The investigator must assess adherence to the dosing regimen.

For patients 12 years of age and older, the trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made.

Following the End of Taper visit (or date of final dosing), the IVRS seizure reporting diary should be completed up to the Follow-up visit.

4.6 Safety Telephone Call

This visit is required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P. The Safety Telephone Call will be conducted 2 weeks (+3 days) after the patient’s last dose of GWP42003-P (including final taper period dose). During this call, caregivers will be asked for information on:

• AEs
• Epilepsy-related hospitalizations
• Concomitant medications and/or changes to medication

Following this call, the IVRS seizure reporting diary should be completed up to the Follow-up visit.

4.7 Follow-up Visit

This visit is required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P. The Follow-up visit will take place 4 weeks (+3 days) after the patient’s last dose of GWP42003-P (including final taper period dose) and can be conducted by telephone. During this visit/call, caregivers will be asked for information on:

• AEs
• Epilepsy-related hospitalizations
• Concomitant medications and/or changes to medication
5 INFORMED CONSENT/ASSENT

An institutional review board/independent ethics committee-approved informed consent/assent form will be given to eligible patients prior to Visit B10 of the parent trial (please refer to Section 9.1.2.11 of the main trial protocol) which will reflect the additional implications of this annex.

6 DATA ANALYSIS

6.1 Patients to Analyze

Patients in the US who continue to participate in years 2, 3, and 4 of the OLE will be analyzed in accordance with the statistical considerations detailed in Section 13 of the main protocol.

7 IMPLEMENTATION OF THE ANNEX

This clinical protocol annex will be issued in conjunction with the current version of the main clinical trial protocol. It will be kept in the trial master file at GW as well as in each US investigational center file and, if applicable, pharmacy site file.
## APPENDIX 1  SCHEDULE OF ASSESSMENTS

### Open-label Extension

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Week</td>
<td>52</td>
<td>61</td>
<td>70</td>
<td>78</td>
<td>87</td>
<td>96</td>
<td>104</td>
<td>113</td>
<td>122</td>
<td>130</td>
<td>139</td>
<td>148</td>
<td>156</td>
<td>165</td>
<td>174</td>
<td>182</td>
<td>191</td>
<td>200</td>
<td>+7</td>
<td>+7</td>
<td>+7</td>
<td>+7</td>
</tr>
<tr>
<td>Visit Window</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>+7</td>
<td>+3</td>
<td>+3</td>
<td>+3</td>
</tr>
</tbody>
</table>

- **Informed consent/assent**: X
- **Vital signs and BP**: X X X X X X X X
- **Physical examination (including height and body weight)**: X X X X X X X X
- **ECG**: X X X X X X X X
- **Clinical laboratory blood sampling**: X X X X X X X X
- **Clinical laboratory urine sampling (dipstick urinalysis)**: X X X X X X X X
- **Pregnancy test, where appropriate**: X X X X X X X X
- **IGF-1 testing**: X X X X X X X X
- **AED concentration**: X X X X X X X X
- **AEs**: X X X X X X X X X X X X X X
- **Concomitant medications**: X X X X X X X X X X X X X X
- **Inpatient epilepsy-related hospitalizations**: X X X X X X X X X X X X X X
- **Suicidality assessment**: X X X X X X X X X X X X X X

See footnote*: 2 weeks after last dose. 4 weeks after last dose.

Confidential
Clinical Protocol Annex Template
Page 15 of 17
V1, 24Sep15
<table>
<thead>
<tr>
<th>Visit Number</th>
<th>B10</th>
<th>B13</th>
<th>B14</th>
<th>B15</th>
<th>B16</th>
<th>B17</th>
<th>B18</th>
<th>B19</th>
<th>B20</th>
<th>B21</th>
<th>B22</th>
<th>B23</th>
<th>B24</th>
<th>B25</th>
<th>B26</th>
<th>B27</th>
<th>B28</th>
<th>B29</th>
<th>End of Treatment/ Withdrawal Visit</th>
<th>End of Taper Visit(^a)</th>
<th>Safety Telephone Call(^b)</th>
<th>Follow-up Visit(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit Window</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
</tr>
<tr>
<td>Visit Window</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
</tr>
<tr>
<td>Visit Window</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
</tr>
<tr>
<td>Vineland-II</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGIC/CGIC</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGIC</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGIC-SD/CNIC-SD</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>QOLCE/QOLIE-31-P</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wechsler Tests</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBCL/ABCL</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCQ</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanner Staging (where appropriate)</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstruation question (where appropriate)</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient IVRS and paper diary review (seizures, AE information, concomitant AEDs, rescue medication, IMP dosing)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>IMP dispensing</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Collection of IMP</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>IMP compliance review</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Study Medication Use and Behavior Survey</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
a End of Treatment/Withdrawal Visit will occur: 1) following early withdrawal from the trial; 2) in place of the next scheduled clinic visit (assessment or resupply) when GWP42003-P is approved in TSC and is commercially available to the patient; or 3) after a maximum of 4 years of OLE treatment (i.e., 208 weeks [±7 days] from Visit B1); whichever occurs first.
b Only required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P.
c Safety Telephone Call must be made 2 weeks (+3 days) after the patient’s last dose of IMP.
d Follow-up Visit required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P. This must be made 4 weeks (+3 days) after the patient’s last dose of IMP and can be conducted by telephone.
e Performed at final dosing visit (End of Treatment/Withdrawal visit or End of Taper visit, as applicable) for patients 12 years of age and older only.
A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled seizures

Study Code: GWEP1521

EudraCT Number: 2015-002154-12

CLINICAL PROTOCOL ANNEX 1 (US ONLY)
AMENDMENT NUMBER: 2

to be incorporated into the Protocol Annex, creating CLINICAL PROTOCOL ANNEX 1 VERSION 3 (US ONLY), DATE 15 APRIL 2019

GW Research Ltd
Sovereign House
Vision Park
Chivers Way
Histon
Cambridge CB24 9BZ
United Kingdom

Tel: PPD
Fax: PPD

Confidentiality Statement
This document contains confidential information of GW Research Ltd (GW) that must not be disclosed to anyone other than the recipient study staff and members of the institutional review board or independent ethics committee. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW.
2 RATIONALE

This Clinical Protocol Annex 1 (US only) amendment 2 (will be incorporated into the Protocol Annex creating Clinical Protocol Annex 1 [US only] Version 3, Date 15 April 2019) addresses the following issue(s):

2.1 Duration of Open-label Extension Phase

The OLE phase will be extended in duration in the US to ensure continued access to GWP42003-P prior to approval. Patients will complete the OLE phase when GWP42003-P is approved in TSC and is commercially available to the patient, or after a maximum of 4 years of OLE treatment, whichever occurs first. Procedures for each resupply visit and assessment visit have been condensed into single sections in the Annex to minimize repetition.
3 IMPLEMENTATION OF THE AMENDMENT

The changes detailed in this amendment will be issued as Clinical Protocol Annex 1 (US Only) Version 3, Date 15 April 2019. It will be kept in the trial master file at GW as well as in each investigational centre file and, if applicable, pharmacy site file.
A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled seizures

Study Code: GWEP1521

EudraCT Number: 2015-002154-12

CLINICAL PROTOCOL ANNEX 1 (US ONLY)
AMENDMENT NUMBER: 1

to be incorporated into the Protocol Annex, creating CLINICAL PROTOCOL ANNEX 1 VERSION 2 (US ONLY), DATE 26 APRIL 2018

GW Research Ltd
Sovereign House
Vision Park
Chivers Way
Histon
Cambridge CB24 9BZ
United Kingdom

Tel: PPD
Fax: PPD

Confidentiality Statement

This document contains confidential information of GW Research Ltd (GW) that must not be disclosed to anyone other than the recipient study staff and members of the institutional review board or independent ethics committee. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW.
2 RATIONALE

This clinical protocol annex 1 (US only) amendment 1 (will be incorporated into the Protocol Annex creating Clinical Protocol Annex 1 [US Only] Version 2, Date 26 April 2018) addresses the following issue(s): **Duration of Open-label Extension Phase**

The OLE phase will be extended in duration in the US to ensure continued access to GWP42003-P prior to approval. Patients will complete the OLE phase when GWP42003-P is approved in TSC and is commercially available to the patient, or after a maximum of 3 years’ OLE treatment, whichever occurs first. Procedures for each resupply visit and assessment visit have been condensed into single sections in the Annex to minimize repetition.

2.2 Minor Corrections and Clarifications

The following minor corrections/clarifications have been made to the protocol annex:

- Clarification that the End of Taper Visit, Safety Telephone Call, and Follow-up Visit are required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P. Furthermore, the timings of these visits/calls are relative to the End of Treatment/Withdrawal Visit.

- Clarification that Safety Telephone Call is still required for patients who do not taper IMP, that the call window is +3 days, and that the patient’s last dose includes the final taper period dose.

- Clarification that the Follow-up Visit can be a clinic visit or can be conducted by telephone.

- Clarification that the Study Medication Use and Behavior Survey should not be administered at Visit B10 for patients entering the second year of the OLE and should only be administered at the final dosing visit (End of Treatment/Withdrawal visit or End of Taper visit, as applicable).

- Treatment days have been removed in favor of treatment weeks, as this is more compatible with the interactive voice response system.

- Collection of informed consent/assent at Visit B10 was listed in the Schedule of Assessments but was not mentioned in Section 4.1 of the Annex.
• Additional assessments for patients who withdraw early and taper IMP were listed in the End of Taper Visit section of the Annex but had not been denoted in the Schedule of Assessments.

• Abbreviations which are not used in the Annex have been removed from the List of Abbreviations, and abbreviated terms have been defined on first use.

• Terms which are not used in the Annex have been removed from the Definition of Terms.

• Bulleted lists have been used to improve readability.

• References to “the study” has been replaced with “the trial” throughout.

• Minor spelling/punctuation/grammatical corrections have been made to improve consistency and readability; however, in the interest of brevity, these changes are not captured in Section 4 of this amendment document.

3 IMPLEMENTATION OF THE AMENDMENT

The changes detailed in this amendment will be issued as Clinical Protocol Annex 1 (US Only) Version 2, Date 26 April 2018. It will be kept in the trial master file at GW as well as in each investigational site file and, if applicable, pharmacy site file.
A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled seizures

Study Code: GWEP1521

EudraCT Number: 2015-002154-12

CLINICAL PROTOCOL ANNEX 2

(POLAND ONLY)

This annex outlines the assessments and procedures for years 2 and 3 of the open-label extension. This annex will be implemented at Polish sites only.

GW Research Ltd
Sovereign House
Vision Park
Chivers Way
Histon
Cambridge CB24 9BZ
United Kingdom

Tel: PPD
Fax: PPD

Confidentiality Statement

This document contains confidential information of GW Research Ltd (GW) that must not be disclosed to anyone other than the recipient study staff and members of the institutional review board or independent ethics committee. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW.
Investigator Agreement

I have read the attached clinical protocol annex 2 entitled ‘A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled seizures’, dated 26 April 2018 and agree to abide by all provisions set forth therein.

I agree to comply with applicable regulatory requirement(s) the US Food and Drug Administration (FDA) regulations relating to good clinical practice (GCP) and clinical trials, the European Union (EU) Clinical Trials Directive (2001/20/EC), the EU Good Clinical Practice / GCP Directive (2005/28/EC) and subsequent applicable regulatory/statutory instruments, or the International Conference on Harmonisation Tripartite Guidelines for GCP where the EU Clinical Trials and GCP Directives do not apply, and to complete Form FDA 1572, if required. I accept responsibility for the overall medical care of patients during the trial and for all trial-related medical decisions.

I am not aware that any conflicts of interest, financial or otherwise, exist for myself, my spouse [or legal partner] and dependent children and agree to confirm this in writing if required and update as necessary.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW.

Centre No: ____________________________

Print name: ____________________________ Date: ____________________________
Principal investigator (DD Month YYYY)

Signature: ____________________________

GW Authorization

Print name: ____________________________ Date: 01 MAY 2018 (DD Month YYYY)
Senior clinical manager

Signature: ____________________________

Confidential
Clinical Protocol Annex Template
# Table of Contents

Title Page ........................................................................................................ 1  
Table of Contents .......................................................................................... 3  
List of Abbreviations ..................................................................................... 4  
Definition of Terms ........................................................................................ 5  
1  RATIONALE ........................................................................................ 6  
2  SUMMARY OF THE ANNEX ........................................................... 6  
3  TREATMENT SCHEMATIC DIAGRAM ....................................... 7  
4  DESIGN AND PROCEDURES .......................................................... 8  
   4.1 Visit B10 (Week 52)................................................................................ 8  
   4.2 Resupply Visits B13 (Week 61), B14 (Week 70), B16 (Week 87),  
      B17 (Week 96), B19 (Week 113), B20 (Week 122), B22 (Week 139),  
      and B23 (Week 148)............................................................................. 8  
   4.3 Assessment Visits B15 (Week 78), B18 (Week 104), and  
      B21 (Week 130)...................................................................................... 9  
   4.4 End of Treatment/Withdrawal Visit......................................................... 10  
   4.5 End of Taper Visit.................................................................................. 12  
   4.6 Safety Telephone Call........................................................................... 13  
   4.7 Follow-up Visit..................................................................................... 13  
5  INFORMED CONSENT/ASSENT ................................................... 14  
6  DATA ANALYSIS ............................................................................. 14  
   6.1 Patients to Analyze .............................................................................. 14  
7  IMPLEMENTATION OF THE ANNEX ........................................ 14  
APPENDIX 1  SCHEDULE OF ASSESSMENTS............................... 15
List of Abbreviations

ABCL  Adult Behavior Checklist
AE   Adverse event
AED  Antiepileptic drug
CBCL Child Behavior Checklist
CBD  Cannabidiol
CGIC Caregiver Global Impression of Change
CGIC-SD Caregiver Global Impression of Change in Seizure Duration
C-SSRS Columbia-Suicide Severity Rating Scale
ECG  12-lead electrocardiogram
EU   European Union
FDA  US Food and Drug Administration
GCP  Good clinical practice
GW  GW Research Ltd
IGF-1 Insulin-like growth factor-1
IMP  Investigational medicinal product
IVRS Interactive voice response system
OLE  Open-label extension
PGIC Physician Global Impression of Change
QOLCE Quality of Life in Childhood Epilepsy
QOLIE-31-P Quality of Life in Epilepsy
SCQ  Social Communication Questionnaire
SGIC Subject Global Impression of Change
SGIC-SD Subject Global Impression of Change in Seizure Duration
TSC  Tuberous sclerosis complex

(continued)
Vineland-II Vineland Adaptive Behavior Scales, Second Edition

## Definition of Terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of trial</td>
<td>Last patient last visit or last contact, whichever occurs last.</td>
</tr>
<tr>
<td>Enrolled patient</td>
<td>Any patient who has provided written informed consent/assent to take part in the trial.</td>
</tr>
<tr>
<td>Investigational medicinal product</td>
<td>Term used to describe both investigational active product and reference therapy (placebo).</td>
</tr>
<tr>
<td>Investigator</td>
<td>Trial principal investigator or a formally delegated study physician.</td>
</tr>
</tbody>
</table>
1 RATIONALE

Trial GWEP1521 consists of a randomized, parallel-group, 16-week double-blind phase comparing 2 doses of GWP42003-P with placebo, followed by a 1-year open-label extension (OLE) phase. To ensure continued access to GWP42003-P prior to approval, the OLE phase will be extended to a total of 3 years in duration in Poland. Patients will complete the OLE phase when GWP42003-P is approved in tuberous sclerosis complex (TSC) and is commercially available to the patient, or after a maximum of 3 years’ OLE treatment, whichever occurs first. The intent is to ensure continued access to GWP42003-P through compassionate schemes (e.g., Named Patient Supply) in other countries. However, in countries where compassionate access proves difficult prior to first approvals, the OLE duration may also be extended to include these additional countries.

2 SUMMARY OF THE ANNEX

Patients will complete the first year of the OLE at Visit B10 and enter a second year of OLE treatment. Patients completing a second year of OLE treatment will enter a third year of OLE treatment. Dosing will remain consistent and there is no requirement for dose adjustment or further titration upon entry into years 2 or 3.

Assessment visits have been added at Week 78, Week 104, Week 130, and Week 156 (relative to Visit B1). Investigational medicinal product (IMP) dispensing visits have also been added between assessment visits in years 2 and 3 to ensure resupply volumes are manageable for both patients and dispensing staff. Attendance of the patient is not required for the dispensing visits provided the primary caregiver is able to attend. However, it is preferred that the patient attend where possible.

Patients will complete the OLE phase when GWP42003-P is approved in TSC and is commercially available to the patient, or after a maximum of 3 years’ OLE treatment, whichever occurs first. Following completion of the OLE, patients who do not immediately continue to use commercial GWP42003-P will commence a 10-day taper period (tapering 10% per day) before attending an End of Taper visit. A safety follow-up visit will be completed 4 weeks after the End of Taper visit.
3  TREATMENT SCHEMATIC DIAGRAM

<table>
<thead>
<tr>
<th>Visit B10</th>
<th>Visit B15</th>
<th>Visit B18</th>
<th>Visit B21</th>
<th>End of Treatment/Withdrawal Visit</th>
<th>End of Taper Visit</th>
<th>Safety Telephone Call</th>
<th>Follow-up Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 52</td>
<td>Week 78</td>
<td>Week 104</td>
<td>Week 130</td>
<td>(+7 days)</td>
<td>(+3 days)</td>
<td>(±3 days)</td>
<td>(±3 days)</td>
</tr>
<tr>
<td>B13</td>
<td>B14</td>
<td>B16</td>
<td>B17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 61</td>
<td>Week 70</td>
<td>Week 87</td>
<td>Week 96</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B19</td>
<td>B20</td>
<td>B22</td>
<td>B23</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 113</td>
<td>Week 122</td>
<td>Week 139</td>
<td>Week 148</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **OLE Year 1**
  - 26 weeks

- **OLE Year 2**
  - 26 weeks

- **OLE Year 3**
  - 26 weeks

- **End of Taper Period**
  - 10 days

- **Safety Follow-up Period**
  - 4 weeks

---

**Notes:**

a. End of Treatment/Withdrawal Visit will occur: 1) following early withdrawal from the trial; 2) in place of the next scheduled clinic visit (assessment or resupply) when GWP42003-P is approved in TSC and is commercially available to the patient; or 3) after a maximum of 3 years’ OLE treatment (i.e., 156 weeks ±7 days) from Visit B1; whichever occurs first.

b. Only required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P.

c. Safety Telephone Call must be made 2 weeks (+3 days) after the patient’s last dose of IMP.

d. This must be made 4 weeks (+3 days) after the patient’s last dose of IMP and can be conducted by telephone.

e. Visits B13, B14, B16, B17, B19, B20, B22, B23 – Resupply visits (±7 days).
4 DESIGN AND PROCEDURES

Patients and their parent(s)/legal representative will be invited to participate in years 2 and 3 of the OLE when they reach Visit B10 of the OLE phase. They will be issued with additional OLE patient information and informed assent or the patient/parent(s)/legal representative information and informed consent (as applicable). Following adequate time to discuss the additional visits with the investigator, nurse, relatives or caregiver, patients/parent(s)/legal representatives who provide written informed consent/assent at Visit B10 will continue in the OLE.

Patients will continue to make weekly interactive voice response system (IVRS) diary calls throughout their second and third years of OLE participation.

4.1 Visit B10 (Week 52)

In addition to the visit schedule outlined in Section 9.1.2.10 of the main protocol, patients treated in Poland who provide written informed consent/assent (see Section 5) will receive sufficient open-label IMP for 9 weeks’ home dosing and will be instructed to maintain consistent dosing. An additional dose calculator and paper diary will be issued, and patients will be trained on their appropriate use.

The Study Medication Use and Behavior Survey should not be administered at Visit B10 for patients entering the second year of the OLE. The investigator must record the patient’s attendance at the visit and confirm their continued participation.

4.2 Resupply Visits B13 (Week 61), B14 (Week 70), B16 (Week 87), B17 (Week 96), B19 (Week 113), B20 (Week 122), B22 (Week 139), and B23 (Week 148)

Visits B13, B14, B16, B17, B19, B20, B22, and B23 will occur 61, 70, 87, 96, 113, 122, 139, and 148 weeks after Visit B1, respectively. A visit window of ±7 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

Attendance of the patient is not required for resupply visits provided the primary caregiver is able to attend. However, it is preferred that the patient attend where possible.

Each visit will comprise a review of concomitant medications (including antiepileptic drugs [AEDs]), epilepsy-related hospitalizations and adverse events (AEs).
The investigator must assess adherence to the dosing regimen by reviewing the patient’s diary and IVRS data, record the patient’s/caregiver’s attendance at the visit, and confirm the outcome of the visit.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients/caregivers will then receive sufficient IMP until the next scheduled visit.

4.3 Assessment Visits B15 (Week 78), B18 (Week 104), and B21 (Week 130)

Visits B15, B18, and B21 will occur 78, 104, and 130 weeks after Visit B1, respectively. A visit window of ±7 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

The following assessments will be made at each visit:

- Concomitant medications (including AEDs)
- Physical examination (including height and body weight)
- 12-lead electrocardiogram (ECG)
- Vital signs
- Epilepsy-related hospitalizations
- AEs
- Subject Global Impression of Change in Seizure Duration (SGIC-SD)/Caregiver Global Impression of Change in Seizure Duration (CGIC-SD)
- Suicidality, assessed in accordance with Section 9.2.12.8 of the main protocol

At each assessment visit, clinical laboratory samples (blood and urine [where possible]), including a pregnancy test if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry, urinalysis, and determination of serum insulin-like growth factor-1 (IGF-1) levels (for patients less than 18 years of age) to be performed by the central laboratory. Provided that the risk/benefit outcome is favorable in the investigator’s opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs.
The investigator must assess adherence to the dosing regimen by reviewing the patient’s diary and IVRS data, record the patient’s attendance at the visit, and confirm the outcome of the visit.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients/caregivers will then receive sufficient IMP until the next scheduled visit.

In addition to the above, the following assessments will be made at Visit B18 only:

- Details of menstruation (for females)
- Tanner staging (patients aged 10–17 [inclusive] only)
- Quality of Life in Childhood Epilepsy (QOLCE)/Quality of Life in Epilepsy (QOLIE-31-P)
- Subject Global Impression of Change (SGIC)/Caregiver Global Impression of Change (CGIC)
- Physician Global Impression of Change (PGIC)
- Wechsler Tests
- Child Behavior Checklist (CBCL)/Adult Behavior Checklist (ABCL)
- Social Communication Questionnaire (SCQ)
- Vineland Adaptive Behavior Scales, Second Edition (Vineland-II)

4.4 End of Treatment/Withdrawal Visit

This visit will occur: 1) following early withdrawal from the trial; 2) in place of the next scheduled clinic visit (assessment or resupply) when GWP42003-P is approved in TSC and is commercially available to the patient; or 3) after a maximum of 3 years’ OLE treatment (i.e., 156 weeks [±7 days] from Visit B1); whichever occurs first.

The following assessments will be made at the End of Treatment/Withdrawal visit:

- Vital signs
- Physical examination (including height and body weight)
- Details of menstruation (for females)
- Tanner staging (patients aged 10–17 [inclusive] only)
• ECG
• IVRS and paper diary information (including information regarding seizures, AEs, usage of rescue medication, concomitant AEDs, and IMP dosing)
• Epilepsy-related hospitalizations
• Concomitant medications and/or changes to medication
• AEs
• QOLCE/QOLIE-31-P
• SGIC/CGIC
• PGIC
• SGIC-SD/CGIC-SD
• Wechsler Tests
• CBCL/ABCL
• SCQ
• Vineland-II
• Suicidality, assessed in accordance with Section 9.2.12.8 of the main protocol

Clinical laboratory samples (blood and urine [where possible]), including a pregnancy test if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry, urinalysis and determination of serum IGF-1 levels (for patients less than 18 years of age) to be performed by the central laboratory. Provided that the risk/benefit outcome is favorable in the investigator’s opinion, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs. The investigator must assess adherence to the dosing regimen.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. For patients who withdraw early, the IVRS will be contacted to confirm withdrawal from the trial. For patients who immediately continue to use commercial GWP42003-P following the End of Treatment visit, the IVRS will be contacted to confirm the patient’s completion of this trial and the paper diaries will be collected. For patients 12 years of age and older who complete treatment and immediately continue to use commercial GWP42003-P, or for patients 12 years of age and older who withdraw early and do not taper IMP, the trained investigator or study
The coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.

For patients who complete treatment but do not immediately continue to use commercial GWP42003-P following the End of Treatment visit, IMP will be tapered at home (10% per day for 10 days). Additional IMP will be dispensed, if required, and instructions for tapering the dose will be provided. Patients who withdraw early should also begin the taper period following the Withdrawal visit unless continued dosing is not possible due to an AE. Information will continue to be recorded in the paper diary during the taper period.

Following the End of Treatment/Withdrawal visit, the IVRS seizure reporting diary should be completed up to the Follow-up visit.

### 4.5 End of Taper Visit

This visit is required for patients who: 1) withdraw from the trial and taper IMP; or 2) complete treatment but do not immediately continue to use commercial GWP42003-P.

The End of Taper visit will take place 10 (+3) days after the End of Treatment/Withdrawal visit. For patients who begin to taper IMP but subsequently withdraw/do not complete the full taper period, this visit should occur on the final day of dosing or as soon as possible after this date.

The following assessments will be made:

- Vital signs
- Physical examination (including height and body weight)
- IVRS and paper diary information (including information regarding seizures, AEs, usage of rescue medication, concomitant AEDs, and IMP dosing)
- Epilepsy-related hospitalizations
- Concomitant medications and/or changes to medication
- AEs
- Suicidality, assessed in accordance with Section 9.2.12.8 of the main protocol
- ECG
- Clinical laboratory samples (blood and urine for hematology, biochemistry and urinalysis)
The investigator must assess adherence to the dosing regimen.

For patients 12 years of age and older, the trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made.

Following the End of Taper visit (or date of final dosing), the IVRS seizure reporting diary should be completed up to the Follow-up visit.

4.6 Safety Telephone Call

This visit is required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P. The Safety Telephone Call will be conducted 2 weeks (+3 days) after the patient’s last dose of GWP42003-P (including final taper period dose). During this call, caregivers will be asked for information on:

- AEs
- Epilepsy-related hospitalizations
- Concomitant medications and/or changes to medication

Following this call, the IVRS seizure reporting diary should be completed up to the Follow-up visit.

4.7 Follow-up Visit

This visit is required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P. The Follow-up visit will take place 4 weeks (+3 days) after the patient’s last dose of GWP42003-P (including final taper period dose) and can be conducted by telephone. During this visit/call, caregivers will be asked for information on:

- AEs
- Epilepsy-related hospitalizations
- Concomitant medications and/or changes to medication
5 INFORMED CONSENT/ASSENT

An institutional review board/independent ethics committee-approved informed consent/assent form will be given to eligible patients prior to Visit B10 of the parent trial (please refer to Section 9.1.2.11 of the main trial protocol) which will reflect the additional implications of this annex.

6 DATA ANALYSIS

6.1 Patients to Analyze

Patients in Poland who continue to participate in years 2 and 3 of the OLE will be analyzed in accordance with the statistical considerations detailed in Section 13 of the main protocol.

7 IMPLEMENTATION OF THE ANNEX

This clinical protocol annex will be issued in conjunction with the current version of the main clinical trial protocol. It will be kept in the trial master file at GW as well as in each Polish investigational site file and, if applicable, pharmacy site file.
# APPENDIX 1  SCHEDULE OF ASSESSMENTS

Open-label Extension

<table>
<thead>
<tr>
<th>Visit Number</th>
<th>B10</th>
<th>B13</th>
<th>B14</th>
<th>B15</th>
<th>B16</th>
<th>B17</th>
<th>B18</th>
<th>B19</th>
<th>B20</th>
<th>B21</th>
<th>B22</th>
<th>B23</th>
<th>See footnote a</th>
<th>End of Treatment/Withdrawal Visit</th>
<th>End of Taper Visit b</th>
<th>Safety Telephone Call b, c</th>
<th>Follow-up Visit b, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit Window</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>10 days after End of Treatment</td>
<td>+3</td>
<td>+3</td>
<td>+3</td>
<td>+3</td>
</tr>
</tbody>
</table>

- **Informed consent/assent**
  - X

- **Vital signs and BP**
  - X

- **Physical examination (including height and body weight)**
  - X

- **ECG**
  - X

- **Clinical laboratory blood sampling**
  - X

- **Clinical laboratory urine sampling (dipstick urinalysis)**
  - X

- **Pregnancy test, where appropriate**
  - X

- **IGF-1 testing**
  - X

- **AED concentration**
  - X

- **AEs**
  - X

- **Concomitant medications**
  - X
<table>
<thead>
<tr>
<th>Visit Number</th>
<th>B10</th>
<th>B13</th>
<th>B14</th>
<th>B15</th>
<th>B16</th>
<th>B17</th>
<th>B18</th>
<th>B19</th>
<th>B20</th>
<th>B21</th>
<th>B22</th>
<th>B23</th>
<th>Re-supply</th>
<th>Assessment</th>
<th>Re-supply</th>
<th>Assessment</th>
<th>Re-supply</th>
<th>Assessment</th>
<th>Re-supply</th>
<th>End of Treatment/Withdrawal Visit</th>
<th>10 days after End of Treatment</th>
<th>Safety Telephone Call</th>
<th>2 weeks after last dose</th>
<th>4 weeks after last dose</th>
<th>Follow-up b, d Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit Window</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>See footnote a</td>
<td>10 days after End of Treatment</td>
<td>Safety Telephone Call</td>
<td>2 weeks after last dose</td>
<td>4 weeks after last dose</td>
<td>Follow-up b, d Visit</td>
<td></td>
</tr>
<tr>
<td>Inpatient epilepsy-related hospitalizations</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Suicidality assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Vineland-II</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SGIC/CGIC</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>PGIC</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SGIC-SD/CGIC-SD</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>QOLCE/QOLIE-31-P</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Wechsler Tests</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CBCL/ABCL</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SCQ</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tanner Staging (where appropriate)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Menstruation question (where appropriate)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Patient IVRS and paper diary review (seizures, AE information, concomitant AEDs, rescue medication, IMP dosing)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Confidential
Clinical Protocol Annex Template
<table>
<thead>
<tr>
<th>Visit Number</th>
<th>B10</th>
<th>B13</th>
<th>B14</th>
<th>B15</th>
<th>B16</th>
<th>B17</th>
<th>B18</th>
<th>B19</th>
<th>B20</th>
<th>B21</th>
<th>B22</th>
<th>B23</th>
<th>End of Treatment/Withdrawal Visit</th>
<th>End of Taper Visit</th>
<th>Safety Telephone Call</th>
<th>Follow-up Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>week</td>
<td>52</td>
<td>61</td>
<td>70</td>
<td>78</td>
<td>87</td>
<td>96</td>
<td>104</td>
<td>113</td>
<td>122</td>
<td>130</td>
<td>139</td>
<td>148</td>
<td>See footnote&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10 days after End of Treatment</td>
<td>2 weeks after last dose</td>
<td>4 weeks after last dose</td>
</tr>
<tr>
<td>Visit Window</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>+3</td>
<td>+3</td>
<td>+3</td>
<td>+3</td>
</tr>
<tr>
<td>IMP dispensing</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collection of IMP</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMP compliance review</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Medication Use and Behavior Survey</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> End of Treatment/Withdrawal Visit will occur: 1) following early withdrawal from the trial; 2) in place of the next scheduled clinic visit (assessment or resupply) when GWP42003-P is approved in TSC and is commercially available to the patient; or 3) after a maximum of 3 years’ OLE treatment (i.e., 156 weeks [±7 days] from Visit B1); whichever occurs first.

<sup>b</sup> Only required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P.

<sup>c</sup> Safety Telephone Call must be made 2 weeks (+3 days) after the patient’s last dose of IMP.

<sup>d</sup> Follow-up Visit required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P. This must be made 4 weeks (+3 days) after the patient’s last dose of IMP and can be conducted by telephone.

<sup>e</sup> Performed at final dosing visit (End of Treatment/Withdrawal visit or End of Taper visit, as applicable) for patients 12 years of age and older only.
A double-blind, randomized, placebo-controlled study to investigate the
efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on
therapy in patients with tuberous sclerosis complex who experience
inadequately-controlled seizures

Study Code: GWEP1521

EudraCT Number: 2015-002154-12

CLINICAL PROTOCOL ANNEX 2 (POLAND ONLY)
AMENDMENT NUMBER: 1

to be incorporated into the Protocol Annex, creating
CLINICAL PROTOCOL ANNEX 2 VERSION 2
(POLAND ONLY), DATE 26 APRIL 2018

GW Research Ltd
Sovereign House
Vision Park
Chivers Way
Histon
Cambridge CB24 9BZ
United Kingdom

Confidentiality Statement
This document contains confidential information of GW Research Ltd (GW) that must
not be disclosed to anyone other than the recipient study staff and members of the
institutional review board or independent ethics committee. This information cannot be
used for any purpose other than the evaluation or conduct of the clinical investigation
without the prior written consent of GW.
2 RATIONALE

This clinical protocol annex 2 (Poland only) amendment 1 (will be incorporated into the Protocol Annex creating Clinical Protocol Annex 2 [Poland Only] Version 2, Date 26 April 2018) addresses the following issue(s): **Duration of Open-label Extension Phase**

The OLE phase will be extended in duration in Poland to ensure continued access to GWP42003-P prior to approval. Patients will complete the OLE phase when GWP42003-P is approved in TSC and is commercially available to the patient, or after a maximum of 3 years’ OLE treatment, whichever occurs first. Procedures for each resupply visit and assessment visit have been condensed into single sections in the Annex to minimize repetition.

2.2 Minor Corrections and Clarifications

The following minor corrections/clarifications have been made to the protocol annex:

- Clarification that the End of Taper Visit, Safety Telephone Call, and Follow-up Visit are required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P. Furthermore, the timings of these visits/calls are relative to the End of Treatment/Withdrawal Visit.

- Clarification that Safety Telephone Call is still required for patients who do not taper IMP, that the call window is +3 days, and that the patient’s last dose includes the final taper period dose.

- Clarification that the Follow-up Visit can be a clinic visit or can be conducted by telephone.

- Clarification that the Study Medication Use and Behavior Survey should not be administered at Visit B10 for patients entering the second year of the OLE and should only be administered at the final dosing visit (End of Treatment/Withdrawal visit or End of Taper visit, as applicable).

- Treatment days have been removed in favor of treatment weeks, as this is more compatible with the interactive voice response system.

- Collection of informed consent/assent at Visit B10 was listed in the Schedule of Assessments but was not mentioned in Section 4.1 of the Annex.
• Additional assessments for patients who withdraw early and taper IMP were listed in the End of Taper Visit section of the Annex but had not been denoted in the Schedule of Assessments.

• Abbreviations which are not used in the Annex have been removed from the List of Abbreviations, and abbreviated terms have been defined on first use.

• Terms which are not used in the Annex have been removed from the Definition of Terms.

• Bulleted lists have been used to improve readability.

• References to “the study” has been replaced with “the trial” throughout.

• Minor spelling/punctuation/grammatical corrections have been made to improve consistency and readability; however, in the interest of brevity, these changes are not captured in Section 4 of this amendment document.

3 IMPLEMENTATION OF THE AMENDMENT

The changes detailed in this amendment will be issued as Clinical Protocol Annex 2 (Poland Only) Version 2, Date 26 April 2018. It will be kept in the trial master file at GW as well as in each investigational site file and, if applicable, pharmacy site file.
GW Research Ltd.

Trial Code: GWEP1521

A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF CANNABIDIOL (GWP42003-P, CBD) AS ADD-ON THERAPY IN PATIENTS WITH TUBEROUS SCLEROSIS COMPLEX WHO EXPERIENCE INADEQUATELY-CONTROLLED SEIZURES

Statistical Analysis Plan

17 April 2019
CONTENTS

1. INTRODUCTION 6
   1.1 Rationale 6

2. TRIAL OBJECTIVES 7
   2.1 Primary Objective 7
   2.2 Secondary Objectives 7
   2.3 Exploratory Objectives 7

3. INVESTIGATIONAL PLAN 8
   3.1 Trial Design 8
   3.2 Definition of Sample Size 9
   3.3 Efficacy and Safety Endpoints 9
      3.3.1 Primary Efficacy Endpoint 9
      3.3.2 Secondary Efficacy Endpoints 9
      3.3.3 Exploratory Endpoints (Double-blind and Open-label Extension) 11

4. BLINDED DATA REVIEW MEETING 12

5. STATISTICAL METHODS 12
   5.1 General Considerations 12
      5.1.1 Missing Data 14
      5.1.2 Day Numbering 15
      5.1.3 Definitions 15
      5.1.4 Interim Analysis 16
   5.2 Analysis Sets and Protocol Deviations 18
      5.2.1 Safety Analysis Set 18
      5.2.2 Intention to Treat Analysis Set 18
      5.2.3 Per Protocol Analysis Set and Protocol Deviations 18
      5.2.4 OLE Safety Analysis Set 18
   5.3 Listings 18
   5.4 Demographic Data and Patient Characteristics 19
      5.4.1 Patient Disposition 19
      5.4.2 Analysis Sets 19
      5.4.3 Demographic Data and Baseline Characteristics 19
      5.4.4 Epilepsy History 20
      5.4.5 Medical and Surgical History and Current Medical Conditions 21
   5.5 Efficacy Analysis 21
      5.5.1 General Approach 21
      5.5.2 Primary Efficacy Endpoint 22
      5.5.3 Secondary Efficacy Endpoints 27
      5.5.4 Exploratory Efficacy Endpoints 33
      5.5.5 Subgroup Analyses 43
   5.6 Safety Evaluation 43
5.6.1 Exposure to IMP 43
5.6.2 Adverse Events 44
5.6.3 Clinical Laboratory Evaluation 47
5.6.4 Vital Signs, Other Physical Findings and Other Safety Data 49

5.7 Other Measures 51
5.7.1 Concomitant Medication 51
5.7.2 Pharmacokinetics of CBD and its Major Metabolites 52
5.7.3 Plasma Concentrations of Concomitant AEDs 54
5.7.4 Study Medication Use and Behavior Survey 54
5.7.5 Supplemental Drug Accountability Form 54
5.7.6 Supplemental Adverse Event Form 54
5.7.7 Site Classification Form 55
5.7.8 IVRS Compliance 55

5.8 Changes in the Conduct of the Trial or Planned Analysis 56

6. REFERENCES 56
7. AMENDMENTS 56
8. ATTACHMENTS AND APPENDICES 57
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-COOH-CBD</td>
<td>7-carboxy-CBD</td>
</tr>
<tr>
<td>7-OH-CBD</td>
<td>7-hydroxy-CBD</td>
</tr>
<tr>
<td>ABCCL</td>
<td>Adult Behavior Checklist</td>
</tr>
<tr>
<td>AEDs</td>
<td>Antiepileptic Drugs</td>
</tr>
<tr>
<td>AEs</td>
<td>Adverse Events</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of Covariance</td>
</tr>
<tr>
<td>ALQ</td>
<td>Above Limit of Quantification</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical</td>
</tr>
<tr>
<td>BDRM</td>
<td>Blinded Data Review Meeting</td>
</tr>
<tr>
<td>BLQ</td>
<td>Below Limit of Quantification</td>
</tr>
<tr>
<td>CBCL</td>
<td>Child Behavior Checklist</td>
</tr>
<tr>
<td>CBD</td>
<td>Cannabidiol</td>
</tr>
<tr>
<td>CGIC</td>
<td>Caregiver Global Impression of Change</td>
</tr>
<tr>
<td>CGICSD</td>
<td>Caregiver Global Impression of Change in Seizure Duration</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CMH</td>
<td>Cochran–Mantel–Haenszel</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>C-SSRS</td>
<td>Columbia-Suicide Severity Rating Scale</td>
</tr>
<tr>
<td>CWS</td>
<td>Cannabis Withdrawal Scale</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>IGF-1</td>
<td>Insulin-like Growth Factor-1</td>
</tr>
<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention to Treat</td>
</tr>
<tr>
<td>IVRS</td>
<td>Interactive Voice Response System</td>
</tr>
<tr>
<td>LGS</td>
<td>Lennox-Gastaut Syndrome</td>
</tr>
<tr>
<td>LOCF</td>
<td>Last Observation Carried Forward</td>
</tr>
<tr>
<td>MAR</td>
<td>Missing at Random</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>MI</td>
<td>Multiple Imputation</td>
</tr>
<tr>
<td>MNAR</td>
<td>Missing Not at Random</td>
</tr>
<tr>
<td>NOCB</td>
<td>Next Observation Carried Backward</td>
</tr>
<tr>
<td>NRS</td>
<td>Numerical Rating Scale</td>
</tr>
<tr>
<td>OLE</td>
<td>Open Label Extension</td>
</tr>
<tr>
<td>PCWS</td>
<td>Pediatric Cannabinoid Withdrawal Scale</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>PGIC</td>
<td>Physician Global Impression of Change</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>PP</td>
<td>Per Protocol</td>
</tr>
<tr>
<td>QOLCE</td>
<td>Quality of Life in Childhood Epilepsy</td>
</tr>
<tr>
<td>QOLIE-31-P</td>
<td>Quality of Life in Epilepsy, version 2</td>
</tr>
<tr>
<td>RM</td>
<td>Rescue Medication</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
</tr>
<tr>
<td>SGIC</td>
<td>Subject Global Impression of Change</td>
</tr>
<tr>
<td>SGICSD</td>
<td>Subject Global Impression of Change in Seizure Duration</td>
</tr>
<tr>
<td>SOC</td>
<td>System Organ Class</td>
</tr>
<tr>
<td>SCQ</td>
<td>Social Communication Questionnaire</td>
</tr>
<tr>
<td>TAND</td>
<td>TSC-associated Neuropsychiatric Disorders</td>
</tr>
<tr>
<td>TEAE</td>
<td>Treatment Emergent Adverse Event</td>
</tr>
<tr>
<td>TSC</td>
<td>Tuberous Sclerosis Complex</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper Limit of Normal</td>
</tr>
<tr>
<td>Vineland-II</td>
<td>Vineland Adaptive Behavior Scales, Second Edition</td>
</tr>
</tbody>
</table>
1. INTRODUCTION

This statistical analysis plan (SAP) documents the statistical reporting to be performed for trial GWEP1521.

This SAP has been prepared based on the following protocol:


1.1 Rationale

Tuberous sclerosis complex (TSC) is a genetic disorder characterized by the formation of nonmalignant tumors (tubers) in multiple organ systems. The clinical signs of TSC arise as a result of inactivating mutations in either of two tumor suppressor genes: TSC1 (located on chromosome 9q34.13) or TSC2 (located on chromosome 16p13.3). Thus, inactivating mutations in TSC1 and TSC2 lead to inadequate suppression of mTOR signaling, resulting in abnormal cellular growth and tumorigenesis.

Mutations in TSC1 account for approximately 15% of all cases of TSC whilst approximately 70% of all cases are due to mutations in TSC2; ~15% of TSC patients have no identifiable mutation in the coding regions of either gene. Generally, TSC2 mutations result in a more severe disease phenotype compared with TSC1 mutations. The birth incidence of TSC is estimated to be 1 in 6,000 with approximately 50,000 individuals in the United States and 1 million individuals worldwide affected.

Tumors in TSC patients can occur in any major organ yet develop primarily in the brain, eyes, heart, kidney, skin and lungs.

Epileptic seizures are the most common clinical manifestation of TSC, affecting more than 70% of patients. Seizure onset occurs within the first year of life in approximately two-thirds of TSC patients and occurs within the first 3 years of life in 80% of TSC patients. The onset of epilepsy in TSC commonly manifests as focal motor seizures, which in approximately one-third of TSC patients coexist with infantile spasms.

Virtually all TSC patients with infantile spasms and approximately half of all epileptic TSC patients without them develop multiple seizure types, including complex focal seizures (with or without secondary generalization), generalized tonic–clonic seizures, atonic seizures, and atypical absences. Although infantile spasms resolve with time, the frequency and severity of other seizures tend to increase throughout early childhood and nearly two-thirds of TSC patients develop medically intractable epilepsy, including Lennox–Gastaut syndrome.

Early management of seizures is therefore important in preventing subsequent epileptic encephalopathy and in reducing the associated cognitive and neuropsychiatric consequences.

The pharmacological therapies currently available for TSC-associated epilepsy often produce serious adverse effects, and a significant proportion of patients (37–63%) become resistant to treatment. Consequently, there is a clear need for new, efficacious pharmaceutical treatments for refractory epilepsy. Given the limitations of current synthetic antiepileptic drugs (AEDs), it has been suggested that CBD should be tested for anticonvulsive efficacy in randomized controlled clinical trials, especially in infantile epileptic syndromes. Although there are no published reports to date investigating the efficacy of CBD for seizures in TSC patients, a recent parent survey has reported that 84% of children with treatment-resistant epilepsy experienced a reduction in seizures whilst taking CBD-enriched cannabis, with over half of those reporting >80% reduction in seizure frequency.
The CBD-enriched cannabis was behaviorally well tolerated and children often experienced improved sleep, increased alertness, and better mood.

2. TRIAL OBJECTIVES

The protocol defined the trial objectives as:

2.1 Primary Objective

Blinded Phase:

To evaluate the efficacy of GWP42003-P as add-on therapy in reducing the frequency of seizures when compared with placebo in patients with TSC.

Open-label Extension:

To evaluate via the adverse events (AE) profile the long term safety and tolerability of GWP42003-P as add-on therapy in children and adults with TSC who experience inadequately-controlled seizures.

2.2 Secondary Objectives

Blinded Phase:

- To evaluate the effect of GWP42003-P compared with placebo on antiepileptic measures.
- To evaluate the effect of GWP42003-P on growth and development (in patients less than 18 years old) compared with placebo.
- To evaluate the effects of GWP42003-P on quality of life compared with placebo.
- To evaluate the safety and tolerability of GWP42003-P compared with placebo.

Open-label Extension:

- To evaluate the long term effects of GWP42003-P, as add-on therapy, on antiepileptic measures.
- To evaluate the long term effect of GWP42003-P on growth and development (in patients less than 18 years old).
- To evaluate the long term effects of GWP42003-P on quality of life.
- To evaluate the long term safety and tolerability of GWP42003-P.

2.3 Exploratory Objectives

Blinded Phase:

- To evaluate the effect of GWP42003-P on TSC-associated neuropsychiatric disorders (TAND), including cognitive and behavioral function and autistic features compared with placebo.
- To determine the pharmacokinetics (PK) of CBD, and its major metabolites following single and multiple doses of GWP42003-P.
- To evaluate the effects of GWP42003-P on plasma concentrations of concomitant AEDs, if applicable.
Open-label Extension:

- To evaluate the long term effect of GWP42003-P on TAND, including cognitive and behavioral function and autistic features compared with placebo.

3. INVESTIGATIONAL PLAN

3.1 Trial Design

This multicenter trial consists of a randomized, placebo-controlled, double-blind phase followed by an open-label extension (OLE) phase.

Blinded Phase:

The blinded phase of the trial is a randomized, double-blind, parallel-group, 16-week comparison of two doses of GWP42003-P vs. placebo. Patients will complete a 1-week screening period and a 4-week baseline period before they are randomized to receive either 25 mg/kg/day GWP42003-P, 50 mg/kg/day GWP42003-P or placebo. Randomization will be stratified by age according to the following ranges: 1–6, 7–11, 12–17 years and 18–65 years. Patients will begin a 4-week dose escalation period, titrating up to their assigned dose, before continuing on a stable dose of blinded Investigational Medicinal Product (IMP) for 12 weeks.

Dose escalation for each patient is subject to the investigator’s assessment of safety and tolerability. If a dose becomes poorly tolerated, the investigator may consider temporarily or permanently reducing the dose for the remainder of the trial.

Following completion of the blinded phase, patients will be invited to continue to receive GWP42003-P in an OLE.

Those patients opting not to enter the OLE will complete a 10-day taper period (down-titrating 10% per day for 10 days).

Open-label Extension Transition:

In order to maintain consistent exposure to IMP and maintain the integrity of the blind, patients will enter a 2-week blinded transition to the OLE. OLE IMP will be titrated up to 25 mg/kg/day whilst blinded IMP is simultaneously tapered down to zero. All patients will complete the transition and enter the OLE taking 25 mg/kg/day GWP42003-P:

- Patients from the placebo arm will titrate up to 25 mg/kg/day GWP42003-P.
- Patients from the 25 mg/kg/day GWP42003-P arm will continue to take 25 mg/kg/day GWP42003-P.
- Patients from the 50 mg/kg/day GWP42003-P arm will taper down (10% per day) to 25 mg/kg/day GWP42003-P.

Open-label Extension:

The OLE consists of a 3-week titration period followed by a maintenance period and a 10-day taper period. The initial OLE period will last for a maximum of 1 year.

Following titration according to the titration schedule, patients will continue with their optimal GWP42003-P dose. However, investigators may decrease the dose if a patient experiences intolerance, or increase the dose to a maximum of 50 mg/kg/day if required for better seizure control, until the optimal dose is found.
3.2 Definition of Sample Size

Blinded Phase:

A total of 210 patients will be enrolled. The 210 patients will be randomly allocated to 1 of 4 treatment arms (GWP42003-P 25 mg/kg/day, GWP42003 P 50 mg/kg/day, placebo 25 mg/kg/day dose volume equivalent, or placebo 50 mg/kg/day dose volume equivalent) at a 2:2:1:1 ratio. The placebo arms will be pooled for the analyses of efficacy.

If it is assumed that patients in the placebo arm will experience a mean reduction in seizure frequency of 15% (from baseline), patients receiving GWP42003-P will experience at least a 50% reduction in seizures and a common standard deviation of 60%, then this sample size of 70 patients per arm will be sufficient to detect a difference in response distributions with 90% power. This test is based on a two-sided non-parametric Mann-Whitney-Wilcoxon test for continuous response data with a 5% significance level.

Open-label Extension:

All patients who wish to continue on IMP following the blinded phase.

3.3 Efficacy and Safety Endpoints

3.3.1 Primary Efficacy Endpoint

Blinded Phase:

The primary endpoint is the change in number of TSC associated seizures* during the treatment period (maintenance and titration) compared to baseline in patients taking GWP42003-P compared with placebo.

*Primary endpoint TSC-associated seizures include: focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures (tonic–clonic, tonic, clonic or atonic) that are countable.

Open-label Extension:

The safety of GWP42003-P will be evaluated by assessing the incidence, type and severity of AEs.

3.3.2 Secondary Efficacy Endpoints

Blinded Phase:

The following endpoints will be compared between treatment arms over the 16-week, double-blind treatment period (all changes relative to baseline):

Key:

1. Number of patients considered treatment responders defined as those with a ≥ 50% reduction in TSC-associated seizure frequency (see Section 5.1.3.7).
2. Change in Caregiver Global Impression of Change (CGIC) or Subject Global Impression of Change (SGiC) score.
3. Change in total seizures.
Other:

**Antiepileptic Efficacy Measures:**

- Number of patients considered treatment responders defined as those with a ≥ 25%, ≥ 50%, ≥ 75% or 100% reduction in TSC-associated seizure frequency.
- Number of patients experiencing a > 25% worsening, −25 to +25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in TSC-associated seizure frequency.
- Change in number of TSC-associated seizure-free days.
- Change in number of ‘other’ seizures (absence, myoclonic, focal sensory and infantile/epileptic spasms).

**Growth and Development (in patients less than 18 years old):**

- Change in serum insulin-like growth factor-1 (IGF-1) levels.
- Change in Tanner Staging score (for patients aged 10–17 [inclusive]).

**Quality of Life:**

- Changes in the Quality of Life in Childhood Epilepsy (QOLCE; patients 2–18 years) or Quality of Life in Epilepsy (QOLIE-31-P; patients 19+ years) score.
- Change in Physician Global Impression of Change (PGIC) score.

**Safety and Tolerability:**

- AEs.
- Clinical laboratory parameters.
- 12-lead electrocardiogram (ECG).
- Physical examination parameters.
- Vital signs.
- Columbia-Suicide Severity Rating Scale (C-SSRS: 19+ years) or C-SSRS Children’s (6–18 years) score, where applicable.
- Number of inpatient hospitalizations due to epilepsy.
- Abuse liability.
- Effects on menstruation cycles (in females).

**Open Label Extension:**

The following endpoints will be assessed relative to the pre-randomization baseline of the blinded phase:

**Key:**

- Percentage change in number of TSC-associated seizures (average per 28 days).
- Number of patients considered treatment responders defined as those with a ≥ 50% reduction in TSC-associated seizure frequency.
- Change in CGIC or SGIC score.
- Change in total seizures.
Other:

**Antiepileptic Efficacy Measures:**

- Number of patients considered treatment responders defined as those with a ≥ 25%, ≥ 50%, ≥ 75% or 100% reduction in TSC-associated seizure frequency.
- Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in TSC-associated seizure frequency.
- Change in number of TSC-associated seizure-free days.
- Change in number of ‘other’ seizures (absence, myoclonic, focal sensory and infantile/epileptic spasms).

**Growth and Development (patients less than 18 years):**

- Change in serum IGF-1 levels.
- Change in Tanner Staging score (for patients aged 10–17 inclusive).

**Quality of Life:**

- Changes in the QOLCE (patients 2–18 years) or QOLIE-31-P (patients 19+ years) score.
- Change in PGIC score.

**Safety and Tolerability:**

- Clinical laboratory parameters.
- ECG.
- Physical examination parameters (including height and weight).
- Vital signs.
- C-SSRS (19+ years) or C-SSRS Children’s (6–18 years) score, where applicable.
- Number of inpatient hospitalizations due to epilepsy.
- Abuse liability.
- Effects on menstruation cycles (in females).

**3.3.3 Exploratory Endpoints (Double-blind and Open-label Extension)**

**Antiepileptic Efficacy Measures:**

- Change in composite focal seizure score (frequency × severity).
- Change in number of seizures by subtype.
- Change in use of rescue medication.
- Change in the number of episodes of status epilepticus (convulsive and non-convulsive).
- Changes in duration of seizure subtypes as assessed by the Subject Global Impression of Change in Seizure Duration (SGIC-SD) or the Caregiver Global Impression of Change in Seizure Duration (CGIC-SD).

**TAND:**

**Cognitive and Behavioral Function:**

• Changes in Wechsler Scales (pre-school, primary, children, adult).
• Changes in Achenbach Child Behavior Checklists (CBCL) and Adult Behavior Checklist (ABCL).

Autistic Features:

Change in Social Communication Questionnaire (SCQ) score.

PK (Double-blind only):

• The plasma concentrations will be summarized by time window for CBD and its major metabolites following single and multiple doses of GWP42003-P. Where data allows, the area under the plasma concentration curve (AUC) from time zero to the last measurable time-point will be calculated.
• Plasma concentrations of concomitant AEDs before and after treatment with GWP42003-P, where available.

4. BLINDED DATA REVIEW MEETING

Prior to breaking the blind, it is anticipated that a Blinded Data Review Meeting (BDRM) will take place. The objectives of the meeting will include the identification and agreement on major protocol deviations and the need for a per protocol (PP) analysis set.

The meeting will have access to the following blinded summary tables and listings:

• Pre-randomization patient data
• Patient efficacy data
• Concomitant medication data
• Patient safety data
• Patient protocol deviation logs

This SAP documents the currently planned analyses for this trial that will be approved prior to breaking the blind for the trial. Changes to the analyses planned within any previously approved versions of the SAP will be summarized in Section 7 and integrated into the text of the SAP. The minutes of the BDRM will be documented separately.

5. STATISTICAL METHODS

5.1 General Considerations

In all tables, listings and figures for the double-blind phase, the trial medications will be referred to and labelled as per Table 1.

Table 1  Blinded Phase Trial Treatments

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Actual Treatment</th>
<th>Treatment Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Pooled Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Safety</td>
<td>25 mg/kg/day Placebo</td>
<td>Placebo 25 mg/kg</td>
</tr>
<tr>
<td></td>
<td>50 mg/kg/day Placebo</td>
<td>Placebo 50 mg/kg</td>
</tr>
<tr>
<td>All</td>
<td>25 mg/kg/day GWP42003-P</td>
<td>25 mg/kg</td>
</tr>
<tr>
<td>All</td>
<td>50 mg/kg/day GWP42003-P</td>
<td>50 mg/kg</td>
</tr>
</tbody>
</table>

For safety tables where placebo is split by dosing volume, an additional Pooled Placebo column will be included.
For OLE tables, columns will be included for treatment received during the double-blind phase (GWP42003-P or placebo, i.e. not split by dose) and overall.

In all tables, listings and figures, the trial visits will be referred to and labelled as per Table 2.

### Table 2 Trial Visits

<table>
<thead>
<tr>
<th>Actual Visit</th>
<th>Visit Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1: Screening</td>
<td>Day -35</td>
</tr>
<tr>
<td>Visit 2: Day -28, baseline visit</td>
<td>Day -28</td>
</tr>
<tr>
<td>Visit 3: Day 1, Randomization</td>
<td>Day 1</td>
</tr>
<tr>
<td>Visit 4: Day 15</td>
<td>Day 15</td>
</tr>
<tr>
<td>Visit 5: Day 29</td>
<td>Day 29</td>
</tr>
<tr>
<td>Visit 6: Day 43</td>
<td>Day 43</td>
</tr>
<tr>
<td>Visit 7: Day 57</td>
<td>Day 57</td>
</tr>
<tr>
<td>Visit 8: Day 71, Telephone</td>
<td>Day 71</td>
</tr>
<tr>
<td>Visit 9: Day 85</td>
<td>Day 85</td>
</tr>
<tr>
<td>Visit 10: Day 113</td>
<td>End of Treatment</td>
</tr>
<tr>
<td>Visit 11: Day 123</td>
<td>End of Taper</td>
</tr>
<tr>
<td>Visit 12: Day 151</td>
<td>Safety Follow-Up</td>
</tr>
<tr>
<td>Visit B1: Day 1, Enrollment</td>
<td>OLE Day 1</td>
</tr>
<tr>
<td>Visit B2: Day 15</td>
<td>OLE Day 15</td>
</tr>
<tr>
<td>Visit B3: Day 36</td>
<td>OLE Day 36</td>
</tr>
<tr>
<td>Visit B4: Day 92</td>
<td>OLE Day 92</td>
</tr>
<tr>
<td>Visit B5: Day 141, Re-stocking of supplies</td>
<td>OLE Day 141</td>
</tr>
<tr>
<td>Visit B6: Day 183</td>
<td>OLE Day 183</td>
</tr>
<tr>
<td>Visit B7: Day 232, Re-stocking of supplies</td>
<td>OLE Day 232</td>
</tr>
<tr>
<td>Visit B8: Day 274</td>
<td>OLE Day 274</td>
</tr>
<tr>
<td>Visit B9: Day 323, Re-stocking of supplies</td>
<td>OLE Day 323</td>
</tr>
<tr>
<td>Visit B10: Day 365</td>
<td>OLE End of Treatment</td>
</tr>
<tr>
<td>Visit B11: Day 375</td>
<td>OLE End of Taper</td>
</tr>
<tr>
<td>Visit B12: Day 389</td>
<td>OLE Post-taper Safety Telephone Call</td>
</tr>
<tr>
<td>Day 403</td>
<td>OLE Follow-Up</td>
</tr>
</tbody>
</table>

Unless stated otherwise, continuous variables will be summarized showing the number of non-missing values (n), mean, standard deviation, median, minimum and maximum and categorical variables will be summarized showing the number and percentage of patients falling in each category. For continuous summaries of seizure frequency, the lower and upper quartiles will also be presented.

Minimum and maximum values will be presented to the same decimal precision as the raw data. Mean and median will be presented to one more decimal place than the raw data, and standard deviation to 2 more decimal places than the raw data. Percentages will be presented to one decimal place.

Unless otherwise specified, tables for the blinded phases will be summarized by randomized treatment arm, and for the open-label extension phase will be summarized by double-blind randomized treatment arm and overall.

All analyses and summaries will be produced using SAS Version 9.3 or higher.
5.1.1 Missing Data

5.1.1.1 Handling of Missing Data for the Primary Efficacy Endpoint

If a patient withdraws during the treatment period, then the primary analysis variable will be calculated from all the available data, during the treatment period, including any data available after the patient withdraws.

Section 5.5.2.1 describes sensitivity analyses to account for missing data arising from unreported days in the interactive voice response system (IVRS), and missing data arising from patients withdrawing during the treatment period.

5.1.1.2 Handling of Missing Data for the Secondary Efficacy Endpoints

5.1.1.2.1 Quality of Life in Childhood Epilepsy (2–18 Years)

The calculations of subscale and overall scores for the QOLCE will treat responses of ‘Not Applicable’ as missing values.

For each subscale, if fewer than 50% of the items within the subscale are missing (including ‘Not Applicable’) then the subscale score will be calculated using the mean of the non-missing items. If 50% or more of the items within the subscale are missing then the subscale score will not be calculated and will be missing.

For the overall quality of life score, if less than 8 of the 16 subscale scores are missing then the overall quality of life score will be calculated using the mean of the non-missing subscale scores. If 8 or more of the subscale scores are missing then the overall quality of life score will not be calculated and will be missing.

5.1.1.2.2 Quality of Life in Epilepsy, Version 2 (19 Years and Above)

For missing questions within subscales, the following rule will be applied:
- For subscales containing 4 or more questions (not including the ‘distress’ item), apply the following:
  - If less than or equal to 50% of the questions within the subscale are missing then the converted score for the missing questions will be set to the average of the non-missing question converted scores.
  - If more than 50% of the questions within the subscale are missing then the subscale weighted score will be set to missing.
- For subscales containing less than 4 questions (not including the ‘distress’ item) the subscale weighted score will be set to missing.

For missing ‘distress’ items, the following rule will be applied:
- If the corresponding subscale weighted score is missing then no imputation is needed and the ‘distress’ item converted score will be missing.
- If the corresponding subscale weighted score is not missing then set to the average of the non-missing ‘distress’ item converted scores.

For missing subscale weighted scores or missing ‘distress’ item converted scores, the following rule will be applied when calculating the total score:
- If 3 or more of the ‘distress’ item converted scores are missing then the total score will be set to missing.
- If 3 or more of the subscale weighted scores are missing then the total score will be set to missing.
• If less than 3 ‘distress’ item converted scores are missing and less than 3 subscale weighted scores are missing, then the total score will be calculated based on the available non-missing data, following the rules above.

Note: it is possible that a subscale weighted score is missing, but that the corresponding ‘distress’ item was answered and the converted score is not missing. Following the rules above, the total score would include the non-missing ‘distress’ item converted score in the calculation even though the corresponding subscale weighted score is missing and hence not included.

5.1.1.3 Adverse Events

Missing and/or incomplete dates/times for AEs will be imputed in a manner resulting in the earliest onset or the longest duration during the treatment period, taking into account that the start date/time should not be after the stop date/time. Stop dates/times will not be imputed if the AE is ongoing.

The imputation method will only be used to determine treatment emergence, and imputed dates/times will not be presented in AE outputs.

A worst-case approach will be followed in the event of missing severity or causality data. If the severity is missing, ‘Severe’ will be imputed. If causality data is missing, ‘Yes’ will be imputed for the question ‘Plausible relationship to study medication’.

5.1.1.4 Concomitant Medication

Missing concomitant medication dates will be handled in a similar fashion as described for AEs in Section 5.1.1.3.

5.1.2 Day Numbering

Blinded Phase:

The first day of treatment (Day 1) will be taken from the Study Medication case report form (CRF) page at Visit 3. However, if this date is missing then the date of Visit 3 will be used.

Any days prior to Day 1 will be numbered relative to this day and calculated as:

\[ \text{Date} - (\text{Date of Day 1}); \text{to give Day} -1, -2, -3 \text{ etc.} \]

Any days post Day 1 will be calculated as:

\[ 1 + \text{Date} - (\text{Date of Day 1}) \]

Open-label Extension:

The first day of treatment in the OLE (OLE Day 1) will be day of entry into the OLE, which is expected to be the same day as the end of treatment visit from the blinded phase. OLE day will be calculated as above but relative to OLE Day 1.

5.1.3 Definitions

5.1.3.1 Baseline

For clinic visit based endpoints, baseline is defined as the last record or measure collected prior to the first dose of IMP.
For IVRS based endpoints, baseline will include all available data from the day of Visit 2 to Day 1 of the blinded phase.

5.1.3.2 Last Visit

Last visit for endpoints assessed at clinic visits is defined as the last scheduled visit (not including the end of taper or safety follow-up visits) at which patient's last evaluation is performed.

5.1.3.3 Last 12 Weeks (OLE Only)

The last 12 weeks (84 days) of the OLE for IVRS based endpoints is defined as all available data from 12 weeks prior to the earliest of the date of the patient completing the OLE, or the last call to IVRS.

5.1.3.4 Treatment Period

The treatment period of the double-blind phase is defined as Day 1 to Day 113.

5.1.3.5 Titration Period

The titration period of the double-blind phase is defined as Day 1 to Day 28.

5.1.3.6 Maintenance Period

The maintenance period of the double-blind phase is defined as Day 29 to Day 113.

5.1.3.7 TSC-associated Seizures

TSC-associated seizures are defined as focal motor seizures without impairment of consciousness or awareness, focal seizures with impairment of consciousness or awareness, focal seizures evolving to bilateral generalized convulsive seizures, and generalized seizures (tonic-clonic, tonic, clonic and atonic) that are countable.

5.1.3.8 Other Seizures

Other seizures are defined as absence, myoclonic, partial (focal) sensory seizures, and infantile or epileptic spasms.

5.1.3.9 Total Seizures

Total seizures are defined as the combination of TSC-associated seizures and other seizures.

5.1.3.10 Focal Seizures

Focal seizures are defined as Type 1, Type 2 or Type 3 as follows:

- Type 1: focal motor seizures without impairment of consciousness or awareness.
- Type 2: focal seizures with impairment of consciousness or awareness.
- Type 3: focal seizures evolving to bilateral convulsive seizures.

5.1.4 Interim Analysis

No formal interim analysis is to be conducted in this trial. However, interim reporting of the OLE may be required to support regulatory filings. This SAP contains details for the final reporting of the double-blind and OLE phases of the trial. For interim reporting of the OLE,
the rules described in the SAP will be followed. However, only a subset of outputs including OLE data may be required to support regulatory filings.

If interim reporting of the OLE is required, then only data available up to and including the date of the data cut will be included. The below section describes how data will be selected for the interim reporting.

5.1.4.1 Selection of Data and Handling of Partial Dates

For data that has an associated visit date or date of collection but does not have an associated start or end date, there is expected to be no partial date information. Therefore, data of this type that are collected after the date of data cut will not be included as part of the interim analysis. For non-medical history data that have an associated start date or end date, such as AEs or concomitant medications, the following rules will be followed in order to determine whether the records are included in the interim analysis.

Partial Start and/or End Dates

The following procedures will be followed in the event that a record has partial start or end dates:

Partial start date:

- If the start date is partial, then it will be assumed to have started at the earliest possible date based on the partial date provided, for the purposes of determining if the data should be included in the interim analysis only.

Partial end date:

- If the end date is partial, then it will be assumed to have ended at the latest possible date based on the partial date provided. However, if the patient withdrew from the trial, completed the trial or died prior to this imputed date, then the maximum of the last available visit date and the withdrawal/completion or death date will be used instead.

Once the dates have been suitably imputed, the processes for complete start or end dates, specified below, can then be followed to determine whether the record should be included in the data cut and how it should be adapted.

Complete Start or End Dates

The following procedures will be followed in the event that a record has complete start or end dates:

- If the start date falls on or before the date of data cut and the end date falls after the date of data cut, then the record will be included in the data cut but the end date will be set to missing and depending on the type of data, the following adjustments will be made:
  - For an AE record, the outcome will be set to “Continuing”.
  - For a concomitant medication record, the record will be set to “Ongoing at the End of the Trial”.
- If the start date falls after the date of data cut, then the record will not be included in the data cut.
5.2 Analysis Sets and Protocol Deviations

5.2.1 Safety Analysis Set
All randomized patients who received at least 1 dose of IMP will be included and analyzed according to the treatment received. Only patients for whom it has been confirmed that they did not take any IMP will be excluded from this safety analysis set.

5.2.2 Intention to Treat Analysis Set
All randomized patients who received at least one dose of IMP will be included and analyzed according to their randomized treatment arm.

The intention to treat (ITT) analysis set is the primary analysis set for all efficacy endpoints.

5.2.3 Per Protocol Analysis Set and Protocol Deviations
If there are a sufficient number of significant protocol deviations in the trial, a PP analysis set may also be presented.

All patients who complete the trial with no protocol deviations deemed to compromise the assessment of efficacy, will be included and analyzed according to the treatment arm they were randomized. The rules determining the PP analysis set will be fully defined prior to unblinding of the database.

A listing will be produced of protocol deviations for the clinical study report. These protocol deviations will be imported from the protocol deviations log. Protocol deviations will be classed as minor, important or major, where major deviations are classed as important protocol deviations leading to exclusion from the PP analysis set.

Protocol deviations were reviewed during BDRMs on 22\textsuperscript{nd} and 25\textsuperscript{th} March 2019. In addition to patients in the ITT analysis set who withdrew from the trial during the blinded treatment phase, a number of patients were deemed to have protocol deviations that should lead to exclusion from the PP analysis set. These patients, together with their deviations, are detailed in a separate document finalized prior to unblinding.

5.2.4 OLE Safety Analysis Set
The OLE safety analysis set will be defined as all patients who receive at least one dose of IMP during the OLE phase of the trial. Only patients for whom it has been confirmed that they did not take any OLE IMP will be excluded.

5.3 Listings
All data will be listed and ordered by site, treatment, patient number and, where appropriate, chronological order of assessment. Listings will be created for each of the subsequent sections of the SAP.

Visit date need not be included on all of the listings, but day numbers will be included, where appropriate.

Other derived variables (e.g. changes from baseline values) that are calculated for analysis purposes or to aid interpretation of the data will be added to the listings as appropriate.
5.4 Demographic Data and Patient Characteristics

5.4.1 Patient Disposition

Patient disposition, by site, by country and overall, will be summarized using standard summary statistics. The number screened, number of screen failures and number randomized will be included.

A screen failure disposition table will be presented, including number of patients screened, number failing screening, number randomized and the reasons for failing screening.

Patient disposition for the double-blind and OLE phases, including patients treated, completed the treatment and taper phases, discontinued (including reason for discontinuation) from the treatment and taper phases will be summarized by absolute counts (n) and percentages (%).

A further table split by site, and by country will be produced, showing number of patients randomized, withdrawn and completed the treatment phase at each site or in each country.

5.4.2 Analysis Sets

Patients included in the safety, ITT, PP and OLE safety analysis sets, and patients excluded together with reasons for exclusion, will be summarized by absolute counts (n) and percentages (%).

5.4.3 Demographic Data and Baseline Characteristics

The following demographic data will be summarized by treatment arm and overall for the safety, ITT, PP and OLE safety analysis sets:

- Age (years);
- Age group (1–6 years, 7–11 years, 12–17 years and 18–65 years);
- Sex;
- Race;
- Country;
- Region (US, Rest of the World);
- Weight at baseline (kg);
- Height at baseline (cm);
- Body mass index at baseline (kg/m²).

Age will be calculated as:

\[(\text{Date of screening} - \text{date of birth}) \div 365.25.\]

The following baseline characteristics will be summarized by treatment arm and overall for the safety, ITT, PP and OLE safety analysis sets:

- Average number of TSC-associated seizures per 28 days during baseline.
- Average number of total seizures per 28 days during baseline.
- Number of patients with seizures during the baseline period, by seizure type.
- Number of AEDs a patient has used, prior to the trial and is no longer taking.
- Number of AEDs a patient is currently taking.
- Total number of prior and current AEDs.
- Number of patients taking clobazam (Yes, No, and if no, Prior).
- Number of patients taking valproic acid (Yes, No, and if no, Prior).
- Number of patients taking levetiracetam (Yes, No, and if no, Prior).
- Number of patients taking vigabatrin (Yes, No, and if no, Prior).

The number of prior AEDs no longer taking will be taken from the ‘History of antiepileptic medications and therapies’ CRF page. The number of AEDs a patient is currently taking is based on the ‘Concomitant antiepileptic medications’ CRF page. If a patient has a medication listed on both the ‘History of antiepileptic medications and therapies’ and ‘Concomitant antiepileptic medications’ CRF pages and the medication is considered concomitant (see Section 5.7.1) for the double-blind phase, then this will not be included in the number of prior AEDs no longer taking. AEDs starting after the last dose of IMP during the double-blind phase will not be counted.

Patients taking the same AED type, but where the AED were coded to different generic terms will be counted only once within the AED type. For example, valproate sodium, valproic acid, valproate semisodium and ergenyl chrono will all be counted as valproic acid and counted once under that term.

The number of patients taking clobazam is defined as the number of patients taking clobazam at any point during baseline period or treatment period. The same definition will apply for the number of patients taking each of the other AEDs. The number of patients taking other AED types will also be presented if the overall frequency of patients taking the AED is >25%.

Previous cannabis use will be included within the baseline characteristics listing.

5.4.4 Epilepsy History

5.4.4.1 Genetic Testing History

Genetic testing history data will be listed only.

5.4.4.2 History of Seizures no Longer Occurring and History of Current Seizures

Data will be summarized by treatment arm and overall for the safety analysis set only, separately, for history of seizures no longer occurring and history of current seizures.

The following will be summarized by each seizure type:
- Number of patients with the seizure type.
- Age at onset (years).
- Age of last occurrence (years). For history of seizures no longer occurring only.
- Seizure duration (<2 minutes, 2–10 minutes, >10 minutes, Unknown). For history of current seizures only.

Seizure frequency data will be listed only.

For patients with more than one record for a particular seizure type, the earliest onset, most recent age of last occurrence and longest duration will be used for the summary table.
5.4.4.3 Neuroimaging History

Neuroimaging history data will be listed only.

5.4.5 Medical and Surgical History and Current Medical Conditions

All conditions and diagnoses on the ‘non-epilepsy medical history’ CRF page will be coded using Version 19.1 of the Medical Dictionary for Regulatory Activities (MedDRA v19.1).

The number of patients with relevant or significant non-epilepsy medical or surgical history and medical history by system organ class, and preferred term, will be summarized by absolute counts (n) and percentages (%). Percentages will be calculated based on the number of patients in the specific treatment arm. Two tables will be produced, one including any events classified as resolved at screening, and the other including all current conditions.

5.5 Efficacy Analysis

5.5.1 General Approach

Blinded Phase:

The primary analyses will use the ITT analysis set. Further analyses using the PP analysis set will also be performed for the primary endpoint and secondary endpoints where specified in the sections below.

The primary null hypothesis is:

- Following 16 weeks of treatment there is no difference in effect between the 25 mg/kg/day GWP42003-P treatment arm and the placebo treatment arm in terms of the change in number of TSC-associated seizures during the treatment period compared to baseline.

The null hypothesis will be rejected if there is statistical evidence of a difference between the treatment arms at the $\alpha$-level of 0.05 for the primary endpoint.

Statistical hypothesis testing will be performed on the primary endpoint and other endpoints as appropriate. Each endpoint, including the primary will have 2 comparisons against placebo (25 mg/kg/day GWP42003-P vs. placebo and 50 mg/kg/day GWP42003-P vs. placebo). Also, 3 key secondary endpoints have been defined.

The primary and key secondary endpoints will be tested with their Type I error controlled by use of a hierarchical gate-keeping procedure, in the sequence given in Table 3. One must reject the null hypothesis of an endpoint at the level of 0.05 (2-sided) to test the hypothesis of the subsequent endpoint in the sequence at the level of 0.05 (2-sided). If a null hypothesis is not rejected then testing will stop and all subsequent analyses will be declared not statistically significant.

Table 3 Hierarchy for Analysis

<table>
<thead>
<tr>
<th>Test</th>
<th>Endpoint</th>
<th>Treatment Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Primary endpoint</td>
<td>25 mg/kg/day GWP42003-P vs. Placebo</td>
</tr>
<tr>
<td>2</td>
<td>1st key secondary endpoint</td>
<td>25 mg/kg/day GWP42003-P vs. Placebo</td>
</tr>
<tr>
<td>3</td>
<td>2nd key secondary endpoint</td>
<td>25 mg/kg/day GWP42003-P vs. Placebo</td>
</tr>
<tr>
<td>4</td>
<td>3rd key secondary endpoint</td>
<td>25 mg/kg/day GWP42003-P vs. Placebo</td>
</tr>
<tr>
<td>5</td>
<td>Primary endpoint</td>
<td>50 mg/kg/day GWP42003-P vs. Placebo</td>
</tr>
</tbody>
</table>
All statistical tests will be 2-sided and use the 5% significance level.

The assumptions of normality and homogeneity of variance, for endpoints analyzed using parametric tests, will be checked where appropriate via examination of residual plots as well as computation of summary statistics for normality using the Shapiro-Wilk statistical test. If assumptions are violated then alternative non-parametric techniques will be used. In this instance the original parametric tests will be presented as a sensitivity analysis.

**Open-label Extension:**

All endpoints will be summarized on the OLE safety analysis set, unless specified otherwise.

Endpoints will be summarized by treatment received during the double-blind phase (GWP42003-P or Placebo, i.e. not split by dose) and overall.

For seizure endpoints, the OLE treatment phase will be split into 12 week periods, for example:

- OLE Week 1 (OLE Day 1) to OLE Week 12 (Day 84)
- OLE Week 13 (OLE Day 85) to OLE Week 24 (OLE Day 168)
- OLE Week 25 (OLE Day 169) to OLE Week 36 (OLE Day 252)
- OLE Week 37 (OLE Day 253) to OLE Week 48 (OLE Day 336)
- OLE Week 49 (OLE Day 337) to OLE Week 60 (OLE Day 420)
- Etc.

In addition, seizure data will be presented for the full OLE treatment phase as well as the last 12 weeks of the OLE treatment phase (see Section 5.1.3.3).

### 5.5.2 Primary Efficacy Endpoint

**Blinded Phase:**

The primary endpoint is the change in number of TSC-associated seizures (see Section 5.1.3.7) during the treatment period (see Section 5.1.3.4) compared to baseline period (see Section 5.1.3.1) in patients taking GWP42003-P compared with placebo.

The primary endpoint will be analyzed using a negative binomial regression model with the total number of TSC-associated seizures during the baseline period and treatment period as the response variables.

A mixed effect model with repeated measures will be performed modelling the observed total number of TSC-associated seizures in the baseline period and treatment period implemented within the framework of general linear models using the negative binomial response distribution. The model will include stratified age group (1–6 years, 7–11 years, 12–17 years and 18–65 years), time, treatment arm and treatment arm by time interaction as fixed effects and patient as a random effect. The log transformed number of days in which seizure data were reported will be included as an offset. The time variable corresponds to an indicator for the baseline period and treatment period.
The GLIMMIX procedure in SAS will be utilized to perform the analysis with the option maxopt=300 applied. If the model fails to converge, then the statement ‘nloptions tech=nrridg;’ will be added. If convergence is still not achieved, then ‘method=laplace’ will be utilized. However, if convergence is still not possible, then the model will be changed to utilize the log normal response distribution (log rate model). If the log rate model is required and there are patients with no seizures during the baseline or treatment period then all patients will have their baseline and treatment period seizure count adjusted by adding a value of 1.

The estimated least squares mean seizure rate for each period and the estimated ratio of least squares means for treatment period to baseline period and 95% confidence intervals (CIs) will be presented for each treatment arm. In addition, the estimated ratio of each GWP42003-P arm to placebo and 95% CIs will be presented along with the p-value testing the null hypothesis that this ratio is 1.

For each ratio and upper and lower bound of the 95% CI, the percentage reduction will also be presented, calculated as:

\[1 - \frac{X}{Y}\] ×100%

Where X corresponds to the treatment period estimate, or GWP42003-P ratio, and Y corresponds to the baseline period estimate, or placebo arm ratio.

Primary efficacy analysis will be performed using the ITT analysis set.

TSC-associated seizure frequency (28-day average) and percentage change in seizure frequency will also be presented using summary statistics. Percentage change from baseline in TSC-associated seizure frequency will be calculated as:

\[
\frac{(\text{Frequency during the treatment period} - \text{Frequency during baseline})}{\text{Frequency during baseline}} \times 100
\]

The frequency during each period will be based on 28 day averages and calculated as:

\[
\frac{(\text{Number of seizures in the period} + \text{Number of reported days in IVRS in the period})}{28}
\]

For the TSC-associated seizure endpoints only, if patients are randomized with no TSC-associated seizures during the baseline period then the percentage change from baseline will be calculated as:

\[
\frac{\text{Frequency during the treatment period} + 1}{28}
\]

Open-label Extension:

The primary endpoint for the OLE is the safety of GWP42003-P, evaluated by assessing the incidence, type and severity of AEs. Data will be presented as per Section 5.6.2.

However, percentage change from baseline in TSC-associated seizure frequency is considered a key secondary endpoint for the OLE.

In the OLE, seizures are recorded on a weekly basis rather than daily. Caregivers/patients are expected to call the IVRS system to record the number of seizure subtypes experienced every 7 days during the OLE. TSC-associated seizure frequency per 28 days will be calculated for each of the periods described in Section 5.5.1. All calls that take place during the period in question will contribute to the calculation of the average number of seizures per day in that period only.

The average number of seizures per day in the period will be calculated as the average of:

\[
\frac{\text{Number of seizures reported}}{\text{Number of days since last IVRS call}}
\]
The number of days since the last call will be calculated as follows, and is dependent on whether the call took place <7, 7 or >7 days after the previous call (or after the date of OLE Day 1 in the case of the first call in the first period):

- If the call takes place exactly 7 days after the previous call, then the number of days since the last call will be 7.
- If the call takes place <7 days after the previous call, then the number of days since the last call will be calculated as:
  \[(\text{Date of current call} - \text{date of previous call}) + 1\]
- If the call takes place >7 days after the previous call, then the number of days since the last call will be 7.

Summary statistics will be presented for raw seizure frequencies and percentage change from baseline (from the blinded phase).

5.5.2.1 Sensitivity Analyses for the Primary Efficacy Endpoint

Blinded Phase:

The following sensitivity analyses will be conducted for the primary endpoint of the blinded phase:

- Primary endpoint analysis repeated using the PP analysis set.
- Wilcoxon rank-sum test on percentage change from baseline in TSC-associated seizure frequency during the treatment period. An estimate of the median differences between each GWP42003-P arm and placebo, together with approximate 95% CIs, will be calculated using the Hodges–Lehmann approach.
- A rank analysis of covariance (ANCOVA) on percentage change from baseline in TSC-associated seizure frequency during the treatment period. The ranks of the percentage change from baseline and the baseline TSC-associated seizure frequency will be calculated. The rank of the percentage change from baseline will then be analyzed using an ANCOVA model with the rank of the baseline TSC-associated seizure frequency and stratified age group as covariates and treatment arm as a fixed factor. The estimated least squares means, treatment differences, together with the 95% CIs and p-values will be presented.
- ANCOVA of log transformed TSC-associated seizure frequency during the treatment period.
  The TSC-associated seizure frequency during the treatment period and the baseline TSC-associated seizure frequency will be log transformed prior to analysis. The log transformed TSC-associated seizure frequency during the treatment period will then be analyzed using an ANCOVA model with the log transformed baseline TSC-associated seizure frequency and stratified age group as covariates and treatment arm as a fixed factor. The back transformed estimated treatment ratios, together with the 95% CIs and p-values will be presented.
  If there are any patients with no TSC-associated seizures during the baseline or treatment periods, then 1 will be added to the TSC-associated seizure frequency for all patients prior to log transformation.
- ANCOVA on percentage change from baseline in TSC-associated seizure frequency during the treatment period including baseline and stratified age group as covariates.
and treatment arm as a fixed factor. The estimated least squares means, treatment differences, together with the 95% CIs and p-values will be presented.

- Primary endpoint analysis repeated using the maintenance period (see Section 5.1.3.6) rather than the treatment period.
  This analysis will include only patients who have at least 7 days of seizure data within the maintenance period.

- Primary endpoint analysis repeated using the titration period (see Section 5.1.3.5) each 4 weeks of the maintenance period (Week 1 to 4, Week 5 to 8 and Week 9 to 12 of the 12-week maintenance period).
  These analyses will include only patients who have at least 7 days of seizure data within each corresponding 4 week period.

- Primary endpoint analysis repeated using the worst case of last observation carried forward (LOCF), next observation carried backward (NOCB) and the mean from the non-missing data for each patient (rounded up to the nearest integer) to impute missing data arising from unreported days in IVRS during the treatment period only (not the baseline period).
  Any intermittent missing data for the number of TSC-associated seizures arising from unreported days in IVRS will be imputed using the worst (highest number of seizures) of the following for each patient: LOCF, NOCB and the mean daily number of seizures during the treatment period (rounded up to the nearest integer) based on using non-missing data:

\[
\text{Number of seizures ÷ Number of reported days in IVRS}
\]

- Primary endpoint analysis repeated using multiple imputation (MI) to impute data under the Missing Not at Random (MNAR) assumption (see Section 5.5.2.1.1).

### Open-label Extension:

Open-label summaries will be repeated with the inclusion of an LOCF imputation step, which is described in the following steps:

- If a patient has valid data for ≥1 consecutive periods from and inclusive of the first period but only missing periods thereafter, then imputation of the missing period(s) will be carried out using the last 12 weeks of valid data (see Section 5.1.3.3).

- If a patient has intermittent missing periods (i.e. ≥1 missing period that falls after a populated period 1 and before subsequent populated periods), then the missing period(s) will be imputed with the closest earlier non-missing period of data.

- If the patient has ≥1 consecutive periods of missing data from and inclusive of the first period then no imputation will occur and data from the patient will be excluded from any LOCF presentations.

#### 5.5.2.1.1 Sensitivity Analysis of Missing Data

Missing data in this trial could potentially arise from the mechanism of MNAR. Hence, a sensitivity analysis is required to assess the potential impact that missing data under the mechanism of MNAR may have on the estimated results for the primary endpoint.

To facilitate multiple imputation techniques for missing data due to patients who withdraw from the treatment period, it is necessary to divide the treatment period into smaller periods for which missing seizure data can be imputed. Hence, sensitivity analysis of the primary endpoint will be carried out based on periods corresponding to each 14 days of the
treatment period, by multiple imputations on the average daily TSC-associated seizure frequency. The final period will consist of 15 days to include Day 113, where applicable. Following imputation, the imputed periods will be recombined for each patient in order to repeat the primary analysis.

For each 14 calendar days of the treatment period (15 days for the final period), the average daily TSC-associated seizure frequency will be calculated as:

\[
\text{Average daily TSC-associated seizure frequency} = \frac{\text{Number of TSC-associated seizures in the period} + \text{Number of reported days in IVRS in the period}}{\text{Number of reported days in IVRS in the period}}
\]

For patients with <6 days in a period, the frequency will be set to missing and will be imputed as part of this analysis.

For intermittent missing data, in which subjects have missing values for intermediate periods but have available data at subsequent periods, imputation will be based on the MCMC methodology. Assumptions underlying this partial imputation step are that patients will follow a similar outcome trajectory as patients in their respective treatment arm that have complete data. Intermittent missing values will be imputed using the MCMC method in PROC MI with an IMPUTE=MONOTONE statement for 200 times for each treatment arm separately. To avoid negative results, a minimum of 0 will be specified in the PROC MI statement. As a result, missing intermediate visits will be imputed and the resulting 200 partially imputed datasets will have a monotone missing pattern.

The remaining monotone missing data will then be imputed using predictive mean matching in which missing observations are imputed with an observed value from another patient whose predicted value is close to the predicted value of the patient with the missing observation. The predictive mean matching is performed using the steps below, in which imputation will be carried out on each of the 200 imputed datasets using the SAS MI procedure (with the 200 imputed datasets included in the ‘BY’ statement of the MI procedure):

**Step 1 – Missing at random (MAR) based multiple imputation for the placebo arm:**

- Monotone missing data under the MAR assumption at period t will be imputed using predictive mean matching method from the observed daily TSC-associated seizure frequency at baseline and at each period up to period t (in chronological order).
- The imputation will be realized using the MI procedure with the ‘MONOTONE REGPMM’ option.
- The imputation model will include baseline daily TSC-associated seizure frequency and each period up to period t (in chronological order).

**Step 2 – MNAR based multiple imputation for the GWP42003-P arms (MNAR is assumed for missing values resulting from discontinuation due to any reason or any other monotone missing data):**

- With the data imputed from Step 1, monotone missing data under the MNAR at period t will be imputed using predictive mean matching method.
- At each period t, the input dataset for the MI procedure will include all placebo patients and those patients from each GWP42003-P arm (implemented separately by arm) that have values at that period.
- The imputation will be realized using the MI procedure with the ‘MONOTONE REGPMM’ option.
• The imputation model will include daily TSC-associated seizure frequency at baseline and each period up to period t (in chronological order).

Once all missing values at all periods have been imputed, the TSC-associated seizure count for each period will be calculated as:

(Daily frequency for the period × Number of days in the period for the non-imputed period or 14 for an imputed period), rounded to the nearest whole number

The result will be 200 fully imputed datasets ready to be analyzed using the same analysis method as the primary endpoint, producing 200 analysis results.

The estimated ratio, 95% CI and p-value from analyses of the 200 imputed datasets will be combined using PROC MIANALYZE.

To test the robustness of the analysis to the MNAR imputations a tipping point analysis will be performed. This will be conducted by adding or subtracting a sensitivity parameter, k × standard error of the observed average daily TSC-associated seizure frequency in the placebo arm at each period, to the MNAR imputations only at the corresponding period (where k = 0, ± 0.5, ± 1.0, ± 1.5, etc.).

The tipping point analysis will be used to explore the robustness of the estimated treatment difference to the degree of decrease or increase (positive values of k represent decrease and negative values represent increase) in MNAR efficacy from the placebo patients.

The increment in the positive value of k will stop once the overall p-value is greater than 0.05. The decrease in the negative values of k will continue until the overall p-value becomes smaller than the p-value from the primary efficacy analysis, for the corresponding Dose Level.

5.5.3 Secondary Efficacy Endpoints

5.5.3.1 Key Secondary Efficacy Endpoints

5.5.3.1.1 1st Key Secondary Endpoint: TSC-associated Seizure Treatment Responders (≥50% Reduction in TSC-associated Seizure Frequency)

Blinded Phase:

The proportion of patients considered treatment responders, defined as those with a ≥50% reduction in TSC-associated seizure frequency from baseline during the treatment period, for patients who have not withdrawn from the trial during the treatment period, will be summarized by treatment arm and analyzed using a Cochran–Mantel–Haenszel (CMH) test stratified by age group.

The proportion of patients who are considered treatment responders, the difference in proportions along with the 95% CI for the difference, the estimated odds ratios (GWP42003-P arms vs. placebo), 95% CI for the odds ratios, and the p-values from the CMH test will be presented. If no patients in a particular treatment arm are considered responders then the odds ratio and 95% CI for the odds ratio will not be calculated.

The analysis will be performed on the ITT analysis set and repeated on the PP analysis set. Sensitivity analyses will be performed on the ITT analysis set, repeating the above analysis, using data for the maintenance period only, the titration period and during each 4 weeks of the maintenance period (Week 1 to 4, Week 5 to 8 and Week 9 to 12 of the 12 week maintenance period).
Analyses on the maintenance period, titration period and by each 4 weeks of the maintenance period will include only patients who have at least 7 days of seizure data within each period.

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for OLE periods. However, for the OLE periods, withdrawn patients may be considered responders.

5.5.3.1.2 2nd Key Secondary Endpoint: Subject/Caregiver Global Impression of Change

Blinded Phase:

The SGIC and CGIC comprise the following questions to be rated on a 7-point scale:

CGIC:
- Since your child started treatment, please assess the status of your child’s overall condition (comparing their condition now to their condition before treatment) using the scale below.

SGIC:
- Since you started treatment, please assess the status of your overall condition (comparing your condition now to your condition before treatment) using the scale below.

The possible responses are: Very Much Improved; Much Improved; Slightly Improved; No Change; Slightly Worse; Much Worse; Very Much Worse.

The responses above are based on comparison with a brief description of the patient’s overall condition used as a memory aid from Visit 3.

Each response will be coded with a score from 1 to 7, where 1 = Very Much Improved, and 7 = Very Much Worse.

The SGIC and CGIC response/score, recorded at each visit, will be summarized separately, on both a categorical and continuous scale, by treatment arm.

It is anticipated that only a small percentage of patients will complete the subject version of the questionnaire. Hence, no analyses will be performed for the SGIC.

A combined score will be used as the primary analysis for this endpoint. The combined score will be defined as follows:
- If both a CGIC and SGIC are completed then the CGIC will be used.
- If only a CGIC is completed then the CGIC will be used.
- If only a SGIC is completed then the SGIC will be used.

The score at the end of treatment visit and last visit (if different to the end of treatment) will be analyzed using ordinal logistic regression. Proportional odds modelling will be carried out by including treatment arm as a factor. The estimated odds ratio (GWP42003-P vs. placebo), 95% CI for the odds ratio, and the p-value testing the null hypothesis that the odds ratio is equal to 1, will be presented. Analysis performed at the last visit will be considered the primary analysis for this endpoint, with the analysis at the end of treatment visit considered a sensitivity analysis.
Should the proportional odds assumption not hold, i.e. if the p-value for the score test for proportional odds assumption is <0.05, then, as a sensitivity analysis, the scores will also be analyzed using a Cochran-Armitage trend test. This will be presented together with the results of the ordinal logistic regression.

Since this analysis uses a combination of caregiver and subject ratings, a sensitivity analysis will be performed using only the CGIC score and using the same analyses as above.

The analysis will be performed on the ITT analysis set and repeated on the PP analysis set.

**Open-label Extension:**

Descriptive summaries described above for the blinded phase will be repeated for OLE visits.

5.5.3.1.3 3rd Key Secondary Endpoint: Total Seizures

**Blinded Phase:**

Summaries and analyses of total seizures (see Section 5.1.3.9) will be performed as per the primary endpoint (Section 5.5.2).

The analysis will be performed on the ITT analysis set and repeated on the PP analysis set.

Sensitivity analyses will be performed on the ITT analysis set, repeating the above analysis, using data for only the maintenance period, titration period, and during each 4 weeks of the maintenance period (Week 1 to 4, Week 5 to 8 and Week 9 to 12 of the 12 week maintenance period).

Analyses on the maintenance period, titration period and by each 4 weeks of the maintenance period will include only patients who have at least 7 days of seizure data within each period.

**Open-label Extension:**

Summaries will be performed for the OLE periods as described in the OLE portion of the primary endpoint section (Section 5.5.2).

5.5.3.2 Other Secondary Efficacy Endpoints

5.5.3.2.1 TSC-associated Seizure Treatment Responders and TSC-associated Seizure Freedom

**Blinded Phase:**

The number of patients experiencing a >25% increase, ≥0 to ≤25% increase, >0 to <25% reduction, ≥25 to <50% reduction, ≥50 to <75% reduction or ≥75% reduction in TSC-associated seizure frequency from baseline during the treatment period will be summarized by treatment arm.

In addition to the key secondary endpoint, the proportion of patients considered treatment responders, defined as those with a ≥25% or ≥75% reduction in TSC-associated seizure frequency from baseline and the proportion of patients who are TSC-associated seizure free, defined as those with a 100% reduction in TSC-associated seizure frequency from baseline, during the treatment period, for patients who have not withdrawn from the trial
during the treatment period will be summarized by treatment arm and analyzed using a CMH test stratified by age as described in Section 5.5.3.1.1.

Additionally, the proportion of patients responding will be presented graphically, by treatment arm, by plotting the percent reduction against the cumulative proportion of patients achieving that level of reduction. The x-axis will be the percent reduction from baseline and the y-axis will be the proportion of patients with at least that amount of reduction, i.e. $y = \Pr(X \geq x)$.

Sensitivity analyses will be performed on the ITT analysis set, repeating the above analysis, using data for only the maintenance period, titration period, and during each 4 weeks of the maintenance period (Week 1 to 4, Week 5 to 8 and Week 9 to 12 of the 12 week maintenance period).

Analyses on the maintenance period, titration period and by each 4 weeks of the maintenance period will include only patients who have at least 7 days of seizure data within each period.

**Open-label Extension:**

Descriptive summaries described above for the blinded phase will be repeated for OLE periods.

### 5.5.3.2.2 Number of TSC-associated Seizure Free Days

**Blinded Phase Only:**

The number of TSC-associated seizure free days during each period will be based on 28 day averages and calculated as:

$$(\text{Number of seizure free days in the period} \div \text{Number of reported days in IVRS in the period}) \times 28$$

The change from baseline in TSC-associated seizure free days per 28 days will be analyzed for the treatment period using an ANCOVA approach. The model will include baseline and stratified age group as covariates and treatment arm as fixed factor.

The estimated least squares means, treatment difference, together with the 95% CIs and p-value will be presented.

The analysis will be repeated for the maintenance period.

### 5.5.3.2.3 Other Seizures

**Blinded Phase:**

For other seizures (see Section 5.1.3.8), summaries and analyses will be performed as per the primary endpoint (Section 5.5.2). Patients with no seizures during the baseline period, for a particular seizure type, will be excluded from the analysis of that seizure type.

Other seizure and total seizure responders and freedom will also be summarized and analyzed using the methods described in Section 5.5.3.2.1. However, the summaries and analyses during the maintenance and titration periods and during each 4 weeks of the maintenance period will be produced for total seizures only. Patients with no corresponding other seizures during the baseline period will be excluded from the analysis for other seizures.

**Open-label Extension:**
Descriptive summaries described above for the blinded phase will be repeated for OLE periods.

5.5.3.2.4 Quality of Life in Childhood Epilepsy (2–18 Years)

Blinded Phase:

The QOLCE is a parent-reported questionnaire that evaluates health related quality of life in children aged 2–18 years old. It contains 76 items with 16 subscales covering 7 domains of life function: Physical activities, social activities, cognition, emotional well-being, behavior, general health, and general quality of life.

All items in the questionnaire are rated on a 5-point or 6-point categorical scale. Based on the responses to the items in each domain, scores for 16 subscales are derived. The subscales are presented in Table 4.

Table 4 QOLCE Subscales

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Item Domains</th>
<th>Items Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Restrictions</td>
<td>Physical Activities</td>
<td>3.1 (a to j)</td>
</tr>
<tr>
<td>Energy/Fatigue</td>
<td>Physical Activities</td>
<td>3.2 (a,b)</td>
</tr>
<tr>
<td>Attention/Concentration</td>
<td>Cognition</td>
<td>5.1 (a,d,e,f,g)</td>
</tr>
<tr>
<td>Memory</td>
<td>Cognition</td>
<td>5.1 (j,k,l,m,n,o)</td>
</tr>
<tr>
<td>Language</td>
<td>Cognition</td>
<td>5.1 (p,q,r,s,t,u,v,w)</td>
</tr>
<tr>
<td>Other Cognitive</td>
<td>Cognition</td>
<td>5.1 (b,c,h)</td>
</tr>
<tr>
<td>Depression</td>
<td>Emotional Well-Being</td>
<td>4.1 (a,d,e,l)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Emotional Well-Being</td>
<td>4.1 (b,g,j,n,o,p)</td>
</tr>
<tr>
<td>Control/Helplessness</td>
<td>Emotional Well-Being</td>
<td>4.1 (c,f,h,i)</td>
</tr>
<tr>
<td>Self-esteem</td>
<td>Emotional Well-Being</td>
<td>4.1 (k,m,q,r,s)</td>
</tr>
<tr>
<td>Social Interactions</td>
<td>Social Activities</td>
<td>6.1 (c,f,h)</td>
</tr>
<tr>
<td>Social Activities</td>
<td>Social Activities</td>
<td>6.1 (a,e) and 6.2</td>
</tr>
<tr>
<td>Stigma Item</td>
<td>Social Activities</td>
<td>6.1 (i)</td>
</tr>
<tr>
<td>Behavior</td>
<td>Behavior</td>
<td>7.1 (a,c,f,g,h,i,j,k,l,m,o,q,r,s,t)</td>
</tr>
<tr>
<td>General Health Item</td>
<td>General Health</td>
<td>8.1</td>
</tr>
<tr>
<td>Quality of Life Item</td>
<td>Quality of Life</td>
<td>9.1</td>
</tr>
</tbody>
</table>

Items within each subscale will be coded and linearly transformed, according to the methods of Sabaz et al., to a score of 0 to 100, where 0 represents the lowest or poorest category and 100 represents the highest level of functioning.

A subscale score is calculated for each subscale by computing the mean of the items within the subscale. An ‘Overall Quality of Life Score’ can be calculated by taking the mean of the subscale scores.

Individual items will be listed only. The subscale scores and the overall quality of life score, recorded at each visit, will be summarized, on a continuous scale, by treatment arm. The change from baseline will also be included.

The change from baseline to the end of treatment visit, for the overall quality of life score, and the attention/concentration, memory, language, other cognitive, social interactions and behavior subscale scores only, will be analyzed using analysis of covariance (ANCOVA). The model will include baseline and stratified age group as covariates and treatment arm as fixed factor.

The estimated least squares means, treatment difference, together with the 95% CIs and p-value will be presented. Exploratory analyses may also be performed on other subscale scores.
Missing data will be handled according to Section 5.1.1.2.1.

The QOLCE was to be completed for patients aged 2-18 years old only. The primary analysis will be based on all patients who have a completed questionnaire, regardless of age. Summaries and analyses will be repeated using questionnaires only from patients who were aged 2 to 18 years old at the time of informed consent.

The individual responses will not be listed, only the derived information for each derived score will be listed.

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for OLE visits.

5.5.3.2.5 Quality of Life in Epilepsy, Version 2 (19 Years and Above)

Blinded Phase:

The QOLIE-31-P is a survey of health-related quality of life for adults with epilepsy. It comprises 38 questions about health and daily activities and also includes questions designed to evaluate how much distress the patient feels about problems and worries related to epilepsy. The QOLIE-31-P will be administered to patients aged 19 years or older. Should the patient be unable to complete the QOLIE-31-P independently, it is permissible for their caregiver to assist.

The questionnaire consists of the following 7 subscales: energy, mood, daily activities, cognition, medication effects, seizure worry, and overall quality of life. Each subscale consists of a number of questions in addition to a ‘distress’ item. The raw score for each question and the ‘distress’ item are converted to a 0-100 score according to the scoring manual (higher scores reflecting greater well-being). The converted scores for each question within the subscale are then used to calculate a final subscale weighted score (higher scores reflect better quality of life; lower ones, worse quality of life) as follows:

\[(\text{Sum of converted scores for each question in the subscale} ÷ \text{Number of questions in the subscale}) \times \text{‘distress’ item converted score}\]

The total score (ranging from 0 to 100) is then calculated as:

\[(\text{Sum of all subscale weighted scores} ÷ \text{Sum of all subscale ‘distress’ item converted scores}) \times 100\]

Individual items will be listed only. The weighted subscale scores and the total score, recorded at each visit, will be summarized, on a continuous scale, by treatment arm. The change from baseline will also be included.

The change from baseline to the end of treatment visit, for the weighted subscale scores and the total score, will be analyzed using the same ANCOVA approach as specified in Section 5.5.3.2.4.

Missing data will be handled according to Section 5.1.1.2.2.

The QOLIE-31-P was to be completed for patients aged 19 years and above only. The primary analysis will be based on all patients who have a completed questionnaire, regardless of age. Summaries and analyses will be repeated using questionnaires only from patients who were aged 19 years or older at the time of informed consent.

The individual responses will not be listed, only the derived information for each derived score will be listed.
5.5.3.2.6 Physician Global Impression of Change

Blinded Phase:

The PGIC comprises the following questions to be rated on a 7-point scale:

- Please assess the change in the patient's general functional abilities since Visit 3 (prior to the commencement of study medication).

The possible responses are: Very Much Improved; Much Improved; Slightly Improved; No Change; Slightly Worse; Much Worse; Very Much Worse.

The responses above are based on comparison with a brief description of the patient’s overall condition used as a memory aid from Visit 3.

Each response will be coded with a score from 1 to 7, where 1 = Very Much Improved, and 7 = Very Much Worse.

The PGIC response/score, recorded at each visit, will be summarized separately, on both a categorical and continuous scale, by treatment arm.

The score at the end of treatment visit and last visit (if different to the end of treatment) will be analyzed using ordinal logistic regression. Proportional odds modelling will be carried out by including treatment arm as a factor. The estimated odds ratio (GWP42003-P vs. placebo), 95% CI for the odds ratio, and the p-value testing the null hypothesis that the odds ratio is equal to 1, will be presented. Analysis performed at the last visit will be considered the primary analysis for this endpoint, with the analysis at the end of treatment visit considered a sensitivity analysis.

Should the proportional odds assumption not hold, i.e. if the p-value for the score test for proportional odds assumption is <0.05, then, as a sensitivity analysis, the scores will also be analyzed using a Cochran-Armitage trend test. This will be presented together with the results of the ordinal logistic regression.

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for OLE visits.

5.5.4 Exploratory Efficacy Endpoints

5.5.4.1 Composite Focal Seizure Score

Blinded Phase:

Composite focal seizure score will be calculated as the sum of:

- 1 × Number of focal motor seizures without impairment of consciousness or awareness.
- 2 × Number of focal seizures with impairment of consciousness or awareness.
- 3 × Number of focal seizures evolving to bilateral convulsive seizures.

Summaries and analyses of composite focal seizure score will be performed as per the primary endpoint (Section 5.5.2).

Sensitivity analyses will be performed on the ITT analysis set, repeating the above analysis, using data for only the maintenance period, titration period, and during each 4 weeks of the
maintenance period (Week 1 to 4, Week 5 to 8 and Week 9 to 12 of the 12 week maintenance period).

Analyses on the maintenance period, titration period and by each 4 weeks of the maintenance period will include only patients who have at least 7 days of seizure data within each period.

Open-label Extension:

Summaries will be performed for the OLE periods as described in the OLE portion of the primary endpoint section (Section 5.5.2).

5.5.4.2 Individual Seizure Types

Blinded Phase:

For each individual seizure type (focal motor seizures without impairment of consciousness or awareness, focal seizures with impairment of consciousness or awareness, focal seizures evolving to bilateral generalized convulsive seizures, tonic-clonic, tonic, clonic, atonic, absence, myoclonic and partial sensory seizures, and infantile or epileptic spasms), summaries will be performed as per the primary endpoint (Section 5.5.2). However, analyses will only be performed for the following seizure types:

- Focal motor seizures without impairment of consciousness or awareness;
- Focal seizures with impairment of consciousness or awareness;
- Focal seizures evolving to bilateral generalized convulsive seizures;
- Tonic-clonic; and
- Tonic.

Patients with no seizures during the baseline period, for a particular seizure type, will be excluded from the analysis of that seizure type.

Sensitivity analyses will be performed on the ITT analysis set, repeating the above analyses using data for only the maintenance period, titration period, and during each 4 weeks of the maintenance period (Week 1 to 4, Week 5 to 8 and Week 9 to 12 of the 12 week maintenance period).

Analyses on the maintenance period, titration period and by each 4 weeks of the maintenance period will include only patients who have at least 7 days of seizure data within each period.

Individual seizure type responders and freedom will also be summarized and analyzed using the methods described in Section 5.5.3.2.1, for the following seizure types only:

- Focal motor seizures without impairment of consciousness or awareness;
- Focal seizures with impairment of consciousness or awareness;
- Focal seizures evolving to bilateral generalized convulsive seizures;
- Tonic-clonic; and
- Tonic.

The summaries and analyses during the maintenance and titration periods and during each 4 weeks of the maintenance period will be produced. Patients with no corresponding seizures, for a particular seizure type, during the baseline period will be excluded from the analysis for that seizure type.

Open-label Extension:
Descriptive summaries described above for the blinded phase will be repeated for OLE periods.

5.5.4.3 Rescue Medication Use

Blinded Phase:

The number of days that rescue medication (RM) was taken since the previous visit will be collected throughout the trial at scheduled visits and safety telephone calls.

To standardize between patients, the total number of days RM was taken will be calculated as the sum of all reported records within a period. Hence, the average number of days RM was taken per 28 days within a period will be calculated as follows:

\[(\text{Total number of days RM was taken during the period} \div \text{Number of days in the period}) \times 28\]

This will be calculated for both the baseline period and treatment period. The number of days in a period will be calculated as the number of days from the visit prior to the first recorded value in the period to the day of the last recorded value in the period. The baseline period refers to the period between Visit 2 and Visit 3. The treatment period refers to the period between Visit 3 and Visit 10.

The number of days RM was taken per 28 days will be summarized by period and treatment arm. The change from the baseline period will also be included.

The change from the baseline period to the treatment period will be analyzed using an ANCOVA approach. The model will include the baseline period and stratified age group as covariates and treatment arm as fixed factor.

The estimated least squares means, treatment difference, together with the 95% CIs and p-value will be presented.

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for the OLE period. The OLE period refers to the period between Visit B1 and the last available visit in the OLE phase.

5.5.4.4 Status Epilepticus

The number of episodes of status epilepticus will be collected daily via IVRS for the blinded phase and weekly via IVRS for the open-label extension.

The number of patients with status epilepticus will be presented for the baseline, treatment and OLE periods.

5.5.4.5 Subject/Caregiver Global Impression of Change in Seizure Duration

Blinded Phase:

The SGICSD and CGICSD comprise the following questions to be rated on a 3-point scale for each seizure type:

CGICSD:

- Since the patient started treatment, please assess the average duration of the patient’s seizures (comparing their condition now to their condition before treatment) using the scale below.

SGICSD:
Since you started treatment, please assess the average duration of your seizures (comparing your condition now to your condition before treatment) using the scale below.

The 3 possible responses are:

- Decrease in average duration.
- No change in average duration.
- Increase in average duration.

The patient/caregiver will be asked to assess the average duration of seizures at Visit 3 (prior to commencement of IMP) as a memory aid for assessment further visits.

Each response will be coded with a score from 1 to 3, where 1 = Decrease in average duration, and 3 = Increase in average duration.

For each seizure type, the SGICSD and CGICSD will be summarized separately by treatment arm.

It is anticipated that only a small percentage of patients will complete the subject version of the questionnaire. Hence, no analyses will be performed for the SGICSD.

A combined score will be used as the primary analysis for this endpoint. The combined score will be defined as follows:

- If both a CGICSD and SGICSD are completed then the CGICSD will be used.
- If only a CGICSD is completed then the CGICSD will be used.
- If only a SGICSD is completed then the SGICSD will be used.

Proportional odd modelling will be carried out by including treatment arm and age group as factors. The estimated odds ratio (GWP42003-P vs. placebo), 95% CI for the odds ratio, and the p-value testing the null hypothesis that the odds ratio is equal to 1, will be presented.

Since this analysis uses a combination of caregiver and subject ratings, a sensitivity analysis will be performed using only the CGICSD score and using the same analyses as above.

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for OLE visits.

5.5.4.6 Vineland Adaptive Behavior Scales, Second Edition

Blinded Phase:

The Vineland-II is an individually administered instrument for assessing adaptive behaviors and consists of 4 adaptive behavior domains and a maladaptive behavior domain. The details of each domain are presented in Table 5.
Table 5  Content Description of the Vineland-II

<table>
<thead>
<tr>
<th>Domains and Subdomains</th>
<th>Number of Items</th>
<th>Age Range (Years)</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adaptive Behavior Domains</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Communication Domain</td>
<td>99</td>
<td>≥0</td>
<td>How the individual listens and pays attention, and what he or she understands</td>
</tr>
<tr>
<td>Receptive</td>
<td>20</td>
<td>≥0</td>
<td>How the individual listens and pays attention, and what he or she understands</td>
</tr>
<tr>
<td>Expressive</td>
<td>54</td>
<td>≥0</td>
<td>What the individual says, how he or she uses words and sentences to gather and provide information</td>
</tr>
<tr>
<td>Written</td>
<td>25</td>
<td>≥3</td>
<td>What the individual understands about how letters make words, and what he or she reads and writes</td>
</tr>
<tr>
<td>Daily Living Skills Domain</td>
<td>109</td>
<td>≥0</td>
<td></td>
</tr>
<tr>
<td>Personal</td>
<td>41</td>
<td>≥0</td>
<td>How the individual eats, dresses and practices personal hygiene</td>
</tr>
<tr>
<td>Domestic</td>
<td>24</td>
<td>≥1</td>
<td>What household tasks the individual performs</td>
</tr>
<tr>
<td>Community</td>
<td>44</td>
<td>≥1</td>
<td>How the individual uses time, money, the telephone, the computer and job skills</td>
</tr>
<tr>
<td>Socialization Domain</td>
<td>99</td>
<td>≥0</td>
<td></td>
</tr>
<tr>
<td>Interpersonal Relationships</td>
<td>38</td>
<td>≥0</td>
<td>How the individual interacts with others</td>
</tr>
<tr>
<td>Play and Leisure Time</td>
<td>31</td>
<td>≥0</td>
<td>How the individual plays and uses leisure time</td>
</tr>
<tr>
<td>Coping Skills</td>
<td>30</td>
<td>≥1</td>
<td>How the individual demonstrates responsibility and sensitivity to others</td>
</tr>
<tr>
<td>Motor Skills Domain</td>
<td>76</td>
<td>≥0 to &lt;7</td>
<td>How the individual uses arms and legs for movement and coordination</td>
</tr>
<tr>
<td>Gross</td>
<td>40</td>
<td>≥0 to &lt;7</td>
<td>How the individual uses hands and fingers to manipulate objects</td>
</tr>
<tr>
<td>Fine</td>
<td>36</td>
<td>≥0 to &lt;7</td>
<td>How the individual uses hands and fingers to manipulate objects</td>
</tr>
<tr>
<td>Maladaptive Behavior Domain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maladaptive Behavior Index</td>
<td>36</td>
<td>≥3</td>
<td>A composite of Internalizing, Externalizing, and Other types of undesirable behavior that may interfere with the individual’s adaptive functioning</td>
</tr>
<tr>
<td>Internalizing (Section A)</td>
<td>11</td>
<td>≥3</td>
<td></td>
</tr>
<tr>
<td>Externalizing (Section B)</td>
<td>10</td>
<td>≥3</td>
<td></td>
</tr>
<tr>
<td>Other (Section C)</td>
<td>15</td>
<td>≥3</td>
<td></td>
</tr>
<tr>
<td>Maladaptive Behavior Critical Items</td>
<td>14</td>
<td>≥3</td>
<td>More severe maladaptive behaviors that may provide clinically important information</td>
</tr>
</tbody>
</table>

For each subdomain, a raw score is calculated based on the responses to the individual items within the subdomain. For the maladaptive behavior index, the raw score is the sum of the 3 subdomain raw scores. Using the raw score and the patients’ age the following are obtained:

- v-Scale Score: a type of standard score scale (standardized by age) to describe an individual’s relative level of functioning. Ranging from a score of 1 to 24.
- 90% CI for the v-Scale Score: a range of scores that has a certain likelihood of including the individual’s true score.
• Adaptive Level: a means to describe an individual's performance using terms that are nearly universal (Low, Moderately Low, Adequate, Moderately High, High).
  
  o For the maladaptive behavior index and maladaptive behavior subdomains the adaptive levels are: Average, Elevated or Clinically Significant.

• Age Equivalent: the age at which the raw score is average. Not applicable for the maladaptive behavior index and maladaptive behavior subdomains.

For each adaptive behavior domain, the sum of the v-scale scores of the subdomains is used along with the patients' age to obtain the following:

• Standard Score (standardized by age). Ranging from a score of 20 to 160.

• 90% CI for the domain standard score.

• Percentile Rank: the percentage of people whom the individual outperformed in his or her age group.

• Adaptive Level (Low, Moderately Low, Adequate, Moderately High, High).

• Stanine: whole number score ranging from 1 to 9 and representing a specific range of percentile ranks.

An adaptive behavior composite can then be obtained using the sum of the adaptive behavior domain standard scores (excluding the motor skills domain for patients ≥ 7 years of age). The same derived information as the adaptive behavior domain is obtained for the adaptive behavior composite.

For the maladaptive behavior index, all items within each section must be answered for a raw score to be calculated. If any of the items are missing then the maladaptive behavior index score will be missing.

For the adaptive behavior subdomains, the derivation of the raw score allows for up to 2 missing values or answers of “Don't Know” within the items used for scoring. If there are more than 2 missing values or answers of “Don't Know” then the raw score will not be calculated and the subdomain score, domain score and adaptive behavior composite score will be missing.

The adaptive levels corresponding to the v-scale scores and standard scores are presented in Table 6.

Table 6 Adaptive Levels by v-Scale Scores and Standard Scores

<table>
<thead>
<tr>
<th>Adaptive Level</th>
<th>v-Scale Score for Subdomains and Maladaptive Behavior Index</th>
<th>Standard Score for Domains and Adaptive Behavior Composite</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adaptive Behavior Domains</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1 to 9</td>
<td>20 to 70</td>
</tr>
<tr>
<td>Moderately Low</td>
<td>10 to 12</td>
<td>71 to 85</td>
</tr>
<tr>
<td>Adequate</td>
<td>13 to 17</td>
<td>86 to 114</td>
</tr>
<tr>
<td>Moderately High</td>
<td>18 to 20</td>
<td>115 to 129</td>
</tr>
<tr>
<td>High</td>
<td>21 to 24</td>
<td>130 to 160</td>
</tr>
<tr>
<td><strong>Maladaptive Behavior Domain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically Significant</td>
<td>21 to 24</td>
<td></td>
</tr>
<tr>
<td>Elevated</td>
<td>18 to 20</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>1 to 17</td>
<td></td>
</tr>
</tbody>
</table>
The v-scale score from the 11 adaptive behavior subdomains, 3 maladaptive behavior subdomains and the maladaptive behavior index, and the standard score from the 4 adaptive behavior domains and the adaptive behavior composite, recorded at each visit, will be summarized, on a continuous scale, by treatment arm. The change from baseline will also be included.

The change from baseline to the end of treatment visit, for the 4 adaptive behavior domains, the adaptive behavior composite and the maladaptive behavior index only, will be analyzed using the same ANCOVA approach as specified in Section 5.5.3.2.4.

The adaptive level from the 11 adaptive behavior subdomains, 4 adaptive behavior domains, the adaptive behavior composite, the 3 maladaptive behavior subdomains and the maladaptive behavior index, recorded at each visit, will be summarized, on a categorical scale, by treatment arm.

The adaptive level from the 4 adaptive behavior domains, the adaptive behavior composite and the maladaptive behavior index only will be analyzed using ordinal logistic regression. Factors for treatment and age group will be included along with the baseline adaptive level as a covariate. The estimated odds ratios (GWP42003-P arms vs. placebo), 95% CI for the odds ratios, and the p-values testing the null hypothesis that the odds ratio is equal to 1, will be presented.

Each adaptive level for adaptive behavior will be coded with a score from 1 to 5, where 1 = Low, and 5 = High. Each adaptive level for the maladaptive behavior index will be coded with a score from 1 to 3, where 1 = Clinically Significant, and 3 = Average.

The individual responses within each domain will not be listed, only the derived information for each subdomain and domain will be listed.

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for OLE visits.

5.5.4.7 Wechsler Tests

Blinded Phase:

The Wechsler tests are age specific and will only be administered at a sub-group of centers that have the expertise to conduct the assessments. The age of the patient at entry is used when choosing the items to be administered. The following Wechsler Subtests will be used:

Age 2–6:

- Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition (WPPSI-4) Vocabulary and Matrix Reasoning

Age 6–Adult:

- Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-2) Vocabulary and Matrix Reasoning

The T scores (Vocabulary and Matrix Reasoning), scaled scores (Coding) and forward, backward, longest forward and longest backward scores (Digit Span) will be summarized by visit including the change from baseline.
The change from baseline will be analyzed using an ANCOVA approach. The model will include baseline and stratified age group as covariates and treatment arm as fixed factor. The estimated least squares means, treatment difference, together with the 95% CIs and p-value will be presented.

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for OLE visits.

5.5.4.8 Achenbach Child Behavior Checklists and Adult Behavior Checklist

Blinded Phase:

The Achenbach CBCL is a caregiver questionnaire assessing both behavioral and emotional symptoms in children. Depending on the patients’ age, 1 of 2 versions of the Achenbach CBCL is used. The CBCL/1½-5 is used for children 18 months old to 5 years and 11 months old. For patients ≥6 and ≤17 years old the CBCL/6-18 is used. An adult version of the checklist, the Achenbach ABC (ABC/18-59), is used for patients ≥18 and ≤59 years old.

The CBCL/1½-5 comprises of 100 items, the CBCL/6-18 comprises of 113 items and the ABC/18-59 comprises of 123 items. Response options are 0=not true; 1=somewhat or sometimes true; 2=very true or often true. Similar items are grouped and summed to produce syndrome scale scores, which are further grouped into problem scales as specified in Table 7. Other scales for CBDL/6-18 and ABC/18-59 are also derived.

Derivation instructions for the Achenbach scales are given in Appendix 5. For each questionnaire, the individual item responses will not be listed, only the raw scores for the scales given in Table 7 and Table 8 will be listed. For the Achenbach CBCL/1½-5, no scoring will be performed for the language development survey. For the Achenbach ABC/18-59, no scoring will be performed for the spouse/partner functioning scale or the tobacco, alcohol and drugs substance use scales.

The derived raw scores for the syndrome scales and problem scales as indicated in Table 7, recorded at each visit, will be summarized, on a continuous scale, by questionnaire version and treatment arm. The change from baseline will also be included.

The change from baseline to the end of treatment visit, for the internalizing, externalizing and total problems scales only, will be analyzed for each of the questionnaire versions using the same ANCOVA approach as specified in Section 5.5.3.2.4.

The raw scores for other scales as indicated in Table 8 will also be summarized.

Table 7 Achenbach CBCL and ABCL Syndrome and Problem Scales

<table>
<thead>
<tr>
<th>Questionnaire Version</th>
<th>Problem Scales</th>
<th>Syndrome Scales</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBCL/1½-5</td>
<td>Internalizing</td>
<td>Emotionally Reactive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anxious/Depressed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Somatic Complaints</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Externalizing</td>
<td></td>
<td>Attention Problems</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aggressive Behavior</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>Other Problems</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sleep Problems</td>
</tr>
</tbody>
</table>
Table 8 Achenbach CBCL and ABCL Other Scales

<table>
<thead>
<tr>
<th>Questionnaire Version</th>
<th>Other Scales</th>
<th>Other Sub-Scales</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBDL/6-18</td>
<td>Total Competence</td>
<td>Activities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Social</td>
</tr>
<tr>
<td></td>
<td></td>
<td>School</td>
</tr>
<tr>
<td>ABCL/18-59</td>
<td>Friends</td>
<td>Critical Items</td>
</tr>
</tbody>
</table>

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for OLE visits.

5.5.4.9 Social Communication Questionnaire

Blinded Phase:

The current version of the SCQ will be completed by the caregiver for all patients above the age of 4 years with a mental age of at least 2 years. The scale assesses behavior over the most recent three month period using 40 questions, each to be answered ‘yes’ or ‘no’.

The answer to Item 1 ‘Is she/he now able to talk using short phrases or sentences?’ is not scored and is instead used to determine which of the remaining items relating to abnormal language will contribute to the total score. If the answer to Item 1 is ‘yes’, then the six items relating to abnormal language will be used and the total score will range from 0 to 39 points from items 2 to 40. If the answer to Item 1 is ‘no’ then the six items relating to abnormal language will not be used and the total score will range from 0 to 33 points from items 8 to 40 only.
For Items 2, 9, 19 and 20–40, ‘yes’ will be assigned a score of 0 and ‘no’ a score of 1. For all other items, ‘yes’ will be assigned a score of 1 and ‘no’ a score of 0. The total score is calculated by taking the sum of the scores for each item.

In addition to the total score, the following domain scores will be derived:

- Reciprocal Social Interaction: Items 9, 10, 19, 26-33, 36, 37, 39 and 40.
- Communication: Items 2-6, 20-25, 34 and 35.
- Restricted, Repetitive and Stereotyped Patterns of Behavior: Items 7, 8 and 11-16.

The total score and domain scores will be summarized by visit including the change from baseline. The change from baseline for each score will be analyzed using an ANCOVA approach. The model will include baseline and stratified age group as covariates and treatment arm as fixed factor. Sex will also be included as a covariate in the model only if the p-value of the estimate is <0.05.

The estimated least squares means, treatment difference, together with the 95% CIs and p-value will be presented.

The individual responses will not be listed, only the derived information for each derived score will be listed.

**Open-label Extension:**

Descriptive summaries described above for the blinded phase will be repeated for OLE visits.

**5.5.4.10 Time to Baseline TSC-associated Seizure Frequency**

**Blinded Phase only:**

Time to baseline TSC-associated seizure frequency is defined as the number of reported days in IVRS, from Day 1, that it takes for the cumulative number of TSC-associated seizures experienced to be greater than or equal to the number of seizures (per 28 days) experienced during the baseline period and will be calculated as:

\[
\text{Date criterion was achieved} - \text{Date of Day 1} - \text{Number of unreported days in IVRS between Day 1 and date criterion was achieved} + 1
\]

Patients who complete the trial without experiencing greater than or equal to the number of seizures (per 28 days) experienced during the baseline period, or who withdraw from the trial, will be censored at the earliest of:

- Day 99.
- The date of last dose as recorded on the ‘End of Treatment Study Outcome’ CRF page.

The exact day used for censoring will be the day obtained from above minus the number of unreported days in IVRS between Day 1 and the day obtained from above.

Time to baseline TSC-associated seizure frequency will be summarized on a continuous scale, by treatment arm, for patients in the ITT analysis set. The lower and upper quartiles will also be presented. The Kaplan-Meier estimates for the median time to baseline TSC-associated seizure frequency will be presented along with 95% CIs for the median and p-values from log-rank tests comparing each GWP42003-P arm with placebo. A Kaplan-Meier plot will also be produced.
The above will be repeated using Day 29 instead of Day 1 as the start day for counting the cumulative number of TSC-associated seizures.

5.5.5 Subgroup Analyses

To assess the degree of effect heterogeneity, effect modifier analyses are proposed, on the ITT analysis set, for the primary efficacy endpoint and the key secondary efficacy endpoint of ≥50% reduction in TSC-associated seizure frequency.

For the primary efficacy endpoint, the effect modifier analysis will be performed using the negative binomial regression analysis as described in Section 5.5.2. The model will be updated to include covariates for each level of the effect being tested (excluding a reference level), individually and with interactions with time, interactions with treatment arm and interactions with time and treatment. A separate model will be used for testing each effect. The treatment ratios (GWP42003-P vs. placebo), percent reduction and 95% confidence intervals will be presented for each level of the effect. In addition, the effect by time by treatment arm interaction p-value, testing the hypothesis that the effect level treatment ratios are homogeneous, will be presented.

For the key secondary efficacy endpoint of ≥50% reduction in TSC-associated seizure frequency, patients with a ≥50% reduction in seizure frequency will be modelled using logistic regression, including stratified age group and treatment arm as covariates. The model will also include covariates for each level of the effect being tested (excluding a reference level), individually and with interactions with treatment arm. A separate model will be used for testing each effect. The number and percent of responders, and odds ratios and 95% confidence intervals will be presented for each level of the effect. In addition, the effect by treatment arm interaction p-value, testing the hypothesis that the effect level odds ratios are homogeneous, will be presented.

The following effects will be tested:

- Age group (1-6 years, 7-11 years, 12-17 years, and 18-65 years). Note: stratified age group will be removed as a covariate for this model.
- Sex (Male, Female).
- Region (US, Rest of the World).
- Clobazam use (Yes, No).
- Valproic acid use (Yes, No).
- Levetiracetam use (Yes, No).
- Vigabatrin use (Yes, No).
- Baseline average TSC-associated seizures per 28 days (≤ observed Tertile 1, > observed Tertile 1 to ≤ observed Tertile 2, > observed Tertile 2). The observed tertile values will be rounded to the nearest whole number.
- Number of concurrent AEDs (<3, ≥3).
- Number of prior AEDs (<5, ≥5).
- Number of prior and concurrent AEDs (<8, ≥8).

Effects of patients taking other AED types will also be tested if the overall frequency of patients taking the AED is >25%.

5.6 Safety Evaluation

5.6.1 Exposure to IMP

Blinded Phase:
Patients are required to take IMP twice daily (morning and evening). The first dose will be taken in the clinic on Day 1. The date of final dose in the treatment phase will be recorded on the CRF. The date of final dose, for patients who enter the taper period, will be recorded on the CRF at the end of taper visit.

The total number of dosing days in the treatment phase will be calculated as:

\[(\text{Date of last dose in the treatment phase} - \text{Date of Day 1}) + 1\]

The date of last dose in the treatment phase will be obtained from the CRF at the end of treatment visit.

Any missed doses during treatment should be recorded on the ‘IMP Missed Doses Log’ CRF page. The number of days with any missed doses and the number of days where trial medication was not taken in the AM nor PM will be summarized based on data in the treatment phase (Day 1 to end of treatment visit).

In addition, the number of days in which trial medication was taken at least once (AM or PM) will be summarized and calculated as:

\[\text{Total number of dosing days} - \text{the number of days where trial medication was not taken in the AM nor PM}\]

In addition, the number of days in which trial medication was taken both AM and PM will be summarized and calculated as:

\[\text{Total number of dosing days} - \text{the number of days with any missed doses}\]

The above summaries will be presented for all patients and repeated for patients who completed the treatment phase.

In addition, the expected daily volume of IMP to be administered during the treatment phase, once a patient has titrated to target dose, will be summarized by treatment.

The expected daily volume of IMP will be calculated as:

\[2 \times \left[\frac{\text{Weight (kg) at Day 1}}{8}\right]\text{ and rounded to the nearest 0.1}\]

for patients randomized to the 25 mg/kg/day dose level and:

\[2 \times \left[\frac{\text{Weight (kg) at Day 1}}{4}\right]\text{ and rounded to the nearest 0.1}\]

for patients randomized to the 50 mg/kg/day dose level.

Finally, IMP compliance will be summarized by treatment and calculated as:

\[100 \times (\text{Number of days IMP taken at least once} + \text{number of days IMP taken both AM and PM}) + (2 \times \text{day of completion or withdrawal during the treatment period})\]

**Open-label Extension:**

The total number of dosing days will be calculated for the OLE and presented along with a categorical summary of patients whose largest dose was 25 mg/kg/day or less and patients whose largest dose was over 25 mg/kg/day during the OLE treatment phase.

**5.6.2 Adverse Events**

All reported AEs will be classified by system organ class (SOC), preferred term and lower level term using Version 19.1 of MedDRA.

Summaries will be presented by treatment arm as well as SOC and preferred term.
A blinded phase treatment emergent AE (TEAE) is defined as an AE with a start date on or after the first dose of IMP during the blinded phase up to and including the date of first dose of the OLE phase (OLE Day 1). An OLE phase TEAE is defined as an AE with a start date on or after the OLE Day 1. If an AE has a partial start date and it is unclear from the partial date (or the stop date) whether the AE started prior to or post first dose of IMP then the AE will be considered treatment emergent and if it is unclear which phase the event started, it will be assigned to both phases. If the start date of the AE is the same as the date of first dose of IMP from the blinded phase and the plausible relationship to IMP is marked on the CRF as “Prior to study medication” then the AE will not be considered treatment emergent.

An AE will be considered treatment-related if the plausibility relationship to trial medication is recorded on the CRF as ‘yes’. If the data on plausibility relationship to trial medication is missing then the AE will be considered treatment-related.

An AE will be considered leading to permanent discontinuation of IMP if the action taken with IMP is recorded on the CRF as ‘study medication stopped’ or the outcome is recorded on the CRF as ‘patient died’.

An AE will be considered leading to IMP dose reduction excluding permanent discontinuation if the action taken with IMP is recorded on the CRF as ‘dose reduced’, ‘dose reduced temporarily’ or ‘study medication interrupted’.

An AE will be considered leading to temporary IMP dose reduction if the action taken with IMP is recorded on the CRF as ‘dose reduced temporarily’.

An AE will be considered leading to permanent IMP dose reduction excluding permanent discontinuation if the action taken with IMP is recorded on the CRF as ‘dose reduced’.

An AE will be considered fatal if the outcome is recorded on the CRF as ‘patient died’.

The following summaries will be generated separately for the blinded and OLE phase (counts are by patient unless specified otherwise):

- Overall summary of AEs, including number of patients reporting each of; TEAEs, treatment related TEAEs, TEAEs leading to withdrawal, treatment related TEAEs leading to withdrawal, serious TEAEs, treatment related serious TEAEs.
- Summary of TEAEs.
- Summary of TEAEs by event.
- Summary of treatment-related TEAEs.
- Summary of treatment-related TEAEs by event.
- Summary of TEAEs by maximal severity.
- Summary of TEAEs by sex.
- Summary of serious TEAEs.
- Summary of serious TEAEs by event.
- Summary of non-serious TEAEs.
- Summary of non-serious TEAEs by event.
- Summary of treatment-related serious TEAEs.
- Summary of treatment-related serious TEAEs by event.
- Summary of TEAEs leading to permanent discontinuation of IMP.
• Summary of treatment-related TEAEs leading to permanent discontinuation of IMP.
• Summary of TEAEs leading to IMP dose reduction excluding permanent discontinuation (by resolution and overall).
• Summary of treatment-related TEAEs leading to IMP dose reduction excluding permanent discontinuation (by resolution and overall).
• Summary of TEAEs leading to temporary IMP dose reduction (by resolution and overall).
• Summary of treatment-related TEAEs leading to temporary IMP dose reduction (by resolution and overall).
• Summary of TEAEs leading to permanent IMP dose reduction excluding permanent discontinuation (by resolution and overall).
• Summary of treatment-related TEAEs leading to permanent IMP dose reduction excluding permanent discontinuation (by resolution and overall).
• Summary of fatal TEAEs.
• Summary of TEAEs by time of first onset of AE.
• Summary of TEAEs by time to AE resolution.
• Summary of TEAEs reported in ≥ 2% of patients (after rounding) in the GWP42003-P treatment arms and where the incidence is greater than the placebo treatment arm.
• List of patients experiencing TEAEs by SOC and preferred term.
• Summary of pre-treatment AEs (blinded phase only).

For the summary of TEAEs by maximal severity, for each patient, the worst severity recorded by preferred term, SOC and overall will be used for summary purposes. If severity is missing, the worst case (severe) will be assumed.

For summaries by resolution, AEs with an outcome of ‘recovered’ or ‘recovered with sequelae’ will be summarized as ‘Resolved’ and AEs with an outcome of ‘continuing’, ‘patient died’ or those with a missing outcome will be summarized as ‘Not resolved’.

For the summary of TEAEs by time of first onset of AE, data will be summarized under the following categories:

- Weeks 1 to 2 (Day 1 to 14).
- Weeks 3 to 4 (Day 15 to 28).
- Weeks 5 to 8 (Day 29 to 56).
- Weeks 9 to 12 (Day 57 to 84).
- >12 weeks (> Day 84).

The time to first onset of AE will be calculated for TEAEs as:

\[ \text{Start date of AE} - \text{Date of first dose of IMP} + 1 \]

If patients have multiple occurrences of an AE then the AE will be counted once for the first occurrence only. Percentages will be based on the number of patients in the safety analysis set who have a visit or follow-up call within each time period above.
For the summary of TEAEs by time to AE resolution, data will be summarized under the following categories:

- 1 week (≤7 days).
- 2 weeks (8 to 14 days).
- 3 weeks (15 to 21 days).
- 4 weeks (22 to 28 days).
- >4 weeks (>28 days).
- Ongoing (for AEs not resolved).

The time to AE resolution will be calculated for TEAEs as:

\[
\text{Stop date of AE} - \text{Start date of AE} + 1
\]

If patients have multiple occurrences of an AE then the AE will be counted once for the occurrence with the longest time to AE resolution. However, if any of the AEs are not resolved then the AE will be counted once within the ‘Ongoing’ category.

The start and stop day of the AE relative to the first dose of IMP (as recorded on the CRF) will be calculated as per Section 5.1.2. For partial dates, if it is clear from the partial date that the start/stop day was prior to the first dose of IMP, then ‘pre’ will be listed, similarly if it is clear that the event was post the first dose of IMP then ‘post’ will be listed as the start/stop day as appropriate.

All AEs will be listed. Listings will include the start and stop day of the AE, a flag for treatment emergence, and limited demographic information about the patient (age, sex, race and weight at screening). A separate listing will be provided for pre-treatment AEs, serious AEs and events of special interest (see Appendix 1).

### 5.6.3 Clinical Laboratory Evaluation

#### 5.6.3.1 Hematology and Biochemistry

Summaries will be presented by treatment arm for each laboratory parameter at each visit. Change from baseline to each post-baseline visit will also be presented.

If values for any of the parameters are below or above the limit of quantification of the assay (BLQ or ALQ), then they will be included in the summary tables at the BLQ or ALQ thresholds. However, for estimated creatinine clearance, results >60 are reported only as ‘>60’. Hence, estimated glomerular filtration rate (eGFR) will be calculated as:

For patients who are ≥18 years at screening, the Cockroft-Gault equation will be used:

\[
eGFR \text{ (mL/min)} = \left[ \frac{(140 - \text{age}) \times \text{weight} \times k}{\text{serum creatinine}} \right]
\]

where age is measured in years, weight is measured in kg, \( k = 1.23 \) if male, \( k = 1.04 \) if female and serum creatinine is measured in \( \mu \text{mol/L} \). eGFR will be indexed to body surface area (BSA) using the following formula:

\[
eGFR \text{ (mL/min/1.73m}^2) = eGFR \text{ (mL/min)} \times \frac{1.73}{\text{BSA}}
\]

where BSA is based on the Du Bois and Du Bois formula:

\[
\text{weight} 0.425 \times \text{height} 0.725 \times 0.007184
\]

where weight is measured in kg and height is measured in cm.
For patients who are <18 years at screening, the revised Schwartz estimate will be used:

\[
(36.2 \times \text{height}) / \text{serum creatinine}
\]

where height is measured in cm and serum creatinine is measured in μmol/L. When available, enzymatic serum creatinine will be used. Otherwise, the Jaffe serum creatinine will be used. If height or weight is missing at the collection date, then the closest value to the sample date will be used. If there is more than one height or weight value on the same day or 2 height or weight values equally distant from the collection date, then the mean will be used. The eGFR will be summarized separately for each method.

Where laboratory samples are repeated, the baseline value is defined as the final recorded value prior to the first dose of IMP.

Shift tables for hematology and biochemistry parameters will be constructed, based upon normal ranges and GW toxicity limits (See Section 8), to determine the categorical shifts from baseline to each post-baseline visit. Values will be categorized as ‘Normal’, ‘Low’ or ‘High’ based on normal ranges and ‘Toxically Low’, ‘Toxically Normal’ or ‘Toxically High’ based on GW toxicity limits.

For eGFR, results will be assigned to the following grades:

- Normal: >60 ml/min/1.73 m²
- Grade 1: 60 ml/min/1.73 m²
- Grade 2: ≥30 and <60 ml/min/1.73 m²
- Grade 3: ≥15 and <30 ml/min/1.73 m²
- Grade 4: <15 ml/min/1.73 m²

A separate shift table will be produced for eGFR based upon the above grades to determine the categorical shifts from baseline to each post-baseline visit.

For the blinded phase, scatter plots will be produced for each laboratory parameter presenting the maximum post baseline result divided by the upper limit of normal (ULN) on the Y-axis, and the baseline result divided by the ULN on the X-axis. However, for prothrombin international normalized ratio (INR), both axes will present the raw results rather than dividing by ULN.

An additional table will be produced for the blinded phase only, summarizing the number of patients meeting the following criteria:

- Alanine aminotransferase (ALT) > 1×ULN at baseline
- Aspartate aminotransferase (AST) > 1×ULN at baseline
- AT > 1×ULN at baseline
- Treatment emergent ALT > 3×ULN, > 5×ULN and > 8×ULN
- Treatment emergent AST > 3×ULN, > 5×ULN and > 8×ULN
- Treatment emergent AT > 3×ULN, > 5×ULN and > 8×ULN
- Treatment emergent AT > 3×ULN and either bilirubin > 2×ULN or INR > 1.5

where AT is AST or ALT, and treatment emergent is defined as criteria not met at baseline but met at any time post-baseline. The above will be summarized overall and for the following subgroups:

- Sex (Male, Female).
• Valproic acid use (Yes, No).
• Clobazam use (Yes, No).
• Valproic acid use and Clobazam use (Yes/Yes, Yes/No, No/Yes, No/No).
• Patients taking 3 or more current AEDs.
• Patients taking 4 or more current AEDs.

A separate table will be produced, by treatment arm and visit, presenting the incidence of patients with urinalysis or blood results indicative of a medical condition at Visit 1 and indicative of an adverse event after Visit 1.

All laboratory data will be listed; listings will include limited demographic information about the patient (age, sex, race and weight at baseline). Abnormal laboratory values will be listed separately. A further listing will be created for the laboratory reference ranges and toxicity limits.

5.6.3.2 Urinalysis

Urinalysis is assessed, using dipsticks, at the same visits as biochemistry and hematology. Urinalysis results will be listed only.

5.6.3.3 Pregnancy Test and Urine THC Screen

Serum pregnancy test results and urine THC screen results will be summarized by treatment arm and visit.

5.6.4 Vital Signs, Other Physical Findings and Other Safety Data

5.6.4.1 Vital Signs

At Visit 1, 3 and B3, systolic and diastolic blood pressure are collected in the sitting, supine and standing positions. At all other visits, systolic and diastolic blood pressure are collected in the sitting position only.

Summaries will be presented by treatment arm for each vital sign parameter at each visit. Change from baseline to each post-baseline visit will also be presented.

Body mass index will be calculated, for each visit in which height and weight are recorded, as:

\[
\text{Weight (kg) } \div \text{ height (m)}^2
\]

A separate table will be produced, by treatment arm and visit, presenting the incidence of patients with vital signs indicative of a medical condition at Visit 1 and indicative of an adverse event after Visit 1.

Based on the criteria presented in Section 8, clinically significant changes from baseline in vital signs measurements and other defined flagged values will be identified at each visit. The number of patients with a clinically significant change from baseline will be summarized by parameter, visit and treatment arm. The number of patients with at least one post-baseline flagged vital sign parameter value will be summarized by parameter, flagged criteria and treatment arm for the blinded phase and repeated for the OLE phase.
5.6.4.2 Electrocardiogram

Summaries will be presented by treatment arm for ventricular rate, PR interval, QRS duration, QT interval and QTcB, at each visit. Change from baseline to each post-baseline visit will also be presented.

A separate table will be produced, by treatment arm and visit, presenting the incidence of patients with an ECG indicative of a medical condition at Visit 1 and indicative of an adverse event after Visit 1.

Based on the criteria presented in Section 8, defined flagged values will be identified at each visit. The number of patients with at least one post-baseline flagged ECG parameter value will be summarized by parameter, flagged criteria and treatment arm for the blinded phase and repeated for the OLE phase.

5.6.4.3 Physical Examination

Any relevant findings at screening are included as part of the patient’s medical history. Any changes seen after screening that are indicative of an AE are to be recorded as such on the AE form and included as part of the AE summaries.

Additionally, height and weight are recorded as part of the physical examination. Height and weight will be summarized and listed together with the vital signs parameters.

Incidence of patients with a physical examination indicative of a medical condition at Visit 1 and indicative of an adverse event after Visit 1 will be summarized by treatment arm and visit.

5.6.4.4 Columbia-Suicide Severity Rating Scale

The C-SSRS is completed for patients who are 6 years and older and capable of understanding and answering the questions, in the investigator’s opinion. Questions are asked on suicidal behavior, suicidal ideation and intensity of ideation. At the screening visit, questions are in relation to lifetime experiences and all subsequent questioning in relation to the last assessment.
The following C-SSRS data will be summarized by treatment arm at each visit for patients in the safety analysis set:

- Incidence of the following suicidal ideation:
  - Wish to be dead.
  - Non-specific active suicidal thoughts.
  - Active suicidal ideation with any methods (not plan) without intent to act.
  - Active suicidal ideation with some intent to act, without specific plan.
  - Active suicidal ideation with specific plan and intent.

- Incidence of the following suicidal behavior:
  - Actual attempt.
  - Interrupted attempt.
  - Aborted attempt.
  - Preparatory acts or behavior.
  - Suicidal behavior.
  - Completed suicide.

5.6.4.5 Inpatient Hospitalizations due to Epilepsy

The number of inpatient epilepsy-related hospitalizations since the previous visit are recorded at every visit starting from Visit 2.

The number of patients with inpatient epilepsy-related hospitalizations will be presented by visit, including OLE visits.

5.6.4.6 Growth and Development

IGF-1 levels will be analyzed as part of the clinical laboratory testing. IGF-1 levels will be summarized on a continuous scale, including change from baseline, by treatment arm.

For the blinded phase only, change from baseline to the end of treatment visit for IGF-1 levels will also be plotted against the Tanner Stages, weight, and height recorded at baseline.

The pubic hair growth (both sexes), genital (males only) and breast (females only) development of all adolescent patients (i.e., 10 to less than 18 years of age at the time of signing the informed consent form, or earlier if clinically indicated by onset of menarche or other signs of precocious puberty) will be assessed using Tanner Staging. The patients will undergo a discreet physical examination and be assigned a value under each category of Pubic Hair Growth (both sexes), Genitals (male patients only), and Breasts (female patients only).

Tanner Stages will be summarized on a categorical scale, by treatment arm.

5.6.4.7 Menstruation

Menstruation details will be summarized as appropriate, including any changes in normal cycles, by treatment arm.

5.7 Other Measures

5.7.1 Concomitant Medication

A medication will be considered concomitant for each phase if it has a start date on or after the first dose of IMP for the corresponding phase or if it was started prior to the first dose of IMP and was ongoing. If a medication has a partial or missing start/stop date and it is unclear from the date whether the medication was taken after the first dose of IMP then it will be considered concomitant.

For summaries and listings of medications the following approach will be used to determine the Anatomical Therapeutic Chemical (ATC) term to be presented:

- If coded to level 4 then the level 4 coded term will be presented.
- If coding is not performed at level 4 but level 3 coding is present, then level 3 coded term will be presented.
- If coding is not performed at level 3 but level 2 coding is present, then the level 2 coded term will be presented.
- If coding is not performed at level 2 but level 1 coding is present, then the level 1 coded term will be presented.

Summaries of each of the following by ATC term and preferred term will be summarized by absolute counts (n) and percentages (%), separately for the blinded and OLE phase (unless stated otherwise):

- History of AEDs (blinded phase only);
- Concomitant AEDs;
- Concomitant rescue medications; and
- Other concomitant medications.

The ATC term, preferred term, reported generic name and reported brand name will be listed.

An additional summary table will be produced for concomitant antiepileptic therapies, displaying the number and percentage of patients with a vagus nerve stimulation device or on a ketogenic diet.

The start day and stop day will be included in the listing according to Section 5.1.2. If the date is partial and the exact day is unknown then the text ‘pre’ or ‘post’ will replace the start or stop day if it is clear from the partial date that the medication started or stopped prior to or after the first dose of IMP.

5.7.2 Pharmacokinetics of CBD and its Major Metabolites

Samples for PK analysis are taken on Visit 3 (first dose, Day 1) and Visit 10 (last maintenance dose of the blinded phase, Day 113) for patients weighing more than 20 kg. For patients recruited under Protocol Version 2, PK samples were taken at the following time-points:

- Prior to administration of IMP, \( \leq 0.0 \) hours pre-dose on Visit 3 or \( C_{\text{trough}} \) at steady state (Visit 10).
- \( \geq 4.0 \) hours to \( \leq 5.0 \) hours.
- \( \geq 6.0 \) hours to \( \leq 7.0 \) hours.
- \( \geq 8.0 \) hours to \( \leq 10.0 \) hours, for patients 18 years or older.
Patients recruited under Protocol Version 3 onwards, PK samples were taken at the following time-points:

- Prior to administration of IMP, ≤0.0 hours pre-dose on Visit 3 or C_{trough} at steady state (Visit 10).
- ≥2.0 hours to ≤3.0 hours.
- ≥4.0 hours to ≤6.0 hours.
- ≥8.0 hours to ≤10.0 hours, for patients 18 years or older.

The nominal mid-point time of 0, 2.5, 4.5, 5, 6.5 and 9 hours will be used for summaries of plasma concentrations. Plasma concentrations and PK parameters will be summarized showing the number of non-missing values (n), arithmetic mean, standard deviation, coefficient of variation (%), median, minimum and maximum. Where samples are reported as BLQ, a value of zero will be used in the summaries. Summary statistics will be presented to 3 significant figures.

Where data allow, the PK parameter AUC_{0-t}, will be derived at each visit by the PK vendor. A dose-normalized AUC_{0-t} will be calculated as AUC_{0-t} divided by the randomized dose per administration (12.5 or 25 mg/kg). This will include Visit 3, for consistency, where the first dose of IMP will be 2.5 mg/kg.

Plasma concentrations of CBD and its major metabolites 7-hydroxy-CBD (7-OH-CBD) and 7-carboxy-CBD (7-COOH-CBD) will be summarized by nominal mid-point time, visit and GWP42003-P arm. In addition, a dot plot of plasma concentrations for each patient, by nominal mid-point time will be created for each visit and GWP42003-P arm. The arithmetic mean will be highlighted on the plot. Additionally, a line plot of the arithmetic mean plasma concentration will be created with standard error bars by nominal mid-point time for each visit and GWP42003-P arm. These plots will be presented both a linear and semi-logarithmic scale for plasma concentration.

AUC_{0-t} and dose normalized AUC_{0-t}, for CBD and its major metabolites 7-OH-CBD and 7-COOH-CBD, will be summarized by visit and GWP42003-P arm. In addition, the ratio of 7-OH-CBD AUC_{0-t} to CBD AUC_{0-t} and the ratio of 7-COOH-CBD AUC_{0-t} to CBD AUC_{0-t} will be summarized. Box plots of AUC_{0-t} will be produced comparing visit on the x-axis, by parent and metabolite, and GWP42003-P arm. This will be repeated with parent and metabolite on the x-axis, by visit and GWP42003-P arm. Summaries and plots of AUC_{0-t} will be repeated by stratified age group.

Plasma concentration and AUC_{0-t} summaries may exclude individual time-points or visits for patients deemed to meet certain criteria that could affect exposure. These criteria include:

- Patients vomiting on or 1 day prior to the PK visit.
- Missed doses prior to the PK visit.
- IMP dose reduction.
- Cases of severe diarrhoea.
- Use of disallowed concomitant medication.

All exclusion will be detailed in a separate document finalized prior to unblinding. All data will be listed with data excluded from summaries flagged along with the reason for exclusion.
5.7.3 Plasma Concentrations of Concomitant AEDs

Blood sampling for AEDs will be performed at Visit 3 (Day 1), Visit 5, Visit 7, Visit 9 and Visit 10 (end of treatment) of the blinded phase. For each AED, plasma concentrations will be summarized by treatment arm at each visit for patients in the safety analysis set.

5.7.4 Study Medication Use and Behavior Survey

This form consists of 18 questions regarding the use of the IMP. The trained investigator or trial coordinator will complete this survey as an interview with the patient/caregiver at the final dosing visit.

The form will be completed for all patients 12 years of age and older in the trial.

Each question will be summarized, on a categorical scale, by treatment arm. Percentages will be based on the number of patients completing the survey, in each treatment arm. The summary will be presented separately for all patients with a completed form and patients 12 years of age and older.

5.7.5 Supplemental Drug Accountability Form

This form consists of 7 questions regarding various aspects of drug accountability and patient usage. It is completed as part of an interview with the patient/caregiver when a triggering drug accountability discrepancy is identified.

The triggering drug accountability discrepancies are as follows:

- Missing bottle(s).
- Compliance issues where one or more bottles are used compared to what was the expected use, according to the IVRS report and paper diary.
- Returned IMP supply with evidence of tampering.
- Greater than the target daily dose as recorded in the IVRS report and paper diary.

The number of patients with a completed form will be summarized separately for the blinded phase and OLE phase. The summary will be presented separately for all patients with a completed form and patients 12 years of age and older.

5.7.6 Supplemental Adverse Event Form

This form consists of 15 questions regarding the AE and use of IMP. It is completed as part of an interview with the patient/caregiver when a triggering AE of interest is reported.

The categories for triggering AEs of interest are:

- Euphoria or inappropriate elation.
- Inappropriate laughter or exhilaration.
- Mood changes.
- Drunk, high or intoxicated.
- Hallucinations (visual or auditory), dissociations, disorientation, agitation.
- Disturbance in cognition, memory, or attention.
- Drug abuse.
- Drug withdrawal or drug withdrawal syndrome.
- Addiction.
- Overdose.
- Misuse of IMP.
- Thoughts of suicide, attempted suicide or suicide.
The number of patients with a completed form will be summarized separately for the blinded phase and OLE phase. The summary will be presented separately for all patients with a completed form and patients 12 years of age and older.

### 5.7.7 Site Classification Form

The investigator reviews the applicable Supplemental Adverse Event Form or Supplemental Drug Accountability Form, and then completes a Site Classification Form. For each Supplemental Adverse Event Form or Supplemental Drug Accountability Form completed, there should be an associated Site Classification Form.

The Site Classification Form requires the investigator to assign the finding to an appropriate classification and then to also assign the possible relationship to the IMP. The investigator is also required to indicate the level of the certainty of the classification.

The number of patients with a completed form a will be summarized, along with the form associated to, separately for the blinded phase and OLE phase. The summary will be presented separately for all patients with a completed form and patients 12 years of age and older.

### 5.7.8 IVRS Compliance

For the blinded phase only, the number of unreported days in IVRS, during the baseline and treatment periods, will be summarized, on a continuous and categorical scale, by treatment arm for patients in the ITT analysis set. For the summary on a continuous scale, the lower and upper quartiles will also be presented.

The percentage IVRS compliance, during the baseline and treatment periods, will also be summarized, on a continuous and categorical scale, and calculated as:

\[
\text{Percentage IVRS compliance} = \left( \frac{\text{Number of reported days in IVRS}}{\text{Number of reported days in IVRS} + \text{Number of unreported days in IVRS}} \right) \times 100
\]
5.8 Changes in the Conduct of the Trial or Planned Analysis

During the OLE, seizure counts are collected every 7 days rather than daily. Hence, the endpoint of TSC-associated seizure free days has been defined for the blinded phase only.

The endpoint of number of patients experiencing a >25% worsening, −25 to +25% no change, 25–50% improvement, 50–75% improvement or >75% improvement in convulsive seizures from baseline has been updated to the following:

- Number of patients experiencing a >25% increase, ≥0 to ≤25% increase, >0 to <25% reduction, ≥25 to <50% reduction, ≥50 to <75% reduction or ≥75% reduction in convulsive seizures from baseline.

6. REFERENCES


2 QOLIE Development Group. Scoring Manual for the QOLIE-31-P: Patient-Weighted Quality of Life in Epilepsy (v2).

7. AMENDMENTS

Notable changes to the SAP that were completed prior to unblinding, are given below. Minor changes, clarifications and corrections are not listed.

<table>
<thead>
<tr>
<th>Date</th>
<th>Section</th>
<th>Description of Change</th>
</tr>
</thead>
</table>
8. ATTACHMENTS AND APPENDICES

Appendix 1  Adverse Events of Special Interest – Abuse Liability

<table>
<thead>
<tr>
<th>Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug withdrawal convulsions</td>
</tr>
<tr>
<td>Drug withdrawal headache</td>
</tr>
<tr>
<td>Drug withdrawal maintenance therapy</td>
</tr>
<tr>
<td>Drug withdrawal syndrome</td>
</tr>
<tr>
<td>Drug withdrawal syndrome neonatal</td>
</tr>
<tr>
<td>Drug rehabilitation</td>
</tr>
<tr>
<td>Rebound effect</td>
</tr>
<tr>
<td>Steroid withdrawal syndrome</td>
</tr>
<tr>
<td>Withdrawal arrhythmia</td>
</tr>
<tr>
<td>Withdrawal syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug abuse and dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine dysregulation syndrome</td>
</tr>
<tr>
<td>Drug abuse</td>
</tr>
<tr>
<td>Drug abuser</td>
</tr>
<tr>
<td>Drug dependence</td>
</tr>
<tr>
<td>Drug dependence, antepartum</td>
</tr>
<tr>
<td>Drug dependence, postpartum</td>
</tr>
<tr>
<td>Intentional drug misuse</td>
</tr>
<tr>
<td>Intentional overdose</td>
</tr>
<tr>
<td>Maternal use of illicit drugs</td>
</tr>
<tr>
<td>Neonatal complications of substance abuse</td>
</tr>
<tr>
<td>Polysubstance dependence</td>
</tr>
<tr>
<td>Substance abuse</td>
</tr>
<tr>
<td>Substance abuser</td>
</tr>
<tr>
<td>Accidental overdose</td>
</tr>
<tr>
<td>Dependence</td>
</tr>
<tr>
<td>Disturbance in social behaviour</td>
</tr>
<tr>
<td>Drug administered at inappropriate site</td>
</tr>
<tr>
<td>Drug detoxification</td>
</tr>
<tr>
<td>Drug diversion</td>
</tr>
<tr>
<td>Drug level above therapeutic</td>
</tr>
<tr>
<td>Drug level increased</td>
</tr>
<tr>
<td>Drug screen</td>
</tr>
<tr>
<td>Drug screen positive</td>
</tr>
<tr>
<td>Drug tolerance</td>
</tr>
<tr>
<td>Drug tolerance decreased</td>
</tr>
<tr>
<td>Drug tolerance increased</td>
</tr>
<tr>
<td>Medication overuse headache</td>
</tr>
<tr>
<td>Narcotic bowel syndrome</td>
</tr>
<tr>
<td>Needle track marks</td>
</tr>
<tr>
<td>Overdose</td>
</tr>
<tr>
<td>Prescribed overdose</td>
</tr>
<tr>
<td>Prescription form tampering</td>
</tr>
<tr>
<td>Substance use</td>
</tr>
<tr>
<td>Substance-induced mood disorder</td>
</tr>
<tr>
<td>Substance-induced psychotic disorder</td>
</tr>
<tr>
<td>Toxicity to various agents</td>
</tr>
</tbody>
</table>
Appendix 2  Ranges for Clinically Significant Changes and Other Defined Flagged Values in Vital Signs

The range of values that will be used to identify clinically significant changes in vital signs parameters (See Section 5.6.4.1) are presented in Table 9.

Table 9  Ranges for Clinically Significant Changes in Vital Signs

<table>
<thead>
<tr>
<th>Vital Sign</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting Systolic BP</td>
<td>Change: &lt; -20, &gt; 20</td>
</tr>
<tr>
<td>Sitting Diastolic BP</td>
<td>Change: &lt; -10, &gt; 10</td>
</tr>
<tr>
<td>Pulse Rate</td>
<td>Change: &lt; -10, &gt; 10</td>
</tr>
<tr>
<td>Weight</td>
<td>Percent Change: ≤ -7, ≥ 7</td>
</tr>
</tbody>
</table>

Defined flagged values that will be used to identify low or high vital signs parameters (See Section 5.6.4.1) are presented in Table 10.

Table 10  Other Defined Flagged Values for Vital Signs

<table>
<thead>
<tr>
<th>Vital Sign</th>
<th>Flag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting Systolic BP</td>
<td>&lt; 90, &gt; 140, &gt; 160</td>
</tr>
<tr>
<td>Sitting Diastolic BP</td>
<td>&lt; 50, &gt; 90, &gt; 100</td>
</tr>
<tr>
<td>Pulse Rate</td>
<td>&lt; 60, &gt; 100</td>
</tr>
<tr>
<td>Temperature</td>
<td>&gt; 38.0, &lt; 36.0</td>
</tr>
<tr>
<td>Respiratory Rate</td>
<td>&lt; 12, &gt; 20</td>
</tr>
</tbody>
</table>
Appendix 3  Defined Flagged Values in ECG Parameters

Defined flagged values that will be used to identify low or high ECG parameters (See Section 5.6.4.2) are presented in Table 11.

### Table 11  Defined Flagged Values for ECG Parameters

<table>
<thead>
<tr>
<th>ECG Parameter</th>
<th>Flag</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc</td>
<td>&gt; 450, &gt; 480, &gt; 500</td>
</tr>
</tbody>
</table>
Appendix 4  Toxicity Criteria for Laboratory Parameters

The toxicity criteria that will be used to identify abnormal laboratory parameters are presented in Table 12 and Table 13.

### Table 12  Toxicity Criteria for Biochemistry Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Toxicity Decrease</th>
<th>Toxicity Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloride</td>
<td>( \leq 0.96 \times LL )</td>
<td>( \geq 1.04 \times UL )</td>
</tr>
<tr>
<td>Calcium</td>
<td>( \leq 0.89 \times LL )</td>
<td>( \geq 1.16 \times UL )</td>
</tr>
<tr>
<td>Sodium</td>
<td>( \leq 0.96 \times LL )</td>
<td>( \geq 1.04 \times UL )</td>
</tr>
<tr>
<td>Potassium</td>
<td>( \leq 0.90 \times LL )</td>
<td>( \geq 1.10 \times UL )</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>( \leq 3.2 )</td>
<td>( \geq 16 )</td>
</tr>
<tr>
<td>Phosphate</td>
<td>( \leq 0.79 \times LL )</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>( \leq 0.85 \times LL )</td>
<td>( \geq 1.6 \times UL )</td>
</tr>
<tr>
<td>AST</td>
<td></td>
<td>( \geq 3 \times UL )</td>
</tr>
<tr>
<td>ALT</td>
<td></td>
<td>( \geq 3 \times UL )</td>
</tr>
<tr>
<td>Lactate Dehydrogenase</td>
<td></td>
<td>( \geq 2.6 \times UL )</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td></td>
<td>( \geq 2 \times UL )</td>
</tr>
<tr>
<td>Gamma GT</td>
<td></td>
<td>( \geq 2.6 \times UL )</td>
</tr>
<tr>
<td>Bilirubin</td>
<td></td>
<td>( \geq 2 \times UL )</td>
</tr>
<tr>
<td>Albumin</td>
<td>( \leq 0.84 \times LL )</td>
<td>( \geq 1.16 \times UL )</td>
</tr>
<tr>
<td>Total protein</td>
<td>( \leq 0.84 \times LL )</td>
<td>( \geq 1.16 \times UL )</td>
</tr>
<tr>
<td>Urea</td>
<td></td>
<td>( \geq 2.6 \times UL )</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td></td>
<td>( \geq 2.6 \times UL )</td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
<td>( \geq 2.6 \times UL )</td>
</tr>
<tr>
<td>Uric acid</td>
<td></td>
<td>( \geq 1.16 \times UL )</td>
</tr>
</tbody>
</table>

UL = upper limit of reference range
LL = lower limit of reference range
### Table 13   Toxicity Criteria for Hematology Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Toxicity Decrease</th>
<th>Toxicity Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>≤9.4</td>
<td></td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>≤28</td>
<td></td>
</tr>
<tr>
<td>Red cell count</td>
<td>≤0.84xLL</td>
<td></td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>≤0.84xLL</td>
<td>≥1.11xUL</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin</td>
<td>≤0.84xLL</td>
<td></td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin concentration</td>
<td>≤0.84xLL</td>
<td></td>
</tr>
<tr>
<td>Platelets (x10^9/L)</td>
<td>≤74</td>
<td></td>
</tr>
<tr>
<td>Prothrombin time</td>
<td></td>
<td>&gt;1.5xUL</td>
</tr>
<tr>
<td>Prothrombin international normalized ratio</td>
<td></td>
<td>&gt;1.5</td>
</tr>
<tr>
<td>Total white blood cell count (x10^9/L)</td>
<td>≤2.9</td>
<td>≥21</td>
</tr>
<tr>
<td>Total neutrophil count (x10^9/L)</td>
<td>≤1.36</td>
<td>≥14.7</td>
</tr>
<tr>
<td>Segmented neutrophil count (x10^9/L)</td>
<td>≤0.75</td>
<td>≥12.3</td>
</tr>
<tr>
<td>Eosinophils (x10^9/L)</td>
<td></td>
<td>≥1.5</td>
</tr>
<tr>
<td>Basophils (x10^9/L)</td>
<td></td>
<td>≥0.31</td>
</tr>
<tr>
<td>Monocytes (x10^9/L)</td>
<td></td>
<td>≥2.1</td>
</tr>
<tr>
<td>Lymphocytes (x10^9/L) for patients &lt;18 years (auto hematology)</td>
<td>≤1.0</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes (x10^9/L) for patients &lt;18 years (manual hematology)</td>
<td>≤0.2</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes (x10^9/L) for patients ≥18 years</td>
<td>≤0.2</td>
<td></td>
</tr>
</tbody>
</table>

UL = upper limit of reference range   LL = lower limit of reference range
Appendix 5 Derivation Instructions for Achenbach Child Behavior Checklists and Adult Behavior Checklist

CBCL/1½–5
The syndrome scale and problem scale grouping of items is shown in Table 14. If data are missing for more than 8 items (not counting item 100) then the syndrome and problem scales will not be calculated.

Each of the items is scored 0, 1 or 2 as indicated on the questionnaire. The individual items associated with each syndrome scale are presented in Table 14.

The syndrome scale scores will be calculated as the sum of the individual items associated with that scale. The problem scale scores will then be calculated as the sum of the corresponding syndrome scale scores as per Table 7 in Section 5.5.4.8. The total problem scale score will be calculated as the sum of the internalizing, externalizing and other problem scales.

Table 14 Syndrome Scale Items for Achenbach CBCL/1½–5

<table>
<thead>
<tr>
<th>Problem Scales</th>
<th>Syndrome Scales</th>
<th>Items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internalizing</td>
<td>Emotionally Reactive</td>
<td>21, 46, 51, 79, 82, 83, 92, 97, 99</td>
</tr>
<tr>
<td></td>
<td>Anxious/Depressed</td>
<td>10, 33, 37, 43, 47, 68, 87, 90</td>
</tr>
<tr>
<td></td>
<td>Somatic Complaints</td>
<td>1, 7, 12, 19, 24, 39, 45, 52, 78, 86, 93</td>
</tr>
<tr>
<td></td>
<td>Withdrawn</td>
<td>2, 4, 23, 62, 67, 70, 71, 98</td>
</tr>
<tr>
<td>Externalizing</td>
<td>Attention Problems</td>
<td>5, 6, 56, 59, 96</td>
</tr>
<tr>
<td></td>
<td>Aggressive Behavior</td>
<td>8, 15, 16, 18, 20, 27, 29, 35, 40, 42, 44, 53, 58, 66, 69, 81, 85, 88, 96</td>
</tr>
<tr>
<td>Other</td>
<td>Other Problems</td>
<td>3, 9, 11, 13, 14, 17, 25, 26, 28, 30, 31, 32, 34, 36, 41, 49, 50, 54, 55, 57, 60, 61, 63, 65, 72, 73, 75, 76, 77, 80, 89, 91, 100</td>
</tr>
<tr>
<td></td>
<td>Sleep Problems</td>
<td>22, 38, 48, 64, 74, 84, 94</td>
</tr>
</tbody>
</table>

CBCL/6–18
The syndrome scale and problem scale grouping of items is shown in Table 15. If data are missing for more than 8 items (not counting items 56h or 113) then the syndrome and problem scales will not be calculated.

Each of the items is scored 0, 1 or 2 as indicated on the questionnaire. The individual items associated with each syndrome scale are presented in Table 15.

The syndrome scale scores will be calculated as the sum of the individual items associated with that scale. The problem scale scores will then be calculated as the sum of the corresponding syndrome scale scores as per Table 7 in Section 5.5.4.8. The total problem scale score will be calculated as the sum of the internalizing, externalizing and other problem scales.
Table 15 Syndrome Scale Items for Achenbach CBCL/6–18

<table>
<thead>
<tr>
<th>Problem Scales</th>
<th>Syndrome Scales</th>
<th>Items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internalizing</td>
<td>Anxious/Depressed</td>
<td>14, 29, 30, 31, 32, 33, 35, 45, 50, 52, 71, 91, 112</td>
</tr>
<tr>
<td></td>
<td>Withdrawn/Depressed</td>
<td>5, 42, 65, 69, 75, 102, 103, 111</td>
</tr>
<tr>
<td></td>
<td>Somatic Complaints</td>
<td>47, 49, 51, 54, 56a-g</td>
</tr>
<tr>
<td>Externalizing</td>
<td>Rule-breaking Behavior</td>
<td>2, 26, 28, 39, 43, 63, 67, 72, 73, 81, 82, 90, 96, 99, 101, 105, 106</td>
</tr>
<tr>
<td></td>
<td>Aggressive Behavior</td>
<td>3, 16, 19, 20, 21, 22, 37, 57, 68, 86, 87, 88, 89, 94, 95, 97, 104</td>
</tr>
<tr>
<td>Other</td>
<td>Social Problems</td>
<td>11, 12, 25, 27, 34, 36, 38, 48, 62, 64, 79</td>
</tr>
<tr>
<td></td>
<td>Thought Problems</td>
<td>9, 18, 40, 46, 58, 59, 60, 66, 70, 76, 83, 84, 85, 92, 100</td>
</tr>
<tr>
<td></td>
<td>Attention Problems</td>
<td>1, 4, 8, 10, 13, 17, 41, 61, 78, 80</td>
</tr>
<tr>
<td></td>
<td>Other Problems</td>
<td>6, 7, 15, 24, 44, 53, 55, 56h, 74, 77, 93, 98, 107, 108, 109, 110, 113</td>
</tr>
</tbody>
</table>

The activities scale is made up of 6 scores and the total score for the activities scale is the sum of these 6 scores. If more than 1 of the 6 scores is missing then the total score for the activities scale will not be calculated. If 1 score is missing, then the mean of the other 5 scores will be used for the missing score in calculating the total. However, if the missing score is an answer for question IB, IIB or IVB (see below) and the mean of the other 5 scores is greater than 2, then the missing score will be set to 2. The total activities score should be rounded to the nearest 0.5. The 6 scores used for the total score for the activities scale are derived as follows:

- **Question I, IA:**
  - 0 if ‘None’ is ticked.
  - 1 if 1 sport is listed under a, b or c.
  - 2 if 2 sports are listed under a, b or c.
  - 3 if 3 or more sports are listed under a, b and c.

- **Question I, IB:**
  - 0 if ‘None’ is ticked for IA.
  - Otherwise, for each sport under a, b and c, and for both time and skill the below scores will be assigned and then the mean of these scores (excluding “Don’t know” or blank responses) will be the score for IB:
    - 0 for “Less than average” or “below average”.
    - 1 for “Average”.
    - 2 for “More than average” or “above average”.

- **Question II, IIA:**
  - 0 if ‘None’ is ticked.
  - 1 if 1 activity is listed under a, b or c.
  - 2 if 2 activities are listed under a, b or c.
  - 3 if 3 or more activities are listed under a, b and c.

- **Question II, IIB:**
  - Calculated as per IB.

- **Question IV, IVA:**
  - 0 if ‘None’ is ticked.
  - 1 if 1 job is listed under a, b or c.
• 2 if 2 jobs are listed under a, b or c.
• 3 if 3 or more jobs activities are listed under a, b and c.

• Question IV, IVB:
  o Calculated as per IB.

The social scale is made up of 6 scores and the total score for the social scale is the sum of these 6 scores. If more than 1 of the 6 scores is missing then the total score for the social scale will not be calculated. If 1 score is missing, then the mean of the other 5 scores will be used for the missing score in calculating the total. However, if the missing score is IIIB, V2, VIA or VIB (see below) and the mean of the other 5 scores is greater than 2, then the missing score will be set to 2. The total activities score should be rounded to the nearest 0.5. The 6 scores used for the total score for the social scale are derived as follows:

• Question III, IIIA:
  o 0 if 'None' is ticked.
  o 1 if 1 organization is listed under a, b or c.
  o 2 if 2 organizations are listed under a, b or c.
  o 3 if 3 or more organizations are listed under a, b and c.

• Question III, IIIB
  o Calculated as per IB for the activities scale.

• Question V, V1:
  o 0 if 'None' is ticked.
  o 1 if ‘1’ is ticked.
  o 2 if ‘2 or 3’ is ticked.
  o 3 if ‘4 or more’ is ticked.

• Question V, V2:
  o 0 if ‘less than 1’ is ticked.
  o 1 if ‘1 or 2’ is ticked.
  o 2 if ‘3 or more’ is ticked.

• Question VI, VIA:
  o For a to c, the below scores will be assigned and then the mean of these scores (excluding blank responses) will be the score for VIA:
    ▪ 0 for “Worse”.
    ▪ 1 for “Average”.
    ▪ 2 for “Better”.

• Question VI, VIB:
  o For item d:
    ▪ 0 if ‘Worse’ is ticked.
    ▪ 1 if ‘Average’ is ticked.
    ▪ 2 if ‘Better’ is ticked.

The school scale is made up of 4 scores and the total score for the school scale is the sum of these 4 scores. If any of the 4 scores are missing or the child does not attend school then the total score for the school scale will not be calculated. The total school score should be rounded to the nearest 0.5. The 4 scores used for the total score for the school scale are derived as follows:

• Question VII, VII1:
  o For a to g, the below scores will be assigned and then the mean of these scores (excluding blank responses) will be the score for VII1:
    ▪ 0 for “Failing”.
    ▪ 1 for “Below Average”.
    ▪ 2 for “Average”.

• Question VII, VII2:
  o For h to m, the below scores will be assigned and then the mean of these scores (excluding blank responses) will be the score for VII2:
    ▪ 0 for “Worse”.
    ▪ 1 for “Average”.
    ▪ 2 for “Better”.

• Question VII, VII3:
  o For n to s, the below scores will be assigned and then the mean of these scores (excluding blank responses) will be the score for VII3:
    ▪ 0 for “Worse”.
    ▪ 1 for “Average”.
    ▪ 2 for “Better”.

• Question VII, VII4:
  o For t to y, the below scores will be assigned and then the mean of these scores (excluding blank responses) will be the score for VII4:
    ▪ 0 for “Worse”.
    ▪ 1 for “Average”.
    ▪ 2 for “Better”.

• Question VII, VII5:
  o For z, the below scores will be assigned and then the mean of these scores (excluding blank responses) will be the score for VII5:
    ▪ 0 for “Worse”.
    ▪ 1 for “Average”.
    ▪ 2 for “Better”.
- 3 for “Above Average”.

- Question VII, VII2:
  - 0 if ‘Yes’ is ticked.
  - 1 if ‘No’ is ticked.

- Question VII, VII3:
  - 0 if ‘Yes’ is ticked.
  - 1 if ‘No’ is ticked.

- Question VII, VII4:
  - 0 if ‘Yes’ is ticked for any academic or other problems in school.
  - 1 if ‘No’ is ticked for any academic or other problems in school.

The total competence score will be calculated as the sum of the activities, social and school scale scores. However, if any of these 3 scales are missing then the total competence score will be set to missing.

**ABCL/18–59**

The syndrome scale and problem scale grouping of items is shown in Table 16. If data are missing for more than 8 items (not counting items 2, 4, 15, 49, 73, 80, 88, 98, 106, 109, 110 and 123) then the syndrome and problem scales will not be calculated. If items 56a to 56g are missing then they will be scored as 0.

Each of the items is scored 0, 1 or 2 as indicated on the questionnaire. The individual items associated with each syndrome scale are presented in Table 16.

The syndrome scale scores will be calculated as the sum of the individual items associated with that scale. The problem scale scores will then be calculated as the sum of the corresponding syndrome scale scores as per Table 7 in Section 5.5.4.8. The total problem scale score will be calculated as the sum of the internalizing, externalizing and other problem scales.

**Table 16 Syndrome Scale Items for Achenbach ABCL/18–59**

<table>
<thead>
<tr>
<th>Problem Scales</th>
<th>Syndrome Scales</th>
<th>Items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internalizing</td>
<td>Anxious/Depressed</td>
<td>12, 13, 14, 22, 31, 33, 34, 35, 45, 47, 50, 52, 71, 91, 103, 107, 112, 113</td>
</tr>
<tr>
<td></td>
<td>Withdrawn</td>
<td>25, 30, 42, 48, 60, 65, 67, 69, 111</td>
</tr>
<tr>
<td></td>
<td>Somatic Complaints</td>
<td>51, 54, 56a-i, 100</td>
</tr>
<tr>
<td>Externalizing</td>
<td>Aggressive Behavior</td>
<td>3, 5, 16, 28, 37, 55, 57, 68, 81, 86, 87, 95, 97, 116, 118</td>
</tr>
<tr>
<td></td>
<td>Rule-breaking Behavior</td>
<td>6, 20, 23, 26, 39, 41, 43, 76, 82, 90, 92, 114, 117, 122</td>
</tr>
<tr>
<td></td>
<td>Intrusive</td>
<td>7, 19, 74, 93, 94, 104</td>
</tr>
<tr>
<td>Other</td>
<td>Thought Problems</td>
<td>9, 18, 36, 40, 46, 63, 66, 70, 84, 85</td>
</tr>
<tr>
<td></td>
<td>Attention Problems</td>
<td>1, 8, 17, 53, 59, 61, 64, 78, 101, 102, 105, 108, 119, 121</td>
</tr>
<tr>
<td></td>
<td>Other Problems</td>
<td>10, 21, 24, 27, 29, 32, 38, 44, 58, 62, 72, 75, 77, 79, 83, 89, 96, 99, 110, 115, 120</td>
</tr>
</tbody>
</table>

The critical items scale score will be calculated as the sum of the following 19 problem items scores.
6, 8, 9, 10, 14, 16, 18, 21, 40, 55, 57, 66, 70, 84, 90, 91, 92, 97, 103.

The friends scale is made up of 4 scores and the total score for the friends scale is the sum of these 4 scores. If any of the 4 scores are missing then the total score for the friends scale will not be calculated. The 4 scores used for the total score for the friends scale are derived as follows:

- If ‘None’ is ticked for item IA then 0 will be used for IB and IC.
- Question I, IA:
  - 0 if ‘None’ is ticked.
  - 1 if ‘1’ is ticked.
  - 2 if ‘2 or 3’ is ticked.
  - 3 if ‘4 or more’ is ticked.
- Question I, IB:
  - 0 if ‘Less than 1’ is ticked.
  - 1 if ‘1 or 2’ is ticked.
  - 2 if ‘3 or 4’ is ticked.
  - 3 if ‘5 or more’ is ticked.
- Question I, IC:
  - 0 if ‘Not well’ is ticked.
  - 1 if ‘Average’ is ticked.
  - 2 if ‘Above average’ is ticked.
  - 3 if ‘Far above average’ is ticked.
- Question I, ID:
  - 0 if ‘Less than 1’ is ticked.
  - 1 if ‘1 or 2’ is ticked.
  - 2 if ‘3 or 4’ is ticked.
  - 3 if ‘5 or more’ is ticked.
## Appendix 6  List of Tables, Listings and Figures

### Table 17  List of Blinded Phase Tables

<table>
<thead>
<tr>
<th>Table Number</th>
<th>Title</th>
<th>Analysis Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 1.1.1</td>
<td>Summary of Patient Disposition – Number of Patients Screened and Randomized by Site</td>
<td>All Screened Patients</td>
</tr>
<tr>
<td>Table 1.1.2</td>
<td>Summary of Patient Disposition – Number of Patients Screened and Randomized by Country</td>
<td>All Screened Patients</td>
</tr>
<tr>
<td>Table 1.2</td>
<td>Summary of Patient Disposition – Reasons for Screen Failure</td>
<td>All Screened Patients</td>
</tr>
<tr>
<td>Table 1.3.1</td>
<td>Summary of Patient Disposition by Site</td>
<td>All Randomized Patients</td>
</tr>
<tr>
<td>Table 1.3.2</td>
<td>Summary of Patient Disposition by Country</td>
<td>All Randomized Patients</td>
</tr>
<tr>
<td>Table 1.4</td>
<td>Summary of Overall Patient Disposition</td>
<td>All Randomized Patients</td>
</tr>
<tr>
<td>Table 2.1</td>
<td>Summary of Important Protocol Deviations</td>
<td>All Randomized Patients</td>
</tr>
<tr>
<td>Table 2.2</td>
<td>Summary of Analysis Sets</td>
<td>All Randomized Patients</td>
</tr>
<tr>
<td>Table 3.1.1</td>
<td>Summary of Demographic Data</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 3.1.2</td>
<td>Summary of Demographic Data</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 3.1.3</td>
<td>Summary of Demographic Data</td>
<td>PP Analysis Set</td>
</tr>
<tr>
<td>Table 3.2.1</td>
<td>Summary of Baseline Characteristics</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 3.2.2</td>
<td>Summary of Baseline Characteristics</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 3.2.3</td>
<td>Summary of Baseline Characteristics</td>
<td>PP Analysis Set</td>
</tr>
<tr>
<td>Table 4.1.1</td>
<td>Summary of Seizure Types No Longer Occurring</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 4.1.2</td>
<td>Summary of Current Seizure Types</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 5.1</td>
<td>Summary of Previous Significant Non-Epilepsy Medical or Surgical History Now Resolved</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 5.2</td>
<td>Summary of Significant Non-Epilepsy Medical or Surgical History – Current Conditions</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 6.1</td>
<td>Summary of History of Antiepileptic Drugs</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 6.2</td>
<td>Summary of Concomitant Antiepileptic Therapies</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 6.3</td>
<td>Summary of Concomitant Antiepileptic Drugs</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 6.4</td>
<td>Summary of Concomitant Rescue Medications</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 6.5</td>
<td>Summary of Other Concomitant Medications</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 7.1</td>
<td>Summary of Treatment Compliance</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 7.2</td>
<td>Summary of IVRS Compliance</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 8.1.1</td>
<td>Summary of TSC-associated Seizure Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 8.1.2</td>
<td>Negative Binomial Regression Analysis of TSC-associated Seizure Count During Baseline and Treatment Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 8.2.1.1</td>
<td>Summary of TSC-associated Seizure Frequency</td>
<td>PP Analysis Set</td>
</tr>
<tr>
<td>Table 8.2.1.2</td>
<td>Negative Binomial Regression Analysis of TSC-associated Seizure Count During Baseline and Treatment Periods</td>
<td>PP Analysis Set</td>
</tr>
<tr>
<td>Table Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>---------------</td>
<td>----------------------------------------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Table 8.2.2</td>
<td>Analysis of Percentage Change from Baseline in TSC-associated Seizure Frequency During the Treatment Period – Wilcoxon Rank-Sum Test</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 8.2.3</td>
<td>Analysis of Percentage Change from Baseline in TSC-associated Seizure Frequency During the Treatment Period – Rank ANCOVA</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 8.2.4</td>
<td>Analysis of TSC-associated Seizure Frequency During the Treatment Period – Log-transformed ANCOVA</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 8.2.5</td>
<td>Analysis of Percentage Change from Baseline in TSC-associated Seizure Frequency During the Treatment Period – ANCOVA</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 8.2.6</td>
<td>Negative Binomial Regression Analysis of TSC-associated Seizure Count During Baseline and Titration and Maintenance Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 8.2.7</td>
<td>Negative Binomial Regression Analysis of TSC-associated Seizure Count During Baseline and Treatment Periods After Imputing Unreported Days in IVRS</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 8.2.8</td>
<td>Negative Binomial Regression Analysis of TSC-associated Seizure Count During Baseline and Treatment Periods After Multiple Imputation to Account for MNAR</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.1.1</td>
<td>Summary and Analysis of TSC-associated Seizure Treatment Responders and TSC-associated Seizure Freedom During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.1.2</td>
<td>Summary and Analysis of TSC-associated Seizure Treatment Responders and TSC-associated Seizure Freedom During the Treatment Period</td>
<td>PP Analysis Set</td>
</tr>
<tr>
<td>Table 9.1.3</td>
<td>Summary and Analysis of TSC-associated Seizure Treatment Responders and TSC-associated Seizure Freedom During the Titration and Maintenance Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.2.1.1</td>
<td>Summary of the Subject/Caregiver Global Impression of Change</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.2.1.2</td>
<td>Analysis of the Subject/Caregiver Global Impression of Change</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.2.2.1</td>
<td>Summary of the Subject/Caregiver Global Impression of Change</td>
<td>PP Analysis Set</td>
</tr>
<tr>
<td>Table 9.2.2.2</td>
<td>Analysis of the Subject/Caregiver Global Impression of Change</td>
<td>PP Analysis Set</td>
</tr>
<tr>
<td>Table 9.3.1.1</td>
<td>Summary of Total Seizure Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.3.1.2</td>
<td>Negative Binomial Regression Analysis of Total Seizure Count During Baseline and Treatment Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.3.2.1</td>
<td>Summary of Total Seizure Frequency</td>
<td>PP Analysis Set</td>
</tr>
<tr>
<td>Table 9.3.2.2</td>
<td>Negative Binomial Regression Analysis of Total Seizure Count During Baseline and Treatment Periods</td>
<td>PP Analysis Set</td>
</tr>
<tr>
<td>Table Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Table 9.3.3</td>
<td>Negative Binomial Regression Analysis of Total Seizure Count During Baseline and Titration and Maintenance Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.4.1</td>
<td>Analysis of Change from Baseline in TSC-associated Seizure Free Days Per 28 Days During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.4.2</td>
<td>Analysis of Change from Baseline in TSC-associated Seizure Free Days Per 28 Days During the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.5.1.1</td>
<td>Summary of Other Seizure Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.5.1.2</td>
<td>Negative Binomial Regression Analysis of Other Seizure Count During Baseline and Treatment Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.5.2</td>
<td>Summary and Analysis of Other Seizure Treatment Responders and Other Seizure Freedom During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.6.1</td>
<td>Summary and Analysis of Total Seizure Treatment Responders and Total Seizure Freedom During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.6.2</td>
<td>Summary and Analysis of Total Seizure Treatment Responders and Total Seizure Freedom During the Titration and Maintenance Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.7.1.1</td>
<td>Summary of Quality of Life in Childhood Epilepsy Scores (2-18 Years)</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.7.1.2</td>
<td>Analysis of Change from Baseline in Quality of Life in Childhood Epilepsy Scores (2-18 Years)</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.7.2.1</td>
<td>Summary of Quality of Life in Epilepsy Scores (19 Years and Above)</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.7.2.2</td>
<td>Analysis of Change from Baseline in the Quality of Life in Epilepsy Total Score (19 Years and Above)</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.8.1</td>
<td>Summary of the Physician Global Impression of Change</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.8.2</td>
<td>Analysis of the Physician Global Impression of Change</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.9.1</td>
<td>Summary of Composite Focal Seizure Score</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.9.2</td>
<td>Negative Binomial Regression Analysis of Composite Focal Seizure Score During Baseline and Treatment Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.1.1.1</td>
<td>Summary of Type 1 Focal Seizure Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.1.1.2</td>
<td>Negative Binomial Regression Analysis of Type 1 Focal Seizure Count During Baseline and Treatment Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.1.2</td>
<td>Negative Binomial Regression Analysis of Type 1 Focal Seizure Count During Baseline and Titration and Maintenance Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.1.3</td>
<td>Summary and Analysis of Type 1 Focal Seizure Treatment Responders and Type 1 Focal Seizure Freedom During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>---------------</td>
<td>----------------------------------------------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Table 9.10.1.4</td>
<td>Summary and Analysis of Type 1 Focal Seizure Treatment Responders and Type 1 Focal Seizure Freedom During the Titration and Maintenance Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.2.1.1</td>
<td>Summary of Type 2 Focal Seizure Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.2.1.2</td>
<td>Negative Binomial Regression Analysis of Type 2 Focal Seizure Count During Baseline and Treatment Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.2.2</td>
<td>Negative Binomial Regression Analysis of Type 2 Focal Seizure Count During Baseline and Titration and Maintenance Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.2.3</td>
<td>Summary and Analysis of Type 2 Focal Seizure Treatment Responders and Type 2 Focal Seizure Freedom During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.2.4</td>
<td>Summary and Analysis of Type 2 Focal Seizure Treatment Responders and Type 2 Focal Seizure Freedom During the Titration and Maintenance Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.3.1.1</td>
<td>Summary of Type 3 Focal Seizure Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.3.1.2</td>
<td>Negative Binomial Regression Analysis of Type 3 Focal Seizure Count During Baseline and Treatment Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.3.2</td>
<td>Negative Binomial Regression Analysis of Type 3 Focal Seizure Count During Baseline and Titration and Maintenance Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.3.3</td>
<td>Summary and Analysis of Type 3 Focal Seizure Treatment Responders and Type 3 Focal Seizure Freedom During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.3.4</td>
<td>Summary and Analysis of Type 3 Focal Seizure Treatment Responders and Type 3 Focal Seizure Freedom During the Titration and Maintenance Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.4.1.1</td>
<td>Summary of Tonic-Clonic Seizure Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.4.1.2</td>
<td>Negative Binomial Regression Analysis of Tonic-Clonic Seizure Count During Baseline and Treatment Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.4.2</td>
<td>Negative Binomial Regression Analysis of Tonic-Clonic Seizure Count During Baseline and Titration and Maintenance Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.4.3</td>
<td>Summary and Analysis of Tonic-Clonic Seizure Treatment Responders and Tonic-Clonic Seizure Freedom During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.4.4</td>
<td>Summary and Analysis of Tonic-Clonic Seizure Treatment Responders and Tonic-Clonic Seizure Freedom During the Titration and Maintenance Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.5.1.1</td>
<td>Summary of Tonic Seizure Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.5.1.2</td>
<td>Negative Binomial Regression Analysis of Tonic Seizure Count During Baseline and Treatment Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Table 9.10.5.2</td>
<td>Negative Binomial Regression Analysis of Tonic Seizure Count During Baseline and Titration and Maintenance Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.5.3</td>
<td>Summary and Analysis of Tonic Seizure Treatment Responders and Tonic Seizure Freedom During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.5.4</td>
<td>Summary and Analysis of Tonic Seizure Treatment Responders and Tonic Seizure Freedom During the Titration and Maintenance Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.6</td>
<td>Summary of Clonic Seizure Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.7</td>
<td>Summary of Atonic Seizure Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.8</td>
<td>Summary of Absence Seizure Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.9</td>
<td>Summary of Myoclonic Seizure Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.10</td>
<td>Summary of Partial Sensory Seizure Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.11</td>
<td>Summary of Infantile or Epileptic Spasm Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.12</td>
<td>Summary of Number of Days of Rescue Medication Use</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.11.2</td>
<td>Analysis of Change from Baseline in the Number of Days of Rescue Medication Use</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.12</td>
<td>Summary of Patients with Status Epilepticus</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.13.1</td>
<td>Summary of Subject/Caregiver Global Impression of Change in Seizure Duration</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.13.2</td>
<td>Analysis of Subject/Caregiver Global Impression of Change in Seizure Duration</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.14.1.1</td>
<td>Summary of the Vineland-II Adaptive Behavior Subdomain, Domain and Composite Scores</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.14.1.2</td>
<td>Summary of the Vineland-II Adaptive Behavior Subdomain, Domain and Composite Adaptive Levels</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.14.1.3</td>
<td>Analysis of Change from Baseline in the Vineland-II Adaptive Behavior Domain and Composite Scores</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.14.1.4</td>
<td>Analysis of the Vineland-II Adaptive Behavior Domain and Composite Adaptive Levels</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.14.2.1</td>
<td>Summary of the Vineland-II Maladaptive Behavior Subdomain and Index Scores</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.14.2.2</td>
<td>Summary of the Vineland-II Maladaptive Behavior Subdomain and Index Adaptive Levels</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.14.2.3</td>
<td>Analysis of Change from Baseline in the Vineland-II Maladaptive Behavior Index Score</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.14.2.4</td>
<td>Analysis of the Vineland-II Maladaptive Behavior Index Adaptive Level</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.15.1</td>
<td>Summary of Wechsler Tests</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.15.2</td>
<td>Analysis of Wechsler Tests</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.16.1.1</td>
<td>Summary of Achenbach Child Behavior Checklists</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.16.1.2</td>
<td>Analysis of Achenbach Child Behavior Checklists</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.16.2.1</td>
<td>Summary of Achenbach Adult Behavior Checklist</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.16.2.2</td>
<td>Analysis of Achenbach Adult Behavior Checklist</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.17.1</td>
<td>Summary of Social Communication Questionnaire</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.17.2</td>
<td>Analysis of Social Communication Questionnaire</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Table 9.18.1</td>
<td>Analysis of Time to Baseline TSC-associated Seizure Frequency from the Start of the Treatment Period (Day 1)</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.18.2</td>
<td>Analysis of Time to Baseline TSC-associated Seizure Frequency from the Start of the Maintenance Period (Day 29)</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.19.1</td>
<td>Negative Binomial Regression Effect Modification Analysis of TSC-associated Seizure Count during Baseline and Treatment Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.19.2</td>
<td>Logistic Regression Effect Modification Analysis of TSC-associated Seizure Responders (&gt;=50% Reduction) During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 10.1</td>
<td>Summary of Exposure</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 10.2</td>
<td>Summary of Expected Daily Volumes of IMP Taken Post-Titration</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.1</td>
<td>Overall Summary of Treatment Emergent Adverse Events</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.2</td>
<td>Summary of Treatment Emergent Adverse Events</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.3</td>
<td>Summary of Treatment-Related Treatment Emergent Adverse Events</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.4</td>
<td>Summary of Treatment Emergent Adverse Events by Maximal Severity</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.5</td>
<td>Summary of Treatment Emergent Adverse Events by Sex</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.6</td>
<td>Summary of TEAEs by Time of First Onset of AE</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.7</td>
<td>Summary of TEAEs by Time to AE Resolution</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.8</td>
<td>Summary of TEAEs Reported in &gt;=2% of Patients in the GWP42003-P Treatment Arms</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.9</td>
<td>Summary of Non-Serious Treatment Emergent Adverse Events</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.10</td>
<td>List of Patients Experiencing Treatment Emergent Adverse Events by System Organ Class and Preferred term</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.11</td>
<td>Summary of Pre-Treatment Adverse Events</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.12</td>
<td>Summary of Treatment Emergent Adverse Events by Event</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.13</td>
<td>Summary of Treatment-Related Treatment Emergent Adverse Events by Event</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.14</td>
<td>Summary of Non-Serious Treatment Emergent Adverse Events by Event</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 12.1</td>
<td>Summary of Serious Treatment Emergent Adverse Events</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 12.2</td>
<td>Summary of Treatment-Related Serious Treatment Emergent Adverse Events</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 12.3</td>
<td>Summary of Treatment Emergent Adverse Events Leading to Permanent Discontinuation of IMP</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 12.4</td>
<td>Summary of Treatment-Related Treatment Emergent Adverse Events Leading to Permanent Discontinuation of IMP</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Table 12.5</td>
<td>Summary of Treatment Emergent Adverse Events Leading to IMP Dose Reduction Excluding Permanent Discontinuation and by Resolution and Overall</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 12.6</td>
<td>Summary of Treatment-Related Treatment Emergent Adverse Events Leading to IMP Dose Reduction Excluding Permanent Discontinuation and by Resolution and Overall</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 12.7</td>
<td>Summary of Treatment Emergent Adverse Events Leading to Temporary IMP Dose Reduction by Resolution and Overall</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 12.8</td>
<td>Summary of Treatment-Related Treatment Emergent Adverse Events Leading to Temporary IMP Dose Reduction by Resolution and Overall</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 12.9</td>
<td>Summary of Treatment Emergent Adverse Events Leading to Permanent IMP Dose Reduction Excluding Permanent Discontinuation and by Resolution and Overall</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 12.10</td>
<td>Summary of Treatment-Related Treatment Emergent Adverse Events Leading to Permanent IMP Dose Reduction Excluding Permanent Discontinuation and by Resolution and Overall</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 12.11</td>
<td>Summary of Fatal Treatment Emergent Adverse Events</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 12.12</td>
<td>Summary of Serious Treatment Emergent Adverse Events by Event</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 12.13</td>
<td>Summary of Treatment-Related Serious Treatment Emergent Adverse Events by Event</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 13.1.1</td>
<td>Summary of Laboratory Safety Parameters – Hematology</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 13.1.2</td>
<td>Summary of Laboratory Safety Parameters – Biochemistry</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 13.2.1</td>
<td>Shift Table for Hematology Laboratory Parameters – Based on Reference Ranges</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 13.2.2</td>
<td>Shift Table for Biochemistry Laboratory Parameters – Based on Reference Ranges</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 13.3.1</td>
<td>Shift Table for Hematology Laboratory Parameters – Based on Toxicity Limits</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 13.3.2</td>
<td>Shift Table for Biochemistry Laboratory Parameters – Based on Toxicity Limits</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 13.3.3</td>
<td>Shift Table for eGFR – Based on Derived Grades</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 13.4</td>
<td>Summary of Liver Parameter Flags</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 13.5</td>
<td>Incidence of Laboratory Abnormalities</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 13.6</td>
<td>Summary of Pregnancy Test and Urine THC Screen Results</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 14.1.1</td>
<td>Summary of Vital Signs</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 14.1.2</td>
<td>Incidence of Clinically Significant Changes from Baseline for Vital Signs</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 14.1.3</td>
<td>Incidence of Defined Flagged Vital Signs</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 14.1.4</td>
<td>Incidence of Vital Signs Abnormalities</td>
<td>Safety Analysis Set</td>
</tr>
</tbody>
</table>
### Table 14.2.1
Summary of ECG Parameters

Analysis Set: Safety Analysis Set

### Table 14.2.2
Incidence of Defined Flagged ECG Parameter Values

Analysis Set: Safety Analysis Set

### Table 14.2.3
Incidence of ECG Abnormalities

Analysis Set: Safety Analysis Set

### Table 14.3
Summary of Columbia-Suicide Severity Rating Scale by Type

Analysis Set: Safety Analysis Set

### Table 14.4
Incidence of Physical Examination Abnormalities

Analysis Set: Safety Analysis Set

### Table 14.5
Summary of Tanner Stages

Analysis Set: Safety Analysis Set

### Table 14.6
Summary of Menstruation Details

Analysis Set: Safety Analysis Set

### Table 14.7
Summary of Patients with Inpatient Hospitalizations due to Epilepsy

Analysis Set: Safety Analysis Set

### Table 14.8.1
Summary of Plasma Concentrations

Analysis Set: Safety Analysis Set

### Table 14.8.2.1
Summary of PK Parameters (Overall and by Age Group)

Analysis Set: Safety Analysis Set

### Table 14.8.2.2
Summary of PK Parameter Metabolite to Parent Ratio (Overall and by Age Group)

Analysis Set: Safety Analysis Set

### Table 14.9
Summary of Plasma Concentrations of Concomitant Antiepileptic Drugs

Analysis Set: Safety Analysis Set

### Table 14.10
Summary of Study Medication Use and Behavior Survey

Analysis Set: Safety Analysis Set

### Table 14.11.1
Summary of Supplemental Drug Accountability Form

Analysis Set: Safety Analysis Set

### Table 14.11.2
Summary of Supplemental Adverse Event Form

Analysis Set: Safety Analysis Set

### Table 14.11.3
Summary of Site Classification Form

Analysis Set: Safety Analysis Set

### Table 18 List of OLE Phase Tables

<table>
<thead>
<tr>
<th>Table Number</th>
<th>Title</th>
<th>Analysis Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLE Table 1.1.1</td>
<td>Summary of Patient Disposition by Site</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 1.1.2</td>
<td>Summary of Patient Disposition During by Country</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 1.2</td>
<td>Summary of Overall Patient Disposition</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 2</td>
<td>Summary of Important Protocol Deviations</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 3.1</td>
<td>Summary of Demographic Data</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 3.2</td>
<td>Summary of Baseline Characteristics</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 6.1</td>
<td>Summary of Concomitant Antiepileptic Therapies</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 6.2</td>
<td>Summary of Concomitant Antiepileptic Drugs</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 6.3</td>
<td>Summary of Concomitant Rescue Medications</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 6.4</td>
<td>Summary of Other Concomitant Medications</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>Table Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------------------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>OLE Table 9.1.1.1</td>
<td>Summary of TSC-associated Seizure Frequency</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.1.1.2</td>
<td>Summary of TSC-associated Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.1.1.3</td>
<td>Summary of TSC-associated Seizure Frequency (Patients with Data in OLE Week 37 to 48)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.1.2.1</td>
<td>Summary of TSC-associated Seizure Treatment Responders and TSC-associated Seizure Freedom</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.1.2.2</td>
<td>Summary of TSC-associated Seizure Treatment Responders and TSC-associated Seizure Freedom (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.1.2.3</td>
<td>Summary of TSC-associated Seizure Treatment Responders and TSC-associated Seizure Freedom (Patients with Data in OLE Week 37 to 48)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.2</td>
<td>Summary of the Subject/Caregiver Global Impression of Change</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.3.1.1</td>
<td>Summary of Total Seizure Frequency</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.3.1.2</td>
<td>Summary of Total Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.3.1.3</td>
<td>Summary of Total Seizure Frequency (Patients with Data in OLE Week 37 to 48)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.3.2.1</td>
<td>Summary of Total Seizure Treatment Responders and Total Seizure Freedom</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.3.2.2</td>
<td>Summary of Total Seizure Treatment Responders and Total Seizure Freedom (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.3.2.3</td>
<td>Summary of Total Seizure Treatment Responders and Total Seizure Freedom (Patients with Data in OLE Week 37 to 48)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.4.1.1</td>
<td>Summary of Other Seizure Frequency</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.4.1.2</td>
<td>Summary of Other Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.4.2.1</td>
<td>Summary of Other Seizure Treatment Responders and Other Seizure Freedom</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.4.2.2</td>
<td>Summary of Other Seizure Treatment Responders and Other Seizure Freedom (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.5</td>
<td>Summary of Quality of Life in Childhood Epilepsy Scores (2-18 Years)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.6</td>
<td>Summary of Quality of Life in Epilepsy Scores (19 Years and Above)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.7</td>
<td>Summary of the Physician Global Impression of Change</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.8.1</td>
<td>Summary of Composite Focal Seizure Score</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.8.2</td>
<td>Summary of Composite Focal Seizure Score (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.1.1.1</td>
<td>Summary of Type 1 Focal Seizure Frequency</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>Table Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------------------------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>OLE Table 9.9.1.2</td>
<td>Summary of Type 1 Focal Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.1.1</td>
<td>Summary of Type 1 Focal Seizure Treatment Responders and Type 1 Focal Seizure Freedom</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.1.2</td>
<td>Summary of Type 1 Focal Seizure Treatment Responders and Type 1 Focal Seizure Freedom (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.2.1</td>
<td>Summary of Type 2 Focal Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.2.2</td>
<td>Summary of Type 2 Focal Seizure Treatment Responders and Type 2 Focal Seizure Freedom</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.2.2</td>
<td>Summary of Type 2 Focal Seizure Treatment Responders and Type 2 Focal Seizure Freedom (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.3.1</td>
<td>Summary of Type 3 Focal Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.3.2</td>
<td>Summary of Type 3 Focal Seizure Treatment Responders and Type 3 Focal Seizure Freedom</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.4.1</td>
<td>Summary of Tonic-Clonic Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.4.1</td>
<td>Summary of Tonic-Clonic Seizure Treatment Responders and Tonic-Clonic Seizure Freedom</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.4.2</td>
<td>Summary of Tonic-Clonic Seizure Treatment Responders and Tonic-Clonic Seizure Freedom (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.5.1</td>
<td>Summary of Tonic Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.5.2</td>
<td>Summary of Tonic Seizure Treatment Responders and Tonic Seizure Freedom (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.6.1</td>
<td>Summary of Clonic Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.6.2</td>
<td>Summary of Clonic Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.7.1</td>
<td>Summary of Atonic Seizure Frequency</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.7.2</td>
<td>Summary of Atonic Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>Table Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>OLE Table 9.9.8.1</td>
<td>Summary of Absence Seizure Frequency</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.8.2</td>
<td>Summary of Absence Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.9.1</td>
<td>Summary of Myoclonic Seizure Frequency</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.9.2</td>
<td>Summary of Myoclonic Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.10.1</td>
<td>Summary of Partial Sensory Seizure Frequency</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.10.2</td>
<td>Summary of Partial Sensory Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.11.1</td>
<td>Summary of Infantile or Epileptic Spasm Frequency</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.11.2</td>
<td>Summary of Infantile or Epileptic Spasm Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.10.1</td>
<td>Summary of Number of Days of Rescue Medication Use</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.11</td>
<td>Summary of Patients with Status Epilepticus</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.12.1</td>
<td>Summary of Subject/Caregiver Global Impression of Change in Seizure Duration</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.13.1.1</td>
<td>Summary of the Vineland-II Adaptive Behavior Subdomain, Domain and Composite Scores</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.13.1.2</td>
<td>Summary of the Vineland-II Adaptive Behavior Subdomain, Domain and Composite Adaptive Levels</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.13.2.1</td>
<td>Summary of the Vineland-II Maladaptive Behavior Subdomain and Index Scores</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.13.2.2</td>
<td>Summary of the Vineland-II Maladaptive Behavior Subdomain and Index Adaptive Levels</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.14</td>
<td>Summary of Wechsler Tests</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.15.1.1</td>
<td>Summary of Achenbach Child Behavior Checklists</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.15.2.1</td>
<td>Summary of Achenbach Adult Behavior Checklist</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.16.1</td>
<td>Summary of Social Communication Questionnaire</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 10</td>
<td>Summary of Exposure</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 11.1</td>
<td>Overall Summary of Treatment Emergent Adverse Events</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 11.2</td>
<td>Summary of Treatment Emergent Adverse Events</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 11.3</td>
<td>Summary of Treatment-Related Treatment Emergent Adverse Events</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 11.4</td>
<td>Summary of Treatment Emergent Adverse Events by Maximal Severity</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>Table Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>OLE Table 11.5</td>
<td>Summary of Treatment Emergent Adverse Events by Sex</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 11.6</td>
<td>Summary of TEAEs by Time of First Onset of AE</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 11.7</td>
<td>Summary of TEAEs by Time to AE Resolution</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 11.8</td>
<td>Summary of TEAEs Reported in &gt;=2% of Patients in the GWP42003-P Treatment Arms</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 11.9</td>
<td>Summary of Non-Serious Treatment Emergent Adverse Events</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 11.10</td>
<td>List of Patients Experiencing Treatment Emergent Adverse Events by System Organ Class and Preferred term</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 11.11</td>
<td>Summary of Treatment Emergent Adverse Events by Event</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 11.12</td>
<td>Summary of Treatment-Related Treatment Emergent Adverse Events by Event</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 11.13</td>
<td>Summary of Non-Serious Treatment Emergent Adverse Events by Event</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 12.1</td>
<td>Summary of Serious Treatment Emergent Adverse Events</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 12.2</td>
<td>Summary of Treatment-Related Serious Treatment Emergent Adverse Events</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 12.3</td>
<td>Summary of Treatment Emergent Adverse Events Leading to Permanent Discontinuation of IMP</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 12.4</td>
<td>Summary of Treatment-Related Treatment Emergent Adverse Events Leading to Permanent Discontinuation of IMP</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 12.5</td>
<td>Summary of Treatment Emergent Adverse Events Leading to IMP Dose Reduction Excluding Permanent Discontinuation and by Resolution and Overall</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 12.6</td>
<td>Summary of Treatment-Related Treatment Emergent Adverse Events Leading to IMP Dose Reduction Excluding Permanent Discontinuation and by Resolution and Overall</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 12.7</td>
<td>Summary of Treatment Emergent Adverse Events Leading to Temporary IMP Dose Reduction by Resolution and Overall</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 12.8</td>
<td>Summary of Treatment-Related Treatment Emergent Adverse Events Leading to Temporary IMP Dose Reduction by Resolution and Overall</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 12.9</td>
<td>Summary of Treatment Emergent Adverse Events Leading to Permanent IMP Dose Reduction Excluding Permanent Discontinuation and by Resolution and Overall</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 12.10</td>
<td>Summary of Treatment-Related Treatment Emergent Adverse Events Leading to Permanent IMP Dose Reduction Excluding Permanent Discontinuation and by Resolution and Overall</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>Table Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>OLE Table 12.11</td>
<td>Summary of Fatal Treatment Emergent Adverse Events</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 12.12</td>
<td>Summary of Serious Treatment Emergent Adverse Events by Event</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 12.13</td>
<td>Summary of Treatment-Related Serious Treatment Emergent Adverse Events by Event</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 13.1.1</td>
<td>Summary of Laboratory Safety Parameters – Hematology</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 13.1.2</td>
<td>Summary of Laboratory Safety Parameters – Biochemistry</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 13.2.1</td>
<td>Shift Table for Hematology Laboratory Parameters – Based on Reference Ranges</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 13.2.2</td>
<td>Shift Table for Biochemistry Laboratory Parameters – Based on Reference Ranges</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 13.3.1</td>
<td>Shift Table for Hematology Laboratory Parameters – Based on Toxicity Limits</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 13.3.2</td>
<td>Shift Table for Biochemistry Laboratory Parameters – Based on Toxicity Limits</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 13.3.3</td>
<td>Shift Table for eGFR – Based on Derived Grades</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 13.4</td>
<td>Summary of Liver Parameter Flags</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 13.5</td>
<td>Incidence of Laboratory Abnormalities</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 13.6</td>
<td>Summary of Pregnancy Test and Urine THC Screen Results</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 14.1.1</td>
<td>Summary of Vital Signs</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 14.1.2</td>
<td>Incidence of Clinically Significant Changes from Baseline for Vital Signs</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 14.1.3</td>
<td>Incidence of Defined Flagged Vital Signs</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 14.1.4</td>
<td>Incidence of Vital Signs Abnormalities</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 14.2.1</td>
<td>Summary of ECG Parameters</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 14.2.2</td>
<td>Incidence of Defined Flagged ECG Parameter Values</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 14.2.3</td>
<td>Incidence of ECG Abnormalities</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 14.3</td>
<td>Summary of Columbia-Suicide Severity Rating Scale by Type</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 14.4</td>
<td>Incidence of Physical Examination Abnormalities</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 14.5</td>
<td>Summary of Tanner Stages</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 14.6</td>
<td>Summary of Menstruation Details</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 14.7</td>
<td>Summary of Patients with Inpatient Hospitalizations due to Epilepsy</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>Table Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------------------------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>OLE Table 14.8</td>
<td>Summary of Study Medication Use and Behavior Survey</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 14.9.1</td>
<td>Summary of Supplemental Drug Accountability Form</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 14.9.2</td>
<td>Summary of Supplemental Adverse Event Form</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 14.9.3</td>
<td>Summary of Site Classification Form</td>
<td>OLE Safety Analysis Set</td>
</tr>
</tbody>
</table>
### Table 19 List of Blinded Phase Listings

<table>
<thead>
<tr>
<th>Listing Number</th>
<th>Title</th>
<th>Analysis Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>Listing 1.1</td>
<td>Screen Failures</td>
<td>All Screen Failure Patients</td>
</tr>
<tr>
<td>Listing 1.2.1</td>
<td>Patient Disposition – End of Treatment</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 1.2.2</td>
<td>Patient Disposition – End of Taper</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 1.3</td>
<td>Inclusion/Exclusion Criteria Not Met</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 1.4</td>
<td>Visit Dates</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 2.1.1</td>
<td>Important Protocol Deviations</td>
<td>All Randomized Patients</td>
</tr>
<tr>
<td>Listing 2.1.2</td>
<td>All Protocol Deviations</td>
<td>All Randomized Patients</td>
</tr>
<tr>
<td>Listing 2.2</td>
<td>Analysis Sets</td>
<td>All Randomized Patients</td>
</tr>
<tr>
<td>Listing 3.1</td>
<td>Demography</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 3.2</td>
<td>Baseline Characteristics</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 4.1.1</td>
<td>Genetic Testing History</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 4.2.1</td>
<td>History of Seizures No Longer Occurring</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 4.2.2</td>
<td>History of Current Seizures</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 4.3</td>
<td>Neuroimaging History</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 5</td>
<td>Significant Non-Epilepsy Medical or Surgical History</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 6.1</td>
<td>History of Antiepileptic Drugs</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 6.2</td>
<td>Prior and Concomitant Antiepileptic Therapies</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 6.3</td>
<td>Prior and Concomitant Antiepileptic Drugs</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 6.4</td>
<td>Prior and Concomitant Rescue Medications</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 6.5</td>
<td>Other Prior and Concomitant Medications</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 7</td>
<td>IVRS Compliance</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 8.1.1</td>
<td>IVRS Diary Data – Part 1</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 8.1.2</td>
<td>IVRS Diary Data – Part 2</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 8.2.1</td>
<td>Derived TSC-associated, Other and Total Seizure Data</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 8.2.2</td>
<td>Derived Type 1, 3 and 3 Focal Seizure Data and Composite Focal Seizure Score</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 8.2.3</td>
<td>Derived Tonic-Clonic, Tonic, Clonic, and Atonic Seizure Data</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 8.2.4</td>
<td>Derived Absence, Myoclonic, Partial Sensory Seizure and Infantile or Epileptic Spasm Data</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 8.2.5</td>
<td>Derived Status Epilepticus Data</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 9.1</td>
<td>Subject/Caregiver/Physician Global Impression of Change</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 9.2</td>
<td>TSC-associated Seizure Free Days Per 28 Days</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 9.3</td>
<td>Quality of Life in Childhood Epilepsy (2-18 Years) – Derived Scores</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 9.4</td>
<td>Quality of Life in Epilepsy (19 Years and Above) – Derived Scores</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 9.5</td>
<td>Number of Days of Rescue Medication Use</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------------------------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Listing 9.6</td>
<td>Subject/Caregiver Global Impression of Change in Seizure Duration</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 9.7.1</td>
<td>Vineland-II Adaptive Behavior – Derived Data</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 9.7.2</td>
<td>Vineland-II Maladaptive Behavior – Derived Data</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 9.8</td>
<td>Wechsler Tests</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 9.9.1</td>
<td>Achenbach Child and Adult Behavior Checklist – Problem Scale Scores</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 9.9.2</td>
<td>Achenbach Child and Adult Behavior Checklist – Syndrome Scale Scores</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 9.9.3</td>
<td>Achenbach Child and Adult Behavior Checklist – Other Scale Scores</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 9.10</td>
<td>Social Communication Questionnaire – Derived Data</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 9.11</td>
<td>Time to Baseline TSC-associated Seizure Frequency</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 10.1</td>
<td>Exposure and Compliance</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 10.2</td>
<td>Exposure by Time</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 10.3</td>
<td>IMP Accountability</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 11.1.1</td>
<td>Treatment Emergent Adverse Events</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 11.1.2</td>
<td>Treatment Emergent Adverse Events of Special Interest</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 11.2</td>
<td>Pre-Treatment Adverse Events</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 12</td>
<td>Serious Adverse Events</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 13.1.1</td>
<td>Laboratory Parameters</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 13.1.2.1</td>
<td>Abnormal Laboratory Parameters by Patient</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 13.1.2.2</td>
<td>Abnormal Laboratory Parameters by Parameter</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 13.1.3</td>
<td>Laboratory Comments</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 13.1.4</td>
<td>Laboratory Liver Parameters</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.1.1</td>
<td>Vital Signs – Blood Pressures</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.1.2</td>
<td>Vital Signs – Pulse Rate, Respiratory Rate and Temperature</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.1.3</td>
<td>Vital Signs – Height, Weight and BMI</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.2</td>
<td>Clinically Significant Changes from Baseline for Vital Signs</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.3.1</td>
<td>ECG Data – Part 1</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.3.2</td>
<td>ECG Data – Part 2</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.4.1</td>
<td>Columbia-Suicide Severity Rating Scale (C-SSRS) – Suicidal Ideation and Intensity</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.4.2</td>
<td>Columbia-Suicide Severity Rating Scale (C-SSRS) – Suicidal Behavior</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.4.3</td>
<td>Columbia-Suicide Severity Rating Scale (C-SSRS) – Actual Attempts</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.5</td>
<td>Physical Examination</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.6</td>
<td>Tanner Stages</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.7</td>
<td>Menstruation Details</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.8</td>
<td>Inpatient Hospitalizations due to Epilepsy</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.9.1</td>
<td>Plasma Concentrations</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.9.2</td>
<td>PK Parameters</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------------------------------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Listing 14.10</td>
<td>Plasma Concentrations of Concomitant Antiepileptic Drugs</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.11.1</td>
<td>Study Medication Use and Behavior Survey – Part 1</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.11.2</td>
<td>Study Medication Use and Behavior Survey – Part 2</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.12.1</td>
<td>Supplemental Drug Accountability Form</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.12.2</td>
<td>Supplemental Adverse Events Form</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.12.3</td>
<td>Site Classification Form</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 15</td>
<td>Investigators' General Comments</td>
<td>Safety Analysis Set</td>
</tr>
</tbody>
</table>

**Table 20  List of OLE Phase Listings**

<table>
<thead>
<tr>
<th>Listing Number</th>
<th>Title</th>
<th>Analysis Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLE Listing 1.1.1</td>
<td>Patient Disposition – End of Treatment</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 1.1.2</td>
<td>Patient Disposition – End of Taper</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 1.2</td>
<td>Visit Dates</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 2.1</td>
<td>Important Protocol Deviations</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 6.1</td>
<td>Prior and Concomitant Antiepileptic Therapies</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 6.2</td>
<td>Prior and Concomitant Antiepileptic Drugs</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 6.3</td>
<td>Prior and Concomitant Rescue Medications</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 6.4</td>
<td>Other Prior and Concomitant Medications</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 8.1.1</td>
<td>IVRS Diary Data – Part 1</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 8.1.2</td>
<td>IVRS Diary Data – Part 2</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 8.2.1</td>
<td>Derived TSC-associated, Other and Total Seizure Data</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 8.2.2</td>
<td>Derived Type 1, 3 and 3 Focal Seizure Data and Composite Focal Seizure Score</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 8.2.3</td>
<td>Derived Tonic-Clonic, Tonic, Clonic, and Atonic Seizure Data</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 8.2.4</td>
<td>Derived Absence, Myoclonic, Partial Sensory Seizure and Infantile or Epileptic Spasm Data</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 8.2.5</td>
<td>Derived Status Epilepticus Data</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 9.1</td>
<td>Subject/Caregiver/Physician Global Impression of Change</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 9.2</td>
<td>Quality of Life in Childhood Epilepsy (2-18 Years) – Derived Scores</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>Listing Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------------------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>OLE Listing 9.3</td>
<td>Quality of Life in Epilepsy (19 Years and Above) – Derived Scores</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 9.4</td>
<td>Number of Days of Rescue Medication Use</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 9.5</td>
<td>Subject/Caregiver Global Impression of Change in Seizure Duration</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 9.6.1</td>
<td>Vineland-II Adaptive Behavior – Derived Data</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 9.6.2</td>
<td>Vineland-II Maladaptive Behavior – Derived Data</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 9.7</td>
<td>Wechsler Tests</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 9.8.1</td>
<td>Achenbach Child and Adult Behavior Checklist – Problem Scale Scores</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 9.8.2</td>
<td>Achenbach Child and Adult Behavior Checklist – Syndrome Scale Scores</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 9.8.3</td>
<td>Achenbach Child and Adult Behavior Checklist – Other Scale Scores</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 9.9</td>
<td>Social Communication Questionnaire – Derived Data</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 10.1</td>
<td>Exposure</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 10.2</td>
<td>Exposure by Time</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 10.3</td>
<td>IMP Accountability</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 11.1.1</td>
<td>Treatment Emergent Adverse Events</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 11.1.2</td>
<td>Treatment Emergent Adverse Events of Special Interest</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 12</td>
<td>Serious Adverse Events</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 13.1.1</td>
<td>Laboratory Parameters</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 13.1.2.1</td>
<td>Abnormal Laboratory Parameters by Patient</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 13.1.2.2</td>
<td>Abnormal Laboratory Parameters by Parameter</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 13.1.3</td>
<td>Laboratory Comments</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 13.1.4</td>
<td>Laboratory Liver Parameters</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.1.1</td>
<td>Vital Signs – Blood Pressures</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.1.2</td>
<td>Vital Signs – Pulse Rate, Respiratory Rate and Temperature</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.1.3</td>
<td>Vital Signs – Height, Weight and BMI</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>Listing Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------------------------------------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>OLE Listing 14.2</td>
<td>Clinically Significant Changes from Baseline for Vital Signs</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.3.1</td>
<td>ECG Data – Part 1</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.3.2</td>
<td>ECG Data – Part 2</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.4.1</td>
<td>Columbia-Suicide Severity Rating Scale (C-SSRS) – Suicidal Ideation and Intensity</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.4.2</td>
<td>Columbia-Suicide Severity Rating Scale (C-SSRS) – Suicidal Behavior</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.4.3</td>
<td>Columbia-Suicide Severity Rating Scale (C-SSRS) – Actual Attempts</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.5</td>
<td>Physical Examination</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.6</td>
<td>Tanner Stages</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.7</td>
<td>Menstruation Details</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.8</td>
<td>Inpatient Hospitalizations due to Epilepsy</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.9.1</td>
<td>Study Medication Use and Behavior Survey – Part 1</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.9.2</td>
<td>Study Medication Use and Behavior Survey – Part 2</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.10.1</td>
<td>Supplemental Drug Accountability Form</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.10.2</td>
<td>Supplemental Adverse Events Form</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.10.3</td>
<td>Site Classification Form</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 15</td>
<td>Investigators’ General Comments</td>
<td>OLE Safety Analysis Set</td>
</tr>
</tbody>
</table>

**Table 21** List of Blinded Phase Figures

<table>
<thead>
<tr>
<th>Figure Number</th>
<th>Title</th>
<th>Analysis Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 9.1.1.1</td>
<td>Cumulative Distribution Function for TSC-associated Seizures During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.1.1.2</td>
<td>Cumulative Distribution Function for TSC-associated Seizures During the Treatment Period</td>
<td>PP Analysis Set</td>
</tr>
<tr>
<td>Figure 9.1.2</td>
<td>Cumulative Distribution Function for TSC-associated Seizures During the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.1.3</td>
<td>Cumulative Distribution Function for TSC-associated Seizures During the Titration Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.1.4</td>
<td>Cumulative Distribution Function for TSC-associated Seizures During Weeks 1 to 4 of the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>---------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>9.1.5</td>
<td>Cumulative Distribution Function for TSC-associated Seizures During Weeks 5 to 8 of the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>9.1.6</td>
<td>Cumulative Distribution Function for TSC-associated Seizures During Weeks 9 to 12 of the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>9.2.1</td>
<td>Cumulative Distribution Function for Total Seizures During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>9.2.2</td>
<td>Cumulative Distribution Function for Total Seizures During the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>9.2.3</td>
<td>Cumulative Distribution Function for Total Seizures During the Titration Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>9.2.4</td>
<td>Cumulative Distribution Function for Total Seizures During Weeks 1 to 4 of the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>9.2.5</td>
<td>Cumulative Distribution Function for Total Seizures During Weeks 5 to 8 of the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>9.2.6</td>
<td>Cumulative Distribution Function for Total Seizures During Weeks 9 to 12 of the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>9.3</td>
<td>Cumulative Distribution Function for Other Seizures During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>9.4</td>
<td>Cumulative Distribution Function for Composite Focal Seizure Score During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>9.5.1</td>
<td>Cumulative Distribution Function for Type 1 Focal Seizures During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>9.5.2</td>
<td>Cumulative Distribution Function for Type 1 Focal Seizures During the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>9.5.3</td>
<td>Cumulative Distribution Function for Type 1 Focal Seizures During the Titration Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>9.5.4</td>
<td>Cumulative Distribution Function for Type 1 Focal Seizures During Weeks 1 to 4 of the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>9.5.5</td>
<td>Cumulative Distribution Function for Type 1 Focal Seizures During Weeks 5 to 8 of the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>9.5.6</td>
<td>Cumulative Distribution Function for Type 1 Focal Seizures During Weeks 9 to 12 of the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>9.6.1</td>
<td>Cumulative Distribution Function for Type 2 Focal Seizures During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>9.6.2</td>
<td>Cumulative Distribution Function for Type 2 Focal Seizures During the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>9.6.3</td>
<td>Cumulative Distribution Function for Type 2 Focal Seizures During the Titration Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>9.6.4</td>
<td>Cumulative Distribution Function for Type 2 Focal Seizures During Weeks 1 to 4 of the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>9.6.5</td>
<td>Cumulative Distribution Function for Type 2 Focal Seizures During Weeks 5 to 8 of the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>9.6.6</td>
<td>Cumulative Distribution Function for Type 2 Focal Seizures During Weeks 9 to 12 of the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Period</td>
<td>Figure</td>
<td>Description</td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Cumulative Distribution Function for Type 3 Focal Seizures</td>
<td>9.7.1</td>
<td>During the Treatment Period ITT Analysis Set</td>
</tr>
<tr>
<td>Cumulative Distribution Function for Type 3 Focal Seizures</td>
<td>9.7.2</td>
<td>During the Maintenance Period ITT Analysis Set</td>
</tr>
<tr>
<td>Cumulative Distribution Function for Type 3 Focal Seizures</td>
<td>9.7.3</td>
<td>During the Titration Period ITT Analysis Set</td>
</tr>
<tr>
<td>Cumulative Distribution Function for Type 3 Focal Seizures</td>
<td>9.7.4</td>
<td>During Weeks 1 to 4 of the Maintenance Period ITT Analysis Set</td>
</tr>
<tr>
<td>Cumulative Distribution Function for Type 3 Focal Seizures</td>
<td>9.7.5</td>
<td>During Weeks 5 to 8 of the Maintenance Period ITT Analysis Set</td>
</tr>
<tr>
<td>Cumulative Distribution Function for Type 3 Focal Seizures</td>
<td>9.7.6</td>
<td>During Weeks 9 to 12 of the Maintenance Period ITT Analysis Set</td>
</tr>
<tr>
<td>Cumulative Distribution Function for Tonic-Clonic Seizures</td>
<td>9.8.1</td>
<td>During the Treatment Period ITT Analysis Set</td>
</tr>
<tr>
<td>Cumulative Distribution Function for Tonic-Clonic Seizures</td>
<td>9.8.2</td>
<td>During the Maintenance Period ITT Analysis Set</td>
</tr>
<tr>
<td>Cumulative Distribution Function for Tonic-Clonic Seizures</td>
<td>9.8.3</td>
<td>During the Titration Period ITT Analysis Set</td>
</tr>
<tr>
<td>Cumulative Distribution Function for Tonic-Clonic Seizures</td>
<td>9.8.4</td>
<td>During Weeks 1 to 4 of the Maintenance Period ITT Analysis Set</td>
</tr>
<tr>
<td>Cumulative Distribution Function for Tonic-Clonic Seizures</td>
<td>9.8.5</td>
<td>During Weeks 5 to 8 of the Maintenance Period ITT Analysis Set</td>
</tr>
<tr>
<td>Cumulative Distribution Function for Tonic-Clonic Seizures</td>
<td>9.8.6</td>
<td>During Weeks 9 to 12 of the Maintenance Period ITT Analysis Set</td>
</tr>
<tr>
<td>Cumulative Distribution Function for Tonic Seizures</td>
<td>9.9.1</td>
<td>During the Treatment Period ITT Analysis Set</td>
</tr>
<tr>
<td>Cumulative Distribution Function for Tonic Seizures</td>
<td>9.9.2</td>
<td>During the Maintenance Period ITT Analysis Set</td>
</tr>
<tr>
<td>Cumulative Distribution Function for Tonic Seizures</td>
<td>9.9.3</td>
<td>During the Titration Period ITT Analysis Set</td>
</tr>
<tr>
<td>Cumulative Distribution Function for Tonic Seizures</td>
<td>9.9.4</td>
<td>During Weeks 1 to 4 of the Maintenance Period ITT Analysis Set</td>
</tr>
<tr>
<td>Cumulative Distribution Function for Tonic Seizures</td>
<td>9.9.5</td>
<td>During Weeks 5 to 8 of the Maintenance Period ITT Analysis Set</td>
</tr>
<tr>
<td>Cumulative Distribution Function for Tonic Seizures</td>
<td>9.9.6</td>
<td>During Weeks 9 to 12 of the Maintenance Period ITT Analysis Set</td>
</tr>
<tr>
<td>Cumulative Distribution Function for Clonic Seizures</td>
<td>9.10</td>
<td>During the Treatment Period ITT Analysis Set</td>
</tr>
<tr>
<td>Cumulative Distribution Function for Atonic Seizures</td>
<td>9.11</td>
<td>During the Treatment Period ITT Analysis Set</td>
</tr>
<tr>
<td>Cumulative Distribution Function for Absence Seizures</td>
<td>9.12</td>
<td>During the Treatment Period ITT Analysis Set</td>
</tr>
<tr>
<td>Cumulative Distribution Function for Myoclonic Seizures</td>
<td>9.13</td>
<td>During the Treatment Period ITT Analysis Set</td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------------------------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Figure 9.14</td>
<td>Cumulative Distribution Function for Partial Sensory Seizures During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.15</td>
<td>Cumulative Distribution Function for Infantile or Epileptic Spasms During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.16.1</td>
<td>Kaplan-Meier Plot of Time to Baseline TSC-associated Seizure Frequency from the Start of the Treatment Period (Day 1)</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.16.2</td>
<td>Kaplan-Meier Plot of Time to Baseline TSC-associated Seizure Frequency from the Start of the Maintenance Period (Day 29)</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 14.1.1</td>
<td>Box Plot of Change from Baseline to the End of Treatment Visit in IGF-1 Levels by Tanner Stages at Baseline</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.1.2</td>
<td>Scatter Plot of Change from Baseline to the End of Treatment Visit in IGF-1 Levels Against Weight at Baseline</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.1.3</td>
<td>Scatter Plot of Change from Baseline to the End of Treatment Visit in IGF-1 Levels Against Height at Baseline</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.1.4.1.X</td>
<td>Scatter Plot of Shift from Baseline to Maximum Post First Dose Laboratory Result - Hematology</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.1.4.2.X</td>
<td>Scatter Plot of Shift from Baseline to Maximum Post First Dose Laboratory Result - Biochemistry</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.1.1.1</td>
<td>Dot Plot of Individual CBD Plasma Concentration vs. Time Profiles, Visit 3, 25 and 50 mg/kg/day (Linear Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.1.1.2</td>
<td>Dot Plot of Individual CBD Plasma Concentration vs. Time Profiles, Visit 3, 25 and 50 mg/kg/day (Semi-Log Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.1.2.1</td>
<td>Dot Plot of Individual 7-OH-CBD Plasma Concentration vs. Time Profiles, Visit 3, 25 and 50 mg/kg/day (Linear Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.1.2.2</td>
<td>Dot Plot of Individual 7-OH-CBD Plasma Concentration vs. Time Profiles, Visit 3, 25 and 50 mg/kg/day (Semi-Log Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.1.3.1</td>
<td>Dot Plot of Individual 7-COOH-CBD Plasma Concentration vs. Time Profiles, Visit 3, 25 and 50 mg/kg/day (Linear Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.1.3.2</td>
<td>Dot Plot of Individual 7-COOH-CBD Plasma Concentration vs. Time Profiles, Visit 3, 25 and 50 mg/kg/day (Semi-Log Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.1.4.1</td>
<td>Dot Plot of Individual CBD Plasma Concentration vs. Time Profiles, Visit 10, 25 and 50 mg/kg/day (Linear Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.1.4.2</td>
<td>Dot Plot of Individual CBD Plasma Concentration vs. Time Profiles, Visit 10, 25 and 50 mg/kg/day (Semi-Log Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.1.5.1</td>
<td>Dot Plot of Individual 7-OH-CBD Plasma Concentration vs. Time Profiles, Visit 10, 25 and 50 mg/kg/day (Linear Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure</td>
<td>Dot Plot of Individual 7-OH-CBD Plasma</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>14.2.1.5.2</td>
<td>Concentration vs. Time Profiles, Visit 10, 25 and 50 mg/kg/day (Semi-Log Scale)</td>
<td></td>
</tr>
<tr>
<td>Figure 14.2.1.6.1</td>
<td>Dot Plot of Individual 7-COOH-CBD Plasma Concentration vs. Time Profiles, Visit 10, 25 and 50 mg/kg/day (Linear Scale)</td>
<td></td>
</tr>
<tr>
<td>Figure 14.2.1.6.2</td>
<td>Dot Plot of Individual 7-COOH-CBD Plasma Concentration vs. Time Profiles, Visit 10, 25 and 50 mg/kg/day (Semi-Log Scale)</td>
<td></td>
</tr>
<tr>
<td>Figure 14.2.2.1.1</td>
<td>Line Plot of Mean CBD Plasma Concentration vs. Time Profiles, Visit 3, 25 and 50 mg/kg/day (Linear Scale)</td>
<td></td>
</tr>
<tr>
<td>Figure 14.2.2.1.2</td>
<td>Line Plot of Mean CBD Plasma Concentration vs. Time Profiles, Visit 3, 25 and 50 mg/kg/day (Semi-Log Scale)</td>
<td></td>
</tr>
<tr>
<td>Figure 14.2.2.2.1</td>
<td>Line Plot of Mean 7-OH-CBD Plasma Concentration vs. Time Profiles, Visit 3, 25 and 50 mg/kg/day (Linear Scale)</td>
<td></td>
</tr>
<tr>
<td>Figure 14.2.2.2.2</td>
<td>Line Plot of Mean 7-OH-CBD Plasma Concentration vs. Time Profiles, Visit 3, 25 and 50 mg/kg/day (Semi-Log Scale)</td>
<td></td>
</tr>
<tr>
<td>Figure 14.2.2.3.1</td>
<td>Line Plot of Mean 7-COOH-CBD Plasma Concentration vs. Time Profiles, Visit 3, 25 and 50 mg/kg/day (Linear Scale)</td>
<td></td>
</tr>
<tr>
<td>Figure 14.2.2.3.2</td>
<td>Line Plot of Mean 7-COOH-CBD Plasma Concentration vs. Time Profiles, Visit 3, 25 and 50 mg/kg/day (Semi-Log Scale)</td>
<td></td>
</tr>
<tr>
<td>Figure 14.2.2.4.1</td>
<td>Line Plot of Mean CBD Plasma Concentration vs. Time Profiles, Visit 10, 25 and 50 mg/kg/day (Linear Scale)</td>
<td></td>
</tr>
<tr>
<td>Figure 14.2.2.4.2</td>
<td>Line Plot of Mean CBD Plasma Concentration vs. Time Profiles, Visit 10, 25 and 50 mg/kg/day (Semi-Log Scale)</td>
<td></td>
</tr>
<tr>
<td>Figure 14.2.2.5.1</td>
<td>Line Plot of Mean 7-OH-CBD Plasma Concentration vs. Time Profiles, Visit 10, 25 and 50 mg/kg/day (Linear Scale)</td>
<td></td>
</tr>
<tr>
<td>Figure 14.2.2.5.2</td>
<td>Line Plot of Mean 7-OH-CBD Plasma Concentration vs. Time Profiles, Visit 10, 25 and 50 mg/kg/day (Semi-Log Scale)</td>
<td></td>
</tr>
<tr>
<td>Figure 14.2.2.6.1</td>
<td>Line Plot of Mean 7-COOH-CBD Plasma Concentration vs. Time Profiles, Visit 10, 125 and 50 mg/kg/day (Linear Scale)</td>
<td></td>
</tr>
<tr>
<td>Figure 14.2.2.6.2</td>
<td>Line Plot of Mean 7-COOH-CBD Plasma Concentration vs. Time Profiles, Visit 10, 25 and 50 mg/kg/day (Semi-Log Scale)</td>
<td></td>
</tr>
<tr>
<td>Figure 14.2.3.1.1.1</td>
<td>Box Plot of AUC0-t by Visit for CBD (25 mg/kg/day)</td>
<td></td>
</tr>
<tr>
<td>Figure 14.2.3.1.1.2</td>
<td>Box Plot of AUC0-t by Visit for CBD (25 mg/kg/day), Age 1 to 6 Years</td>
<td></td>
</tr>
<tr>
<td>Figure 14.2.3.1.1.3</td>
<td>Box Plot of AUC0-t by Visit for CBD (25 mg/kg/day), Age 7 to 11 Years</td>
<td></td>
</tr>
</tbody>
</table>

Safety Analysis Set
<table>
<thead>
<tr>
<th>Figure Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.2.3.1.1.4</td>
<td>Box Plot of AUC&lt;sub&gt;0-t&lt;/sub&gt; by Visit for CBD (25 mg/kg/day), Age 12 to 17 Years</td>
</tr>
<tr>
<td>14.2.3.1.1.5</td>
<td>Box Plot of AUC&lt;sub&gt;0-t&lt;/sub&gt; by Visit for 7-OH-CBD (25 mg/kg/day), Age 18 to 65 Years</td>
</tr>
<tr>
<td>14.2.3.1.2.1</td>
<td>Box Plot of AUC&lt;sub&gt;0-t&lt;/sub&gt; by Visit for 7-OH-CBD (25 mg/kg/day), Age 1 to 6 Years</td>
</tr>
<tr>
<td>14.2.3.1.2.2</td>
<td>Box Plot of AUC&lt;sub&gt;0-t&lt;/sub&gt; by Visit for 7-OH-CBD (25 mg/kg/day), Age 7 to 11 Years</td>
</tr>
<tr>
<td>14.2.3.1.2.3</td>
<td>Box Plot of AUC&lt;sub&gt;0-t&lt;/sub&gt; by Visit for 7-OH-CBD (25 mg/kg/day), Age 12 to 17 Years</td>
</tr>
<tr>
<td>14.2.3.1.2.4</td>
<td>Box Plot of AUC&lt;sub&gt;0-t&lt;/sub&gt; by Visit for 7-OH-CBD (25 mg/kg/day), Age 18 to 65 Years</td>
</tr>
<tr>
<td>14.2.3.1.3.1</td>
<td>Box Plot of AUC&lt;sub&gt;0-t&lt;/sub&gt; by Visit for 7-COOH-CBD (25 mg/kg/day), Age 1 to 6 Years</td>
</tr>
<tr>
<td>14.2.3.1.3.2</td>
<td>Box Plot of AUC&lt;sub&gt;0-t&lt;/sub&gt; by Visit for 7-COOH-CBD (25 mg/kg/day), Age 7 to 11 Years</td>
</tr>
<tr>
<td>14.2.3.1.3.3</td>
<td>Box Plot of AUC&lt;sub&gt;0-t&lt;/sub&gt; by Visit for 7-COOH-CBD (25 mg/kg/day), Age 12 to 17 Years</td>
</tr>
<tr>
<td>14.2.3.1.3.4</td>
<td>Box Plot of AUC&lt;sub&gt;0-t&lt;/sub&gt; by Visit for 7-COOH-CBD (25 mg/kg/day), Age 18 to 65 Years</td>
</tr>
<tr>
<td>14.2.3.1.3.5</td>
<td>Box Plot of AUC&lt;sub&gt;0-t&lt;/sub&gt; by Visit for 7-COOH-CBD (25 mg/kg/day), Age 1 to 6 Years</td>
</tr>
<tr>
<td>14.2.3.2.1.1</td>
<td>Box Plot of AUC&lt;sub&gt;0-t&lt;/sub&gt; by Visit for CBD (50 mg/kg/day), Age 1 to 6 Years</td>
</tr>
<tr>
<td>14.2.3.2.1.2</td>
<td>Box Plot of AUC&lt;sub&gt;0-t&lt;/sub&gt; by Visit for CBD (50 mg/kg/day), Age 1 to 6 Years</td>
</tr>
<tr>
<td>14.2.3.2.1.3</td>
<td>Box Plot of AUC&lt;sub&gt;0-t&lt;/sub&gt; by Visit for CBD (50 mg/kg/day), Age 7 to 11 Years</td>
</tr>
<tr>
<td>14.2.3.2.1.4</td>
<td>Box Plot of AUC&lt;sub&gt;0-t&lt;/sub&gt; by Visit for CBD (50 mg/kg/day), Age 12 to 17 Years</td>
</tr>
<tr>
<td>14.2.3.2.1.5</td>
<td>Box Plot of AUC&lt;sub&gt;0-t&lt;/sub&gt; by Visit for CBD (50 mg/kg/day), Age 18 to 65 Years</td>
</tr>
<tr>
<td>14.2.3.2.2.1</td>
<td>Box Plot of AUC&lt;sub&gt;0-t&lt;/sub&gt; by Visit for 7-OH-CBD (50 mg/kg/day), Age 1 to 6 Years</td>
</tr>
<tr>
<td>14.2.3.2.2.2</td>
<td>Box Plot of AUC&lt;sub&gt;0-t&lt;/sub&gt; by Visit for 7-OH-CBD (50 mg/kg/day), Age 1 to 6 Years</td>
</tr>
<tr>
<td>14.2.3.2.2.3</td>
<td>Box Plot of AUC&lt;sub&gt;0-t&lt;/sub&gt; by Visit for 7-OH-CBD (50 mg/kg/day), Age 7 to 11 Years</td>
</tr>
<tr>
<td>14.2.3.2.2.4</td>
<td>Box Plot of AUC&lt;sub&gt;0-t&lt;/sub&gt; by Visit for 7-OH-CBD (50 mg/kg/day), Age 12 to 17 Years</td>
</tr>
<tr>
<td>14.2.3.2.2.5</td>
<td>Box Plot of AUC&lt;sub&gt;0-t&lt;/sub&gt; by Visit for 7-OH-CBD (50 mg/kg/day), Age 18 to 65 Years</td>
</tr>
<tr>
<td>14.2.3.2.3.1</td>
<td>Box Plot of AUC&lt;sub&gt;0-t&lt;/sub&gt; by Visit for 7-COOH-CBD (50 mg/kg/day)</td>
</tr>
<tr>
<td>14.2.3.2.3.2</td>
<td>Box Plot of AUC&lt;sub&gt;0-t&lt;/sub&gt; by Visit for 7-COOH-CBD (50 mg/kg/day), Age 1 to 6 Years</td>
</tr>
<tr>
<td>14.2.3.2.3.3</td>
<td>Box Plot of AUC&lt;sub&gt;0-t&lt;/sub&gt; by Visit for 7-COOH-CBD (50 mg/kg/day), Age 7 to 11 Years</td>
</tr>
<tr>
<td>14.2.3.2.3.4</td>
<td>Box Plot of AUC&lt;sub&gt;0-t&lt;/sub&gt; by Visit for 7-COOH-CBD (50 mg/kg/day), Age 12 to 17 Years</td>
</tr>
</tbody>
</table>
Table 22  List of OLE Phase Figures

<table>
<thead>
<tr>
<th>Figure Number</th>
<th>Title</th>
<th>Analysis Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLE Figure 9.1.1</td>
<td>Percentage Change in TSC-associated Seizure Frequency Over Time</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Figure 9.1.2</td>
<td>Percentage Change in TSC-associated Seizure Frequency Over Time (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Figure 9.1.3</td>
<td>Percentage Change in TSC-associated Seizure Frequency Over Time (Patients with Data in OLE Week 37 to 48)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>OLE Figure 9.2.1</td>
<td>Percentage Change in Total Seizure Frequency Over Time</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Figure 9.2.2</td>
<td>Percentage Change in Total Seizure Frequency Over Time (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Figure 9.2.3</td>
<td>Percentage Change in Total Seizure Frequency Over Time (Patients with Data in OLE Week 37 to 48)</td>
<td>OLE Safety Analysis Set</td>
</tr>
</tbody>
</table>
GW Research Ltd.

Trial Code: GWEP1521

A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF CANNABIDIOL (GWP42003-P, CBD) AS ADD-ON THERAPY IN PATIENTS WITH TUBEROUS SCLEROSIS COMPLEX WHO EXPERIENCE INADEQUATELY-CONTROLLED SEIZURES

Statistical Analysis Plan

24 April 2019
CONTENTS

1. INTRODUCTION 6
   1.1 Rationale 6

2. TRIAL OBJECTIVES 7
   2.1 Primary Objective 7
   2.2 Secondary Objectives 7
   2.3 Exploratory Objectives 7

3. INVESTIGATIONAL PLAN 8
   3.1 Trial Design 8
   3.2 Definition of Sample Size 9
   3.3 Efficacy and Safety Endpoints 9
      3.3.1 Primary Efficacy Endpoint 9
      3.3.2 Secondary Efficacy Endpoints 9
      3.3.3 Exploratory Endpoints (Double-blind and Open-label Extension) 11

4. BLINDED DATA REVIEW MEETING 12

5. STATISTICAL METHODS 12
   5.1 General Considerations 12
      5.1.1 Missing Data 14
      5.1.2 Day Numbering 15
      5.1.3 Definitions 15
      5.1.4 Interim Analysis 16
   5.2 Analysis Sets and Protocol Deviations 18
      5.2.1 Safety Analysis Set 18
      5.2.2 Intention to Treat Analysis Set 18
      5.2.3 Per Protocol Analysis Set and Protocol Deviations 18
      5.2.4 OLE Safety Analysis Set 18
   5.3 Listings 18
   5.4 Demographic Data and Patient Characteristics 19
      5.4.1 Patient Disposition 19
      5.4.2 Analysis Sets 19
      5.4.3 Demographic Data and Baseline Characteristics 19
      5.4.4 Epilepsy History 20
      5.4.5 Medical and Surgical History and Current Medical Conditions 21
   5.5 Efficacy Analysis 21
      5.5.1 General Approach 21
      5.5.2 Primary Efficacy Endpoint 22
      5.5.3 Secondary Efficacy Endpoints 27
      5.5.4 Exploratory Efficacy Endpoints 33
      5.5.5 Subgroup Analyses 43
   5.6 Safety Evaluation 43
5.6.1 Exposure to IMP
5.6.2 Adverse Events
5.6.3 Clinical Laboratory Evaluation
5.6.4 Vital Signs, Other Physical Findings and Other Safety Data
5.7 Other Measures
5.7.1 Concomitant Medication
5.7.2 Pharmacokinetics of CBD and its Major Metabolites
5.7.3 Plasma Concentrations of Concomitant AEDs
5.7.4 Study Medication Use and Behavior Survey
5.7.5 Supplemental Drug Accountability Form
5.7.6 Supplemental Adverse Event Form
5.7.7 Site Classification Form
5.7.8 IVRS Compliance
5.8 Changes in the Conduct of the Trial or Planned Analysis

6. REFERENCES
7. AMENDMENTS
8. ATTACHMENTS AND APPENDICES
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-COOH-CBD</td>
<td>7-carboxy-CBD</td>
</tr>
<tr>
<td>7-OH-CBD</td>
<td>7-hydroxy-CBD</td>
</tr>
<tr>
<td>ABCL</td>
<td>Adult Behavior Checklist</td>
</tr>
<tr>
<td>AEDs</td>
<td>Antiepileptic Drugs</td>
</tr>
<tr>
<td>AEs</td>
<td>Adverse Events</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of Covariance</td>
</tr>
<tr>
<td>ALQ</td>
<td>Above Limit of Quantification</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical</td>
</tr>
<tr>
<td>BDRM</td>
<td>Blinded Data Review Meeting</td>
</tr>
<tr>
<td>BLQ</td>
<td>Below Limit of Quantification</td>
</tr>
<tr>
<td>CBCL</td>
<td>Child Behavior Checklist</td>
</tr>
<tr>
<td>CBD</td>
<td>Cannabidiol</td>
</tr>
<tr>
<td>CGIC</td>
<td>Caregiver Global Impression of Change</td>
</tr>
<tr>
<td>CGICSD</td>
<td>Caregiver Global Impression of Change in Seizure Duration</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CMH</td>
<td>Cochran–Mantel–Haenszel</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>C-SSRS</td>
<td>Columbia-Suicide Severity Rating Scale</td>
</tr>
<tr>
<td>CWS</td>
<td>Cannabis Withdrawal Scale</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>IGF-1</td>
<td>Insulin-like Growth Factor-1</td>
</tr>
<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention to Treat</td>
</tr>
<tr>
<td>IVRS</td>
<td>Interactive Voice Response System</td>
</tr>
<tr>
<td>LGS</td>
<td>Lennox-Gastaut Syndrome</td>
</tr>
<tr>
<td>LOCF</td>
<td>Last Observation Carried Forward</td>
</tr>
<tr>
<td>MAR</td>
<td>Missing at Random</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>MI</td>
<td>Multiple Imputation</td>
</tr>
<tr>
<td>MNAR</td>
<td>Missing Not at Random</td>
</tr>
<tr>
<td>NOCB</td>
<td>Next Observation Carried Backward</td>
</tr>
<tr>
<td>NRS</td>
<td>Numerical Rating Scale</td>
</tr>
<tr>
<td>OLE</td>
<td>Open Label Extension</td>
</tr>
<tr>
<td>PCWS</td>
<td>Pediatric Cannabinoid Withdrawal Scale</td>
</tr>
</tbody>
</table>
PGIC - Physician Global Impression of Change
PK - Pharmacokinetics
PP - Per Protocol
QOLCE - Quality of Life in Childhood Epilepsy
QOLIE-31-P - Quality of Life in Epilepsy, version 2
RM - Rescue Medication
SAP - Statistical Analysis Plan
SGIC - Subject Global Impression of Change
SGICSD - Subject Global Impression of Change in Seizure Duration
SOC - System Organ Class
SCQ - Social Communication Questionnaire
TAND - TSC-associated Neuropsychiatric Disorders
TEAE - Treatment Emergent Adverse Event
TSC - Tuberous Sclerosis Complex
ULN - Upper Limit of Normal
Vineland-II - Vineland Adaptive Behavior Scales, Second Edition
1. INTRODUCTION

This statistical analysis plan (SAP) documents the statistical reporting to be performed for trial GWEP1521.

This SAP has been prepared based on the following protocol:

- Protocol GWEP1521 (Version 8, dated 23rd April 2019).

1.1 Rationale

Tuberous sclerosis complex (TSC) is a genetic disorder characterized by the formation of nonmalignant tumors (tubers) in multiple organ systems. The clinical signs of TSC arise as a result of inactivating mutations in either of two tumor suppressor genes: TSC1 (located on chromosome 9q34.13) or TSC2 (located on chromosome 16p13.3). Thus, inactivating mutations in TSC1 and TSC2 lead to inadequate suppression of mTOR signaling, resulting in abnormal cellular growth and tumorigenesis.

Mutations in TSC1 account for approximately 15% of all cases of TSC whilst approximately 70% of all cases are due to mutations in TSC2; ~15% of TSC patients have no identifiable mutation in the coding regions of either gene. Generally, TSC2 mutations result in a more severe disease phenotype compared with TSC1 mutations. The birth incidence of TSC is estimated to be 1 in 6,000 with approximately 50,000 individuals in the United States and 1 million individuals worldwide affected.

Tumors in TSC patients can occur in any major organ yet develop primarily in the brain, eyes, heart, kidney, skin and lungs.

Epileptic seizures are the most common clinical manifestation of TSC, affecting more than 70% of patients. Seizure onset occurs within the first year of life in approximately two-thirds of TSC patients and occurs within the first 3 years of life in 80% of TSC patients. The onset of epilepsy in TSC commonly manifests as focal motor seizures, which in approximately one-third of TSC patients coexist with infantile spasms.

Virtually all TSC patients with infantile spasms and approximately half of all epileptic TSC patients without them develop multiple seizure types, including complex focal seizures (with or without secondary generalization), generalized tonic–clonic seizures, atonic seizures, and atypical absences. Although infantile spasms resolve with time, the frequency and severity of other seizures tend to increase throughout early childhood and nearly two-thirds of TSC patients develop medically intractable epilepsy, including Lennox–Gastaut syndrome.

Early management of seizures is therefore important in preventing subsequent epileptic encephalopathy and in reducing the associated cognitive and neuropsychiatric consequences.

The pharmacological therapies currently available for TSC-associated epilepsy often produce serious adverse effects, and a significant proportion of patients (37–63%) become resistant to treatment. Consequently, there is a clear need for new, efficacious pharmaceutical treatments for refractory epilepsy. Given the limitations of current synthetic antiepileptic drugs (AEDs), it has been suggested that CBD should be tested for anticonvulsive efficacy in randomized controlled clinical trials, especially in infantile epileptic syndromes. Although there are no published reports to date investigating the efficacy of CBD for seizures in TSC patients, a recent parent survey has reported that 84% of children with treatment-resistant epilepsy experienced a reduction in seizures whilst taking CBD-enriched cannabis, with over half of those reporting >80% reduction in seizure frequency.
The CBD-enriched cannabis was behaviorally well tolerated and children often experienced improved sleep, increased alertness, and better mood.

2. TRIAL OBJECTIVES

The protocol defined the trial objectives as:

2.1 Primary Objective

Blinded Phase:

To evaluate the efficacy of GWP42003-P as add-on therapy in reducing the frequency of seizures when compared with placebo in patients with TSC.

Open-label Extension:

To evaluate via the adverse events (AE) profile the long term safety and tolerability of GWP42003-P as add-on therapy in children and adults with TSC who experience inadequately-controlled seizures.

2.2 Secondary Objectives

Blinded Phase:

- To evaluate the effect of GWP42003-P compared with placebo on antiepileptic measures.
- To evaluate the effect of GWP42003-P on growth and development (in patients less than 18 years old) compared with placebo.
- To evaluate the effects of GWP42003-P on quality of life compared with placebo.
- To evaluate the safety and tolerability of GWP42003-P compared with placebo.

Open-label Extension:

- To evaluate the long term effects of GWP42003-P, as add-on therapy, on antiepileptic measures.
- To evaluate the long term effect of GWP42003-P on growth and development (in patients less than 18 years old).
- To evaluate the long term effects of GWP42003-P on quality of life.
- To evaluate the long term safety and tolerability of GWP42003-P.

2.3 Exploratory Objectives

Blinded Phase:

- To evaluate the effect of GWP42003-P on TSC-associated neuropsychiatric disorders (TAND), including cognitive and behavioral function and autistic features compared with placebo.
- To determine the pharmacokinetics (PK) of CBD, and its major metabolites following single and multiple doses of GWP42003-P.
- To evaluate the effects of GWP42003-P on plasma concentrations of concomitant AEDs, if applicable.
Open-label Extension:

- To evaluate the long term effect of GWP42003-P on TAND, including cognitive and behavioral function and autistic features compared with placebo.

3. INVESTIGATIONAL PLAN

3.1 Trial Design

This multicenter trial consists of a randomized, placebo-controlled, double-blind phase followed by an open-label extension (OLE) phase.

Blinded Phase:

The blinded phase of the trial is a randomized, double-blind, parallel-group, 16-week comparison of two doses of GWP42003-P vs. placebo. Patients will complete a 1-week screening period and a 4-week baseline period before they are randomized to receive either 25 mg/kg/day GWP42003-P, 50 mg/kg/day GWP42003-P or placebo. Randomization will be stratified by age according to the following ranges: 1–6, 7–11, 12–17 years and 18–65 years. Patients will begin a 4-week dose escalation period, titrating up to their assigned dose, before continuing on a stable dose of blinded Investigational Medicinal Product (IMP) for 12 weeks.

Dose escalation for each patient is subject to the investigator's assessment of safety and tolerability. If a dose becomes poorly tolerated, the investigator may consider temporarily or permanently reducing the dose for the remainder of the trial.

Following completion of the blinded phase, patients will be invited to continue to receive GWP42003-P in an OLE.

Those patients opting not to enter the OLE will complete a 10-day taper period (down-titrating 10% per day for 10 days).

Open-label Extension Transition:

In order to maintain consistent exposure to IMP and maintain the integrity of the blind, patients will enter a 2-week blinded transition to the OLE. OLE IMP will be titrated up to 25 mg/kg/day whilst blinded IMP is simultaneously tapered down to zero. All patients will complete the transition and enter the OLE taking 25 mg/kg/day GWP42003-P:

- Patients from the placebo arm will titrate up to 25 mg/kg/day GWP42003-P.
- Patients from the 25 mg/kg/day GWP42003-P arm will continue to take 25 mg/kg/day GWP42003-P.
- Patients from the 50 mg/kg/day GWP42003-P arm will taper down (10% per day) to 25 mg/kg/day GWP42003-P.

Open-label Extension:

The OLE consists of a 3-week titration period followed by a maintenance period and a 10-day taper period. The initial OLE period will last for a maximum of 1 year.

Following titration according to the titration schedule, patients will continue with their optimal GWP42003-P dose. However, investigators may decrease the dose if a patient experiences intolerance, or increase the dose to a maximum of 50 mg/kg/day if required for better seizure control, until the optimal dose is found.
3.2 Definition of Sample Size

Blinded Phase:

A total of 210 patients will be enrolled. The 210 patients will be randomly allocated to 1 of 4 treatment arms (GWP42003-P 25 mg/kg/day, GWP42003 P 50 mg/kg/day, placebo 25 mg/kg/day dose volume equivalent, or placebo 50 mg/kg/day dose volume equivalent) at a 2:2:1:1 ratio. The placebo arms will be pooled for the analyses of efficacy.

If it is assumed that patients in the placebo arm will experience a mean reduction in seizure frequency of 15% (from baseline), patients receiving GWP42003-P will experience at least a 50% reduction in seizures and a common standard deviation of 60%, then this sample size of 70 patients per arm will be sufficient to detect a difference in response distributions with 90% power. This test is based on a two-sided non-parametric Mann-Whitney-Wilcoxon test for continuous response data with a 5% significance level.

Open-label Extension:

All patients who wish to continue on IMP following the blinded phase.

3.3 Efficacy and Safety Endpoints

3.3.1 Primary Efficacy Endpoint

Blinded Phase:

The primary endpoint is the change in number of TSC associated seizures* during the treatment period (maintenance and titration) compared to baseline in patients taking GWP42003-P compared with placebo.

*Primary endpoint TSC-associated seizures include: focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures (tonic–clonic, tonic, clonic or atonic) that are countable.

Open-label Extension:

The safety of GWP42003-P will be evaluated by assessing the incidence, type and severity of AEs.

3.3.2 Secondary Efficacy Endpoints

Blinded Phase:

The following endpoints will be compared between treatment arms over the 16-week, double-blind treatment period (all changes relative to baseline):

Key:

1. Number of patients considered treatment responders defined as those with a ≥ 50% reduction in TSC-associated seizure frequency (see Section 5.1.3.7).
2. Change in Caregiver Global Impression of Change (CGIC) or Subject Global Impression of Change (SGIC) score.
3. Change in total seizures.
Other:

Antiepileptic Efficacy Measures:

- Number of patients considered treatment responders defined as those with a $\geq 25\%$, $\geq 50\%$, $\geq 75\%$ or 100\% reduction in TSC-associated seizure frequency.
- Number of patients experiencing a $> 25\%$ worsening, $- 25$ to $+ 25\%$ no change, 25–50\% improvement, 50–75\% improvement or $> 75\%$ improvement in TSC-associated seizure frequency.
- Change in number of TSC-associated seizure-free days.
- Change in number of 'other' seizures (absence, myoclonic, focal sensory and infantile/epileptic spasms).

Growth and Development (in patients less than 18 years old):

- Change in serum insulin-like growth factor-1 (IGF-1) levels.
- Change in Tanner Staging score (for patients aged 10–17 [inclusive]).

Quality of Life:

- Changes in the Quality of Life in Childhood Epilepsy (QOLCE; patients 2–18 years) or Quality of Life in Epilepsy (QOLIE-31-P; patients 19+ years) score.
- Change in Physician Global Impression of Change (PGIC) score.

Safety and Tolerability:

- AEs.
- Clinical laboratory parameters.
- 12-lead electrocardiogram (ECG).
- Physical examination parameters.
- Vital signs.
- Columbia-Suicide Severity Rating Scale (C-SSRS: 19+ years) or C-SSRS Children's (6–18 years) score, where applicable.
- Number of inpatient hospitalizations due to epilepsy.
- Abuse liability.
- Effects on menstruation cycles (in females).

Open Label Extension:

The following endpoints will be assessed relative to the pre-randomization baseline of the blinded phase:

**Key:**

- Percentage change in number of TSC-associated seizures (average per 28 days).
- Number of patients considered treatment responders defined as those with a $\geq 50\%$ reduction in TSC-associated seizure frequency.
- Change in CGIC or SGIC score.
- Change in total seizures.
Other:

Antiepileptic Efficacy Measures:

- Number of patients considered treatment responders defined as those with a ≥ 25%, ≥ 50%, ≥ 75% or 100% reduction in TSC-associated seizure frequency.
- Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in TSC-associated seizure frequency.
- Change in number of TSC-associated seizure-free days.
- Change in number of 'other' seizures (absence, myoclonic, focal sensory and infantile/epileptic spasms).

Growth and Development (patients less than 18 years):

- Change in serum IGF-1 levels.
- Change in Tanner Staging score (for patients aged 10–17 [inclusive]).

Quality of Life:

- Changes in the QOLCE (patients 2–18 years) or QOLIE-31-P (patients 19+ years) score.
- Change in PGIC score.

Safety and Tolerability:

- Clinical laboratory parameters.
- ECG.
- Physical examination parameters (including height and weight).
- Vital signs.
- C-SSRS (19+ years) or C-SSRS Children’s (6–18 years) score, where applicable.
- Number of inpatient hospitalizations due to epilepsy.
- Abuse liability.
- Effects on menstruation cycles (in females).

3.3.3 Exploratory Endpoints (Double-blind and Open-label Extension)

Antiepileptic Efficacy Measures:

- Change in composite focal seizure score (frequency × severity).
- Change in number of seizures by subtype.
- Change in use of rescue medication.
- Change in the number of episodes of status epilepticus (convulsive and non-convulsive).
- Changes in duration of seizure subtypes as assessed by the Subject Global Impression of Change in Seizure Duration (SGIC-SD) or the Caregiver Global Impression of Change in Seizure Duration (CGIC-SD).

TAND:

Cognitive and Behavioral Function:

• Changes in Wechsler Scales (pre-school, primary, children, adult).
• Changes in Achenbach Child Behavior Checklists (CBCL) and Adult Behavior Checklist (ABCL).

Autistic Features:

Change in Social Communication Questionnaire (SCQ) score.

PK (Double-blind only):

• The plasma concentrations will be summarized by time window for CBD and its major metabolites following single and multiple doses of GWP42003-P. Where data allows, the area under the plasma concentration curve (AUC0-t) from time zero to the last measurable time-point will be calculated.
• Plasma concentrations of concomitant AEDs before and after treatment with GWP42003-P, where available.

4. BLINDED DATA REVIEW MEETING

Prior to breaking the blind, it is anticipated that a Blinded Data Review Meeting (BDRM) will take place. The objectives of the meeting will include the identification and agreement on major protocol deviations and the need for a per protocol (PP) analysis set.

The meeting will have access to the following blinded summary tables and listings:

• Pre-randomization patient data
• Patient efficacy data
• Concomitant medication data
• Patient safety data
• Patient protocol deviation logs

This SAP documents the currently planned analyses for this trial that will be approved prior to breaking the blind for the trial. Changes to the analyses planned within any previously approved versions of the SAP will be summarized in Section 7 and integrated into the text of the SAP. The minutes of the BDRM will be documented separately.

5. STATISTICAL METHODS

5.1 General Considerations

In all tables, listings and figures for the double-blind phase, the trial medications will be referred to and labelled as per Table 1.

Table 1 Blinded Phase Trial Treatments

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Actual Treatment</th>
<th>Treatment Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Pooled Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Safety</td>
<td>25 mg/kg/day Placebo</td>
<td>Placebo 25 mg/kg</td>
</tr>
<tr>
<td>Safety</td>
<td>50 mg/kg/day Placebo</td>
<td>Placebo 50 mg/kg</td>
</tr>
<tr>
<td>All</td>
<td>25 mg/kg/day GWP42003-P</td>
<td>25 mg/kg</td>
</tr>
<tr>
<td>All</td>
<td>50 mg/kg/day GWP42003-P</td>
<td>50 mg/kg</td>
</tr>
</tbody>
</table>

For safety tables where placebo is split by dosing volume, an additional Pooled Placebo column will be included.
For OLE tables, columns will be included for treatment received during the double-blind phase (GWP42003-P or placebo, i.e. not split by dose) and overall.

In all tables, listings and figures, the trial visits will be referred to and labelled as per Table 2.

Table 2 Trial Visits

<table>
<thead>
<tr>
<th>Actual Visit</th>
<th>Visit Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1: Screening</td>
<td>Day -35</td>
</tr>
<tr>
<td>Visit 2: Day -28, baseline visit</td>
<td>Day -28</td>
</tr>
<tr>
<td>Visit 3: Day 1, Randomization</td>
<td>Day 1</td>
</tr>
<tr>
<td>Visit 4: Day 15</td>
<td>Day 15</td>
</tr>
<tr>
<td>Visit 5: Day 29</td>
<td>Day 29</td>
</tr>
<tr>
<td>Visit 6: Day 43</td>
<td>Day 43</td>
</tr>
<tr>
<td>Visit 7: Day 57</td>
<td>Day 57</td>
</tr>
<tr>
<td>Visit 8: Day 71, Telephone</td>
<td>Day 71</td>
</tr>
<tr>
<td>Visit 9: Day 85</td>
<td>Day 85</td>
</tr>
<tr>
<td>Visit 10: Day 113</td>
<td>End of Treatment</td>
</tr>
<tr>
<td>Visit 11: Day 123</td>
<td>End of Taper</td>
</tr>
<tr>
<td>Visit 12: Day 151</td>
<td>Safety Follow-Up</td>
</tr>
<tr>
<td>Visit B1: Day 1, Enrollment</td>
<td>OLE Day 1</td>
</tr>
<tr>
<td>Visit B2: Day 15</td>
<td>OLE Day 15</td>
</tr>
<tr>
<td>Visit B3: Day 36</td>
<td>OLE Day 36</td>
</tr>
<tr>
<td>Visit B4: Day 92</td>
<td>OLE Day 92</td>
</tr>
<tr>
<td>Visit B5: Day 141, Re-stocking of supplies</td>
<td>OLE Day 141</td>
</tr>
<tr>
<td>Visit B6: Day 183</td>
<td>OLE Day 183</td>
</tr>
<tr>
<td>Visit B7: Day 232, Re-stocking of supplies</td>
<td>OLE Day 232</td>
</tr>
<tr>
<td>Visit B8: Day 274</td>
<td>OLE Day 274</td>
</tr>
<tr>
<td>Visit B9: Day 323, Re-stocking of supplies</td>
<td>OLE Day 323</td>
</tr>
<tr>
<td>Visit B10: Day 365</td>
<td>OLE End of Treatment</td>
</tr>
<tr>
<td>Visit B11: Day 375</td>
<td>OLE End of Taper</td>
</tr>
<tr>
<td>Visit B12: Day 389</td>
<td>OLE Post-taper Safety Telephone Call</td>
</tr>
<tr>
<td>Day 403</td>
<td>OLE Follow-Up</td>
</tr>
</tbody>
</table>

Unless stated otherwise, continuous variables will be summarized showing the number of non-missing values (n), mean, standard deviation, median, minimum and maximum and categorical variables will be summarized showing the number and percentage of patients falling in each category. For continuous summaries of seizure frequency, the lower and upper quartiles will also be presented.

Minimum and maximum values will be presented to the same decimal precision as the raw data. Mean and median will be presented to one more decimal place than the raw data, and standard deviation to 2 more decimal places than the raw data. Percentages will be presented to one decimal place.

Unless otherwise specified, tables for the blinded phases will be summarized by randomized treatment arm, and for the open-label extension phase will be summarized by double-blind randomized treatment arm and overall.

All analyses and summaries will be produced using SAS Version 9.3 or higher.
5.1.1 Missing Data

5.1.1.1 Handling of Missing Data for the Primary Efficacy Endpoint

If a patient withdraws during the treatment period, then the primary analysis variable will be calculated from all the available data, during the treatment period, including any data available after the patient withdraws.

Section 5.5.2.1 describes sensitivity analyses to account for missing data arising from unreported days in the interactive voice response system (IVRS), and missing data arising from patients withdrawing during the treatment period.

5.1.1.2 Handling of Missing Data for the Secondary Efficacy Endpoints

5.1.1.2.1 Quality of Life in Childhood Epilepsy (2–18 Years)

The calculations of subscale and overall scores for the QOLCE will treat responses of ‘Not Applicable’ as missing values.

For each subscale, if fewer than 50% of the items within the subscale are missing (including ‘Not Applicable’) then the subscale score will be calculated using the mean of the non-missing items. If 50% or more of the items within the subscale are missing then the subscale score will not be calculated and will be missing.

For the overall quality of life score, if less than 8 of the 16 subscale scores are missing then the overall quality of life score will be calculated using the mean of the non-missing subscale scores. If 8 or more of the subscale scores are missing then the overall quality of life score will not be calculated and will be missing.

5.1.1.2.2 Quality of Life in Epilepsy, Version 2 (19 Years and Above)

For missing questions within subscales, the following rule will be applied:

- For subscales containing 4 or more questions (not including the ‘distress’ item), apply the following:
  - If less than or equal to 50% of the questions within the subscale are missing then the converted score for the missing questions will be set to the average of the non-missing question converted scores.
  - If more than 50% of the questions within the subscale are missing then the subscale weighted score will be set to missing.
- For subscales containing less than 4 questions (not including the ‘distress’ item) the subscale weighted score will be set to missing.

For missing ‘distress’ items, the following rule will be applied:

- If the corresponding subscale weighted score is missing then no imputation is needed and the ‘distress’ item converted score will be missing.
- If the corresponding subscale weighted score is not missing then set to the average of the non-missing ‘distress’ item converted scores.

For missing subscale weighted scores or missing ‘distress’ item converted scores, the following rule will be applied when calculating the total score:

- If 3 or more of the ‘distress’ item converted scores are missing then the total score will be set to missing.
- If 3 or more of the subscale weighted scores are missing then the total score will be set to missing.
If less than 3 ‘distress’ item converted scores are missing and less than 3 subscale weighted scores are missing, then the total score will be calculated based on the available non-missing data, following the rules above.

Note: it is possible that a subscale weighted score is missing, but that the corresponding ‘distress’ item was answered and the converted score is not missing. Following the rules above, the total score would include the non-missing ‘distress’ item converted score in the calculation even though the corresponding subscale weighted score is missing and hence not included.

5.1.1.3 Adverse Events

Missing and/or incomplete dates/times for AEs will be imputed in a manner resulting in the earliest onset or the longest duration during the treatment period, taking into account that the start date/time should not be after the stop date/time. Stop dates/times will not be imputed if the AE is ongoing.

The imputation method will only be used to determine treatment emergence, and imputed dates/times will not be presented in AE outputs.

A worst-case approach will be followed in the event of missing severity or causality data. If the severity is missing, ‘Severe’ will be imputed. If causality data is missing, ‘Yes’ will be imputed for the question ‘Plausible relationship to study medication’.

5.1.1.4 Concomitant Medication

Missing concomitant medication dates will be handled in a similar fashion as described for AEs in Section 5.1.1.3.

5.1.2 Day Numbering

Blinded Phase:

The first day of treatment (Day 1) will be taken from the Study Medication case report form (CRF) page at Visit 3. However, if this date is missing then the date of Visit 3 will be used.

Any days prior to Day 1 will be numbered relative to this day and calculated as:

\[ \text{Date} - (\text{Date of Day 1}); \text{ to give Day} -1, -2, -3 \text{ etc.} \]

Any days post Day 1 will be calculated as:

\[ 1 + \text{Date} - (\text{Date of Day 1}) \]

Open-label Extension:

The first day of treatment in the OLE (OLE Day 1) will be day of entry into the OLE, which is expected to be the same day as the end of treatment visit from the blinded phase. OLE day will be calculated as above but relative to OLE Day 1.

5.1.3 Definitions

5.1.3.1 Baseline

For clinic visit based endpoints, baseline is defined as the last record or measure collected prior to the first dose of IMP.
For IVRS based endpoints, baseline will include all available data from the day of Visit 2 to Day 1 of the blinded phase.

5.1.3.2 Last Visit

Last visit for endpoints assessed at clinic visits is defined as the last scheduled visit (not including the end of taper or safety follow-up visits) at which patient’s last evaluation is performed.

5.1.3.3 Last 12 Weeks (OLE Only)

The last 12 weeks (84 days) of the OLE for IVRS based endpoints is defined as all available data from 12 weeks prior to the earliest of the date of the patient completing the OLE, or the last call to IVRS.

5.1.3.4 Treatment Period

The treatment period of the double-blind phase is defined as Day 1 to Day 113.

5.1.3.5 Titration Period

The titration period of the double-blind phase is defined as Day 1 to Day 28.

5.1.3.6 Maintenance Period

The maintenance period of the double-blind phase is defined as Day 29 to Day 113.

5.1.3.7 TSC-associated Seizures

TSC-associated seizures are defined as focal motor seizures without impairment of consciousness or awareness, focal seizures with impairment of consciousness or awareness, focal seizures evolving to bilateral generalized convulsive seizures, and generalized seizures (tonic-clonic, tonic, clonic and atonic) that are countable.

5.1.3.8 Other Seizures

Other seizures are defined as absence, myoclonic, partial (focal) sensory seizures, and infantile or epileptic spasms.

5.1.3.9 Total Seizures

Total seizures are defined as the combination of TSC-associated seizures and other seizures.

5.1.3.10 Focal Seizures

Focal seizures are defined as Type 1, Type 2 or Type 3 as follows:

- Type 1: focal motor seizures without impairment of consciousness or awareness.
- Type 2: focal seizures with impairment of consciousness or awareness.
- Type 3: focal seizures evolving to bilateral convulsive seizures.

5.1.4 Interim Analysis

No formal interim analysis is to be conducted in this trial. However, interim reporting of the OLE may be required to support regulatory filings. This SAP contains details for the final reporting of the double-blind and OLE phases of the trial. For interim reporting of the OLE,
the rules described in the SAP will be followed. However, only a subset of outputs including OLE data may be required to support regulatory filings.

If interim reporting of the OLE is required, then only data available up to and including the date of the data cut will be included. The below section describes how data will be selected for the interim reporting.

5.1.4.1 Selection of Data and Handling of Partial Dates

For data that has an associated visit date or date of collection but does not have an associated start or end date, there is expected to be no partial date information. Therefore, data of this type that are collected after the date of data cut will not be included as part of the interim analysis. For non-medical history data that have an associated start date or end date, such as AEs or concomitant medications, the following rules will be followed in order to determine whether the records are included in the interim analysis.

Partial Start and/or End Dates

The following procedures will be followed in the event that a record has partial start or end dates:

Partial start date:

- If the start date is partial, then it will be assumed to have started at the earliest possible date based on the partial date provided, for the purposes of determining if the data should be included in the interim analysis only.

Partial end date:

- If the end date is partial, then it will be assumed to have ended at the latest possible date based on the partial date provided. However, if the patient withdrew from the trial, completed the trial or died prior to this imputed date, then the maximum of the last available visit date and the withdrawal/completion or death date will be used instead.

Once the dates have been suitably imputed, the processes for complete start or end dates, specified below, can then be followed to determine whether the record should be included in the data cut and how it should be adapted.

Complete Start or End Dates

The following procedures will be followed in the event that a record has complete start or end dates:

- If the start date falls on or before the date of data cut and the end date falls after the date of data cut, then the record will be included in the data cut but the end date will be set to missing and depending on the type of data, the following adjustments will be made:
  - For an AE record, the outcome will be set to “Continuing”.
  - For a concomitant medication record, the record will be set to “Ongoing at the End of the Trial”.
- If the start date falls after the date of data cut, then the record will not be included in the data cut.
5.2 Analysis Sets and Protocol Deviations

5.2.1 Safety Analysis Set

All randomized patients who received at least 1 dose of IMP will be included and analyzed according to the treatment received. Only patients for whom it has been confirmed that they did not take any IMP will be excluded from this safety analysis set.

5.2.2 Intention to Treat Analysis Set

All randomized patients who received at least one dose of IMP will be included and analyzed according to their randomized treatment arm.

The intention to treat (ITT) analysis set is the primary analysis set for all efficacy endpoints.

5.2.3 Per Protocol Analysis Set and Protocol Deviations

If there are a sufficient number of significant protocol deviations in the trial, a PP analysis set may also be presented.

All patients who complete the trial with no protocol deviations deemed to compromise the assessment of efficacy, will be included and analyzed according to the treatment arm they were randomized. The rules determining the PP analysis set will be fully defined prior to unblinding of the database.

A listing will be produced of protocol deviations for the clinical study report. These protocol deviations will be imported from the protocol deviations log. Protocol deviations will be classed as minor, important or major, where major deviations are classed as important protocol deviations leading to exclusion from the PP analysis set.

Protocol deviations were reviewed during BDRMs on 22nd and 25th March 2019. In addition to patients in the ITT analysis set who withdrew from the trial during the blinded treatment phase, a number of patients were deemed to have protocol deviations that should lead to exclusion from the PP analysis set. These patients, together with their deviations, are detailed in a separate document finalized prior to unblinding.

5.2.4 OLE Safety Analysis Set

The OLE safety analysis set will be defined as all patients who receive at least one dose of IMP during the OLE phase of the trial. Only patients for whom it has been confirmed that they did not take any OLE IMP will be excluded.

5.3 Listings

All data will be listed and ordered by site, treatment, patient number and, where appropriate, chronological order of assessment. Listings will be created for each of the subsequent sections of the SAP.

Visit date need not be included on all of the listings, but day numbers will be included, where appropriate.

Other derived variables (e.g. changes from baseline values) that are calculated for analysis purposes or to aid interpretation of the data will be added to the listings as appropriate.
5.4 Demographic Data and Patient Characteristics

5.4.1 Patient Disposition

Patient disposition, by site, by country and overall, will be summarized using standard summary statistics. The number screened, number of screen failures and number randomized will be included.

A screen failure disposition table will be presented, including number of patients screened, number failing screening, number randomized and the reasons for failing screening.

Patient disposition for the double-blind and OLE phases, including patients treated, completed the treatment and taper phases, discontinued (including reason for discontinuation) from the treatment and taper phases will be summarized by absolute counts (n) and percentages (%).

A further table split by site, and by country will be produced, showing number of patients randomized, withdrawn and completed the treatment phase at each site or in each country.

5.4.2 Analysis Sets

Patients included in the safety, ITT, PP and OLE safety analysis sets, and patients excluded together with reasons for exclusion, will be summarized by absolute counts (n) and percentages (%).

5.4.3 Demographic Data and Baseline Characteristics

The following demographic data will be summarized by treatment arm and overall for the safety, ITT, PP and OLE safety analysis sets:

- Age (years);
- Age group (1–6 years, 7–11 years, 12–17 years and 18–65 years);
- Sex;
- Race;
- Country;
- Region (US, Rest of the World);
- Weight at baseline (kg);
- Height at baseline (cm);
- Body mass index at baseline (kg/m²).

Age will be calculated as:

\[(\text{Date of screening} - \text{date of birth}) \div 365.25.\]

The following baseline characteristics will be summarized by treatment arm and overall for the safety, ITT, PP and OLE safety analysis sets:

- Average number of TSC-associated seizures per 28 days during baseline.
- Average number of total seizures per 28 days during baseline.
- Number of patients with seizures during the baseline period, by seizure type.
- Number of AEDs a patient has used, prior to the trial and is no longer taking.
- Number of AEDs a patient is currently taking.
- Total number of prior and current AEDs.
- Number of patients taking clobazam (Yes, No, and if no, Prior).
- Number of patients taking valproic acid (Yes, No, and if no, Prior).
- Number of patients taking levetiracetam (Yes, No, and if no, Prior).
- Number of patients taking vigabatrin (Yes, No, and if no, Prior).

The number of prior AEDs no longer taking will be taken from the ‘History of antiepileptic medications and therapies’ CRF page. The number of AEDs a patient is currently taking is based on the ‘Concomitant antiepileptic medications’ CRF page. If a patient has a medication listed on both the ‘History of antiepileptic medications and therapies’ and ‘Concomitant antiepileptic medications’ CRF pages and the medication is considered concomitant (see Section 5.7.1) for the double-blind phase, then this will not be included in the number of prior AEDs no longer taking. AEDs starting after the last dose of IMP during the double-blind phase will not be counted.

Patients taking the same AED type, but where the AED were coded to different generic terms will be counted only once within the AED type. For example, valproate sodium, valproic acid, valproate semisodium and ergenyl chrono will all be counted as valproic acid and counted once under that term.

The number of patients taking clobazam is defined as the number of patients taking clobazam at any point during baseline period or treatment period. The same definition will apply for the number of patients taking each of the other AEDs. The number of patients taking other AED types will also be presented if the overall frequency of patients taking the AED is >25%.

Previous cannabis use will be included within the baseline characteristics listing.

5.4.4 Epilepsy History

5.4.4.1 Genetic Testing History

Genetic testing history data will be listed only.

5.4.4.2 History of Seizures no Longer Occurring and History of Current Seizures

Data will be summarized by treatment arm and overall for the safety analysis set only, separately, for history of seizures no longer occurring and history of current seizures.

The following will be summarized by each seizure type:
- Number of patients with the seizure type.
- Age at onset (years).
- Age of last occurrence (years). For history of seizures no longer occurring only.
- Seizure duration (<2 minutes, 2–10 minutes, >10 minutes, Unknown). For history of current seizures only.

Seizure frequency data will be listed only.

For patients with more than one record for a particular seizure type, the earliest onset, most recent age of last occurrence and longest duration will be used for the summary table.
5.4.4.3 Neuroimaging History

Neuroimaging history data will be listed only.

5.4.5 Medical and Surgical History and Current Medical Conditions

All conditions and diagnoses on the ‘non-epilepsy medical history’ CRF page will be coded using Version 19.1 of the Medical Dictionary for Regulatory Activities (MedDRA v19.1).

The number of patients with relevant or significant non-epilepsy medical or surgical history and medical history by system organ class, and preferred term, will be summarized by absolute counts (n) and percentages (%). Percentages will be calculated based on the number of patients in the specific treatment arm. Two tables will be produced, one including any events classified as resolved at screening, and the other including all current conditions.

5.5 Efficacy Analysis

5.5.1 General Approach

Blinded Phase:

The primary analyses will use the ITT analysis set. Further analyses using the PP analysis set will also be performed for the primary endpoint and secondary endpoints where specified in the sections below.

The primary null hypothesis is:

- Following 16 weeks of treatment there is no difference in effect between the 25 mg/kg/day GWP42003-P treatment arm and the placebo treatment arm in terms of the change in number of TSC-associated seizures during the treatment period compared to baseline.

The null hypothesis will be rejected if there is statistical evidence of a difference between the treatment arms at the α-level of 0.05 for the primary endpoint.

Statistical hypothesis testing will be performed on the primary endpoint and other endpoints as appropriate. Each endpoint, including the primary will have 2 comparisons against placebo (25 mg/kg/day GWP42003-P vs. placebo and 50 mg/kg/day GWP42003-P vs. placebo). Also, 3 key secondary endpoints have been defined.

The primary and key secondary endpoints will be tested with their Type I error controlled by use of a hierarchical gate-keeping procedure, in the sequence given in Table 3. One must reject the null hypothesis of an endpoint at the level of 0.05 (2-sided) to test the hypothesis of the subsequent endpoint in the sequence at the level of 0.05 (2-sided). If a null hypothesis is not rejected then testing will stop and all subsequent analyses will be declared not statistically significant.

Table 3 Hierarchy for Analysis

<table>
<thead>
<tr>
<th>Test</th>
<th>Endpoint</th>
<th>Treatment Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Primary endpoint</td>
<td>25 mg/kg/day GWP42003-P vs. Placebo</td>
</tr>
<tr>
<td>2</td>
<td>1st key secondary endpoint</td>
<td>25 mg/kg/day GWP42003-P vs. Placebo</td>
</tr>
<tr>
<td>3</td>
<td>Primary endpoint</td>
<td>50 mg/kg/day GWP42003-P vs. Placebo</td>
</tr>
<tr>
<td>4</td>
<td>1st key secondary endpoint</td>
<td>50 mg/kg/day GWP42003-P vs. Placebo</td>
</tr>
<tr>
<td>5</td>
<td>2nd key secondary endpoint</td>
<td>25 mg/kg/day GWP42003-P vs. Placebo</td>
</tr>
</tbody>
</table>
All statistical tests will be 2-sided and use the 5% significance level.

The assumptions of normality and homogeneity of variance, for endpoints analyzed using parametric tests, will be checked where appropriate via examination of residual plots as well as computation of summary statistics for normality using the Shapiro-Wilk statistical test. If assumptions are violated then alternative non-parametric techniques will be used. In this instance the original parametric tests will be presented as a sensitivity analysis.

**Open-label Extension:**

All endpoints will be summarized on the OLE safety analysis set, unless specified otherwise.

Endpoints will be summarized by treatment received during the double-blind phase (GWP42003-P or Placebo, i.e. not split by dose) and overall.

For seizure endpoints, the OLE treatment phase will be split into 12 week periods, for example:

- OLE Week 1 (OLE Day 1) to OLE Week 12 (Day 84)
- OLE Week 13 (OLE Day 85) to OLE Week 24 (OLE Day 168)
- OLE Week 25 (OLE Day 169) to OLE Week 36 (OLE Day 252)
- OLE Week 37 (OLE Day 253) to OLE Week 48 (OLE Day 336)
- OLE Week 49 (OLE Day 337) to OLE Week 60 (OLE Day 420)
- Etc.

In addition, seizure data will be presented for the full OLE treatment phase as well as the last 12 weeks of the OLE treatment phase (see Section 5.1.3.3).

### 5.5.2 Primary Efficacy Endpoint

#### Blinded Phase:

The primary endpoint is the change in number of TSC-associated seizures (see Section 5.1.3.7) during the treatment period (see Section 5.1.3.4) compared to baseline period (see Section 5.1.3.1) in patients taking GWP42003-P compared with placebo.

The primary endpoint will be analyzed using a negative binomial regression model with the total number of TSC-associated seizures during the baseline period and treatment period as the response variables.

A mixed effect model with repeated measures will be performed modelling the observed total number of TSC-associated seizures in the baseline period and treatment period implemented within the framework of general linear models using the negative binomial response distribution. The model will include stratified age group (1–6 years, 7–11 years, 12–17 years and 18–65 years), time, treatment arm and treatment arm by time interaction as fixed effects and patient as a random effect. The log transformed number of days in which seizure data were reported will be included as an offset. The time variable corresponds to an indicator for the baseline period and treatment period.
The GLIMMIX procedure in SAS will be utilized to perform the analysis with the option maxopt=300 applied. If the model fails to converge, then the statement ‘nloptions tech=nrridg;’ will be added. If convergence is still not achieved, then ‘method=laplace’ will be utilized. However, if convergence is still not possible, then the model will be changed to utilize the log normal response distribution (log rate model). If the log rate model is required and there are patients with no seizures during the baseline or treatment period then all patients will have their baseline and treatment period seizure count adjusted by adding a value of 1.

The estimated least squares mean seizure rate for each period and the estimated ratio of least squares means for treatment period to baseline period and 95% confidence intervals (CIs) will be presented for each treatment arm. In addition, the estimated ratio of each GWP42003-P arm to placebo and 95% CIs will be presented along with the p-value testing the null hypothesis that this ratio is 1.

For each ratio and upper and lower bound of the 95% CI, the percentage reduction will also be presented, calculated as:

\[
\frac{[1 - (X \div Y)] \times 100}{100}
\]

Where X corresponds to the treatment period estimate, or GWP42003-P ratio, and Y corresponds to the baseline period estimate, or placebo arm ratio.

Primary efficacy analysis will be performed using the ITT analysis set.

TSC-associated seizure frequency (28-day average) and percentage change in seizure frequency will also be presented using summary statistics. Percentage change from baseline in TSC-associated seizure frequency will be calculated as:

\[
\frac{((\text{Frequency during the treatment period} - \text{Frequency during baseline}) \div \text{Frequency during baseline}) \times 100}{100}
\]

The frequency during each period will be based on 28 day averages and calculated as:

\[
\frac{(\text{Number of seizures in the period} \div \text{Number of reported days in IVRS in the period}) \times 28}{100}
\]

For the TSC-associated seizure endpoints only, if patients are randomized with no TSC-associated seizures during the baseline period then the percentage change from baseline will be calculated as:

\[
\frac{(\text{Frequency during the treatment period} + 1) \times 100}{100}
\]

**Open-label Extension:**

The primary endpoint for the OLE is the safety of GWP42003-P, evaluated by assessing the incidence, type and severity of AEs. Data will be presented as per Section 5.6.2.

However, percentage change from baseline in TSC-associated seizure frequency is considered a key secondary endpoint for the OLE.

In the OLE, seizures are recorded on a weekly basis rather than daily. Caregivers/patients are expected to call the IVRS system to record the number of seizure subtypes experienced every 7 days during the OLE. TSC-associated seizure frequency per 28 days will be calculated for each of the periods described in Section 5.5.1. All calls that take place during the period in question will contribute to the calculation of the average number of seizures per day in that period only.

The average number of seizures per day in the period will be calculated as the average of:

\[
\frac{\text{Number of seizures reported}}{\text{Number of days since last IVRS call}}
\]
The number of days since the last call will be calculated as follows, and is dependent on whether the call took place <7, 7 or >7 days after the previous call (or after the date of OLE Day 1 in the case of the first call in the first period):

- If the call takes place exactly 7 days after the previous call, then the number of days since the last call will be 7.
- If the call takes place <7 days after the previous call, then the number of days since the last call will be calculated as:
  
  \[(\text{Date of current call} – \text{date of previous call}) + 1\]

- If the call takes place >7 days after the previous call, then the number of days since the last call will be 7.

Summary statistics will be presented for raw seizure frequencies and percentage change from baseline (from the blinded phase).

5.5.2.1 Sensitivity Analyses for the Primary Efficacy Endpoint

Blinded Phase:

The following sensitivity analyses will be conducted for the primary endpoint of the blinded phase:

- Primary endpoint analysis repeated using the PP analysis set.
- Wilcoxon rank-sum test on percentage change from baseline in TSC-associated seizure frequency during the treatment period. An estimate of the median differences between each GWP42003-P arm and placebo, together with approximate 95% CIs, will be calculated using the Hodges–Lehmann approach.
- A rank analysis of covariance (ANCOVA) on percentage change from baseline in TSC-associated seizure frequency during the treatment period.
  
  The ranks of the percentage change from baseline and the baseline TSC-associated seizure frequency will be calculated. The rank of the percentage change from baseline will then be analyzed using an ANCOVA model with the rank of the baseline TSC-associated seizure frequency and stratified age group as covariates and treatment arm as a fixed factor. The estimated least squares means, treatment differences, together with the 95% CIs and p-values will be presented.
- ANCOVA of log transformed TSC-associated seizure frequency during the treatment period.
  
  The TSC-associated seizure frequency during the treatment period and the baseline TSC-associated seizure frequency will be log transformed prior to analysis. The log transformed TSC-associated seizure frequency during the treatment period will then be analyzed using an ANCOVA model with the log transformed baseline TSC-associated seizure frequency and stratified age group as covariates and treatment arm as a fixed factor. The back transformed estimated treatment ratios, together with the 95% CIs and p-values will be presented.
  
  If there are any patients with no TSC-associated seizures during the baseline or treatment periods, then 1 will be added to the TSC-associated seizure frequency for all patients prior to log transformation.
- ANCOVA on percentage change from baseline in TSC-associated seizure frequency during the treatment period including baseline and stratified age group as covariates
and treatment arm as a fixed factor. The estimated least squares means, treatment differences, together with the 95% CIs and p-values will be presented.

- Primary endpoint analysis repeated using the maintenance period (see Section 5.1.3.6) rather than the treatment period.
  This analysis will include only patients who have at least 7 days of seizure data within the maintenance period.

- Primary endpoint analysis repeated using the titration period (see Section 5.1.3.5) each 4 weeks of the maintenance period (Week 1 to 4, Week 5 to 8 and Week 9 to 12 of the 12-week maintenance period).
  These analyses will include only patients who have at least 7 days of seizure data within each corresponding 4 week period.

- Primary endpoint analysis repeated using the worst case of last observation carried forward (LOCF), next observation carried backward (NOCB) and the mean from the non-missing data for each patient (rounded up to the nearest integer) to impute missing data arising from unreported days in IVRS during the treatment period only (not the baseline period).
  Any intermittent missing data for the number of TSC-associated seizures arising from unreported days in IVRS will be imputed using the worst (highest number of seizures) of the following for each patient: LOCF, NOCB and the mean daily number of seizures during the treatment period (rounded up to the nearest integer) based on using non-missing data:

  \[ \text{Number of seizures} \div \text{Number of reported days in IVRS} \]

- Primary endpoint analysis repeated using multiple imputation (MI) to impute data under the Missing Not at Random (MNAR) assumption (see Section 5.5.2.1.1).

**Open-label Extension:**

Open-label summaries will be repeated with the inclusion of an LOCF imputation step, which is described in the following steps:

- If a patient has valid data for ≥1 consecutive periods from and inclusive of the first period but only missing periods thereafter, then imputation of the missing period(s) will be carried out using the last 12 weeks of valid data (see Section 5.1.3.3).

- If a patient has intermittent missing periods (i.e. ≥1 missing period that falls after a populated period 1 and before subsequent populated periods), then the missing period(s) will be imputed with the closest earlier non-missing period of data.

- If the patient has ≥1 consecutive periods of missing data from and inclusive of the first period then no imputation will occur and data from the patient will be excluded from any LOCF presentations.

### 5.5.2.1.1 Sensitivity Analysis of Missing Data

Missing data in this trial could potentially arise from the mechanism of MNAR. Hence, a sensitivity analysis is required to assess the potential impact that missing data under the mechanism of MNAR may have on the estimated results for the primary endpoint.

To facilitate multiple imputation techniques for missing data due to patients who withdraw from the treatment period, it is necessary to divide the treatment period into smaller periods for which missing seizure data can be imputed. Hence, sensitivity analysis of the primary endpoint will be carried out based on periods corresponding to each 14 days of the
treatment period, by multiple imputations on the average daily TSC-associated seizure frequency. The final period will consist of 15 days to include Day 113, where applicable. Following imputation, the imputed periods will be recombined for each patient in order to repeat the primary analysis.

For each 14 calendar days of the treatment period (15 days for the final period), the average daily TSC-associated seizure frequency will be calculated as:

\[
\text{Average daily TSC-associated seizure frequency} = \frac{\text{Number of TSC-associated seizures in the period}}{\text{Number of reported days in IVRS in the period}}
\]

For patients with <6 days in a period, the frequency will be set to missing and will be imputed as part of this analysis.

For intermittent missing data, in which subjects have missing values for intermediate periods but have available data at subsequent periods, imputation will be based on the MCMC methodology. Assumptions underlying this partial imputation step are that patients will follow a similar outcome trajectory as patients in their respective treatment arm that have complete data. Intermittent missing values will be imputed using the MCMC method in PROC MI with an IMPUTE=MONOTONE statement for 200 times for each treatment arm separately. To avoid negative results, a minimum of 0 will be specified in the PROC MI statement. As a result, missing intermediate visits will be imputed and the resulting 200 partially imputed datasets will have a monotone missing pattern.

The remaining monotone missing data will then be imputed using predictive mean matching in which missing observations are imputed with an observed value from another patient whose predicated value is close to the predicated value of the patient with the missing observation. The predictive mean matching is performed using the steps below, in which imputation will be carried out on each of the 200 imputed datasets using the SAS MI procedure (with the 200 imputed datasets included in the ‘BY’ statement of the MI procedure):

**Step 1 – Missing at random (MAR) based multiple imputation for the placebo arm:**

- Monotone missing data under the MAR assumption at period t will be imputed using predictive mean matching method from the observed daily TSC-associated seizure frequency at baseline and at each period up to period t (in chronological order).
- The imputation will be realized using the MI procedure with the ‘MONOTONE REGPMM’ option.
- The imputation model will include baseline daily TSC-associated seizure frequency and each period up to period t (in chronological order).

**Step 2 – MNAR based multiple imputation for the GWP42003-P arms (MNAR is assumed for missing values resulting from discontinuation due to any reason or any other monotone missing data):**

- With the data imputed from Step 1, monotone missing data under the MNAR at period t will be imputed using predictive mean matching method.
- At each period t, the input dataset for the MI procedure will include all placebo patients and those patients from each GWP42003-P arm (implemented separately by arm) that have values at that period.
- The imputation will be realized using the MI procedure with the ‘MONOTONE REGPMM’ option.
• The imputation model will include daily TSC-associated seizure frequency at baseline and each period up to period t (in chronological order).

Once all missing values at all periods have been imputed, the TSC-associated seizure count for each period will be calculated as:

(Daily frequency for the period × Number of days in the period for the non-imputed period or 14 for an imputed period), rounded to the nearest whole number

The result will be 200 fully imputed datasets ready to be analyzed using the same analysis method as the primary endpoint, producing 200 analysis results.

The estimated ratio, 95% CI and p-value from analyses of the 200 imputed datasets will be combined using PROC MIANALYZE.

To test the robustness of the analysis to the MNAR imputations a tipping point analysis will be performed. This will be conducted by adding or subtracting a sensitivity parameter, k × standard error of the observed average daily TSC-associated seizure frequency in the placebo arm at each period, to the MNAR imputations only at the corresponding period (where k = 0, ± 0.5, ± 1.0, ± 1.5, etc.).

The tipping point analysis will be used to explore the robustness of the estimated treatment difference to the degree of decrease or increase (positive values of k represent decrease and negative values represent increase) in MNAR efficacy from the placebo patients.

The increment in the positive value of k will stop once the overall p-value is greater than 0.05. The decrease in the negative values of k will continue until the overall p-value becomes smaller than the p-value from the primary efficacy analysis, for the corresponding Dose Level.

5.5.3 Secondary Efficacy Endpoints

5.5.3.1 Key Secondary Efficacy Endpoints

5.5.3.1.1 1st Key Secondary Endpoint: TSC-associated Seizure Treatment Responders (≥50% Reduction in TSC-associated Seizure Frequency)

Blinded Phase:

The proportion of patients considered treatment responders, defined as those with a ≥50% reduction in TSC-associated seizure frequency from baseline during the treatment period, for patients who have not withdrawn from the trial during the treatment period, will be summarized by treatment arm and analyzed using a Cochran–Mantel–Haenszel (CMH) test stratified by age group.

The proportion of patients who are considered treatment responders, the difference in proportions along with the 95% CI for the odds ratios (GWP42003-P arms vs. placebo), 95% CI for the odds ratios, and the p-values from the CMH test will be presented. If no patients in a particular treatment arm are considered responders then the odds ratio and 95% CI for the odds ratio will not be calculated.

The analysis will be performed on the ITT analysis set and repeated on the PP analysis set.

Sensitivity analyses will be performed on the ITT analysis set, repeating the above analysis, using data for the maintenance period only, the titration period and during each 4 weeks of the maintenance period (Week 1 to 4, Week 5 to 8 and Week 9 to 12 of the 12 week maintenance period).
Analyses on the maintenance period, titration period and by each 4 weeks of the maintenance period will include only patients who have at least 7 days of seizure data within each period.

**Open-label Extension:**

Descriptive summaries described above for the blinded phase will be repeated for OLE periods. However, for the OLE periods, withdrawn patients may be considered responders.

5.5.3.1.2 2nd Key Secondary Endpoint: Subject/Caregiver Global Impression of Change

**Blinded Phase:**

The SGIC and CGIC comprise the following questions to be rated on a 7-point scale:

**CGIC:**
- Since your child started treatment, please assess the status of your child’s overall condition (comparing their condition now to their condition before treatment) using the scale below.

**SGIC:**
- Since you started treatment, please assess the status of your overall condition (comparing your condition now to your condition before treatment) using the scale below.

The possible responses are: Very Much Improved; Much Improved; Slightly Improved; No Change; Slightly Worse; Much Worse; Very Much Worse.

The responses above are based on comparison with a brief description of the patient’s overall condition used as a memory aid from Visit 3.

Each response will be coded with a score from 1 to 7, where 1 = Very Much Improved, and 7 = Very Much Worse.

The SGIC and CGIC response/score, recorded at each visit, will be summarized separately, on both a categorical and continuous scale, by treatment arm.

It is anticipated that only a small percentage of patients will complete the subject version of the questionnaire. Hence, no analyses will be performed for the SGIC.

A combined score will be used as the primary analysis for this endpoint. The combined score will be defined as follows:
- If both a CGIC and SGIC are completed then the CGIC will be used.
- If only a CGIC is completed then the CGIC will be used.
- If only a SGIC is completed then the SGIC will be used.

The score at the end of treatment visit and last visit (if different to the end of treatment) will be analyzed using ordinal logistic regression. Proportional odds modelling will be carried out by including treatment arm as a factor. The estimated odds ratio (GWP42003-P vs. placebo), 95% CI for the odds ratio, and the p-value testing the null hypothesis that the odds ratio is equal to 1, will be presented. Analysis performed at the last visit will be considered the primary analysis for this endpoint, with the analysis at the end of treatment visit considered a sensitivity analysis.
Should the proportional odds assumption not hold, i.e. if the p-value for the score test for proportional odds assumption is <0.05, then, as a sensitivity analysis, the scores will also be analyzed using a Cochran-Armitage trend test. This will be presented together with the results of the ordinal logistic regression.

Since this analysis uses a combination of caregiver and subject ratings, a sensitivity analysis will be performed using only the CGIC score and using the same analyses as above.

The analysis will be performed on the ITT analysis set and repeated on the PP analysis set.

**Open-label Extension:**

Descriptive summaries described above for the blinded phase will be repeated for OLE visits.

### 5.5.3.1.3 3rd Key Secondary Endpoint: Total Seizures

**Blinded Phase:**

Summaries and analyses of total seizures (see Section 5.1.3.9) will be performed as per the primary endpoint (Section 5.5.2).

The analysis will be performed on the ITT analysis set and repeated on the PP analysis set.

Sensitivity analyses will be performed on the ITT analysis set, repeating the above analysis, using data for only the maintenance period, titration period, and during each 4 weeks of the maintenance period (Week 1 to 4, Week 5 to 8 and Week 9 to 12 of the 12 week maintenance period).

Analyses on the maintenance period, titration period and by each 4 weeks of the maintenance period will include only patients who have at least 7 days of seizure data within each period.

**Open-label Extension:**

Summaries will be performed for the OLE periods as described in the OLE portion of the primary endpoint section (Section 5.5.2).

### 5.5.3.2 Other Secondary Efficacy Endpoints

#### 5.5.3.2.1 TSC-associated Seizure Treatment Responders and TSC-associated Seizure Freedom

**Blinded Phase:**

The number of patients experiencing a >25% increase, ≥0 to <25% increase, >0 to <25% reduction, ≥25 to <50% reduction, ≥50 to <75% reduction or ≥75% reduction in TSC-associated seizure frequency from baseline during the treatment period will be summarized by treatment arm.

In addition to the key secondary endpoint, the proportion of patients considered treatment responders, defined as those with a ≥25% or ≥75% reduction in TSC-associated seizure frequency from baseline and the proportion of patients who are TSC-associated seizure free, defined as those with a 100% reduction in TSC-associated seizure frequency from baseline, during the treatment period, for patients who have not withdrawn from the trial
during the treatment period will be summarized by treatment arm and analyzed using a CMH test stratified by age as described in Section 5.5.3.1.1.

Additionally, the proportion of patients responding will be presented graphically, by treatment arm, by plotting the percent reduction against the cumulative proportion of patients achieving that level of reduction. The x-axis will be the percent reduction from baseline and the y-axis will be the proportion of patients with at least that amount of reduction, i.e. \( y = \Pr(X \geq x) \).

Sensitivity analyses will be performed on the ITT analysis set, repeating the above analysis, using data for only the maintenance period, titration period, and during each 4 weeks of the maintenance period (Week 1 to 4, Week 5 to 8 and Week 9 to 12 of the 12 week maintenance period).

Analyses on the maintenance period, titration period and by each 4 weeks of the maintenance period will include only patients who have at least 7 days of seizure data within each period.

**Open-label Extension:**

Descriptive summaries described above for the blinded phase will be repeated for OLE periods.

**5.5.3.2.2 Number of TSC-associated Seizure Free Days**

**Blinded Phase Only:**

The number of TSC-associated seizure free days during each period will be based on 28 day averages and calculated as:

\[
\text{Number of seizure free days in the period} \div \text{Number of reported days in IVRS in the period} \times 28
\]

The change from baseline in TSC-associated seizure free days per 28 days will be analyzed for the treatment period using an ANCOVA approach. The model will include baseline and stratified age group as covariates and treatment arm as fixed factor.

The estimated least squares means, treatment difference, together with the 95% CIs and p-value will be presented.

The analysis will be repeated for the maintenance period.

**5.5.3.2.3 Other Seizures**

**Blinded Phase:**

For other seizures (see Section 5.1.3.8), summaries and analyses will be performed as per the primary endpoint (Section 5.5.2). Patients with no seizures during the baseline period, for a particular seizure type, will be excluded from the analysis of that seizure type.

Other seizure and total seizure responders and freedom will also be summarized and analyzed using the methods described in Section 5.5.3.2.1. However, the summaries and analyses during the maintenance and titration periods and during each 4 weeks of the maintenance period will be produced for total seizures only. Patients with no corresponding other seizures during the baseline period will be excluded from the analysis for other seizures.

**Open-label Extension:**
Descriptive summaries described above for the blinded phase will be repeated for OLE periods.

5.5.3.2.4 Quality of Life in Childhood Epilepsy (2–18 Years)

Blinded Phase:

The QOLCE is a parent-reported questionnaire that evaluates health related quality of life in children aged 2–18 years old. It contains 76 items with 16 subscales covering 7 domains of life function: Physical activities, social activities, cognition, emotional well-being, behavior, general health, and general quality of life.

All items in the questionnaire are rated on a 5-point or 6-point categorical scale. Based on the responses to the items in each domain, scores for 16 subscales are derived. The subscales are presented in Table 4.

Table 4 QOLCE Subscales

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Item Domains</th>
<th>Items Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Restrictions</td>
<td>Physical Activities</td>
<td>3.1 (a to j)</td>
</tr>
<tr>
<td>Energy/Fatigue</td>
<td>Physical Activities</td>
<td>3.2 (a,b)</td>
</tr>
<tr>
<td>Attention/Concentration</td>
<td>Cognition</td>
<td>5.1 (a,d,e,f,g)</td>
</tr>
<tr>
<td>Memory</td>
<td>Cognition</td>
<td>5.1 (j,k,l,m,n,o)</td>
</tr>
<tr>
<td>Language</td>
<td>Cognition</td>
<td>5.1 (p,q,r,s,t,u,v,w)</td>
</tr>
<tr>
<td>Other Cognitive</td>
<td>Cognition</td>
<td>5.1 (b,c,h)</td>
</tr>
<tr>
<td>Depression</td>
<td>Emotional Well-Being</td>
<td>4.1 (a,d,e,l)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Emotional Well-Being</td>
<td>4.1 (b,g,j,n,o,p)</td>
</tr>
<tr>
<td>Control/Helplessness</td>
<td>Emotional Well-Being</td>
<td>4.1 (c,f,h,i)</td>
</tr>
<tr>
<td>Self-esteem</td>
<td>Emotional Well-Being</td>
<td>4.1 (k,m,q,r,s)</td>
</tr>
<tr>
<td>Social Interactions</td>
<td>Social Activities</td>
<td>6.1 (c,f,h)</td>
</tr>
<tr>
<td>Social Activities</td>
<td>Social Activities</td>
<td>6.1 (a,e) and 6.2</td>
</tr>
<tr>
<td>Stigma Item</td>
<td>Social Activities</td>
<td>6.1 (i)</td>
</tr>
<tr>
<td>Behavior</td>
<td>Behavior</td>
<td>7.1 (a,c,f,g,h,l,j,k,l,m,o,q,r,s,t)</td>
</tr>
<tr>
<td>General Health Item</td>
<td>General Health</td>
<td>8.1</td>
</tr>
<tr>
<td>Quality of Life Item</td>
<td>Quality of Life</td>
<td>9.1</td>
</tr>
</tbody>
</table>

Items within each subscale will be coded and linearly transformed, according to the methods of Sabaz et al., to a score of 0 to 100, where 0 represents the lowest or poorest category and 100 represents the highest level of functioning.

A subscale score is calculated for each subscale by computing the mean of the items within the subscale. An ‘Overall Quality of Life Score’ can be calculated by taking the mean of the subscale scores.

Individual items will be listed only. The subscale scores and the overall quality of life score, recorded at each visit, will be summarized, on a continuous scale, by treatment arm. The change from baseline will also be included.

The change from baseline to the end of treatment visit, for the overall quality of life score, and the attention/concentration, memory, language, other cognitive, social interactions and behavior subscale scores only, will be analyzed using analysis of covariance (ANCOVA). The model will include baseline and stratified age group as covariates and treatment arm as fixed factor.

The estimated least squares means, treatment difference, together with the 95% CIs and p-value will be presented. Exploratory analyses may also be performed on other subscale scores.
Missing data will be handled according to Section 5.1.1.2.1.

The QOLCE was to be completed for patients aged 2-18 years old only. The primary analysis will be based on all patients who have a completed questionnaire, regardless of age. Summaries and analyses will be repeated using questionnaires only from patients who were aged 2 to 18 years old at the time of informed consent.

The individual responses will not be listed, only the derived information for each derived score will be listed.

**Open-label Extension:**

Descriptive summaries described above for the blinded phase will be repeated for OLE visits.

### 5.5.3.2.5 Quality of Life in Epilepsy, Version 2 (19 Years and Above)

**Blinded Phase:**

The QOLIE-31-P is a survey of health-related quality of life for adults with epilepsy. It comprises 38 questions about health and daily activities and also includes questions designed to evaluate how much distress the patient feels about problems and worries related to epilepsy. The QOLIE-31-P will be administered to patients aged 19 years or older. Should the patient be unable to complete the QOLIE-31-P independently, it is permissible for their caregiver to assist.

The questionnaire consists of the following 7 subscales: energy, mood, daily activities, cognition, medication effects, seizure worry, and overall quality of life. Each subscale consists of a number of questions in addition to a ‘distress’ item. The raw score for each question and the ‘distress’ item are converted to a 0-100 score according to the scoring manual (higher scores reflecting greater well-being). The converted scores for each question within the subscale are then used to calculate a final subscale weighted score (higher scores reflect better quality of life; lower ones, worse quality of life) as follows:

\[(\text{Sum of converted scores for each question in the subscale} ÷ \text{Number of questions in the subscale}) \times \text{‘distress’ item converted score}\]

The total score (ranging from 0 to 100) is then calculated as:

\[(\text{Sum of all subscale weighted scores} ÷ \text{Sum of all subscale ‘distress’ item converted scores}) \times 100\]

Individual items will be listed only. The weighted subscale scores and the total score, recorded at each visit, will be summarized, on a continuous scale, by treatment arm. The change from baseline will also be included.

The change from baseline to the end of treatment visit, for the weighted subscale scores and the total score, will be analyzed using the same ANCOVA approach as specified in Section 5.5.3.2.4.

Missing data will be handled according to Section 5.1.1.2.2.

The QOLIE-31-P was to be completed for patients aged 19 years and above only. The primary analysis will be based on all patients who have a completed questionnaire, regardless of age. Summaries and analyses will be repeated using questionnaires only from patients who were aged 19 years or older at the time of informed consent.

The individual responses will not be listed, only the derived information for each derived score will be listed.
5.5.3.2.6 Physician Global Impression of Change

Blinded Phase:

The PGIC comprises the following questions to be rated on a 7-point scale:

- Please assess the change in the patient’s general functional abilities since Visit 3 (prior to the commencement of study medication).

The possible responses are: Very Much Improved; Much Improved; Slightly Improved; No Change; Slightly Worse; Much Worse; Very Much Worse.

The responses above are based on comparison with a brief description of the patient’s overall condition used as a memory aid from Visit 3.

Each response will be coded with a score from 1 to 7, where 1 = Very Much Improved, and 7 = Very Much Worse.

The PGIC response/score, recorded at each visit, will be summarized separately, on both a categorical and continuous scale, by treatment arm.

The score at the end of treatment visit and last visit (if different to the end of treatment) will be analyzed using ordinal logistic regression. Proportional odds modelling will be carried out by including treatment arm as a factor. The estimated odds ratio (GWP42003-P vs. placebo), 95% CI for the odds ratio, and the p-value testing the null hypothesis that the odds ratio is equal to 1, will be presented. Analysis performed at the last visit will be considered the primary analysis for this endpoint, with the analysis at the end of treatment visit considered a sensitivity analysis.

Should the proportional odds assumption not hold, i.e. if the p-value for the score test for proportional odds assumption is <0.05, then, as a sensitivity analysis, the scores will also be analyzed using a Cochran-Armitage trend test. This will be presented together with the results of the ordinal logistic regression.

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for OLE visits.

5.5.4 Exploratory Efficacy Endpoints

5.5.4.1 Composite Focal Seizure Score

Blinded Phase:

Composite focal seizure score will be calculated as the sum of:

- 1 × Number of focal motor seizures without impairment of consciousness or awareness.
- 2 × Number of focal seizures with impairment of consciousness or awareness.
- 3 × Number of focal seizures evolving to bilateral convulsive seizures.

Summaries and analyses of composite focal seizure score will be performed as per the primary endpoint (Section 5.5.2).

Sensitivity analyses will be performed on the ITT analysis set, repeating the above analysis, using data for only the maintenance period, titration period, and during each 4 weeks of the
maintenance period (Week 1 to 4, Week 5 to 8 and Week 9 to 12 of the 12 week maintenance period).

Analyses on the maintenance period, titration period and by each 4 weeks of the maintenance period will include only patients who have at least 7 days of seizure data within each period.

Open-label Extension:

Summaries will be performed for the OLE periods as described in the OLE portion of the primary endpoint section (Section 5.5.2).

5.5.4.2 Individual Seizure Types

Blinded Phase:

For each individual seizure type (focal motor seizures without impairment of consciousness or awareness, focal seizures with impairment of consciousness or awareness, focal seizures evolving to bilateral generalized convulsive seizures, tonic-clonic, tonic, clonic, atonic, absence, myoclonic and partial sensory seizures, and infantile or epileptic spasms), summaries will be performed as per the primary endpoint (Section 5.5.2). However, analyses will only be performed for the following seizure types:

- Focal motor seizures without impairment of consciousness or awareness;
- Focal seizures with impairment of consciousness or awareness;
- Focal seizures evolving to bilateral generalized convulsive seizures;
- Tonic-clonic; and
- Tonic.

Patients with no seizures during the baseline period, for a particular seizure type, will be excluded from the analysis of that seizure type.

Sensitivity analyses will be performed on the ITT analysis set, repeating the above analyses using data for only the maintenance period, titration period, and during each 4 weeks of the maintenance period (Week 1 to 4, Week 5 to 8 and Week 9 to 12 of the 12 week maintenance period).

Analyses on the maintenance period, titration period and by each 4 weeks of the maintenance period will include only patients who have at least 7 days of seizure data within each period.

Individual seizure type responders and freedom will also be summarized and analyzed using the methods described in Section 5.5.3.2.1, for the following seizure types only:

- Focal motor seizures without impairment of consciousness or awareness;
- Focal seizures with impairment of consciousness or awareness;
- Focal seizures evolving to bilateral generalized convulsive seizures;
- Tonic-clonic; and
- Tonic.

The summaries and analyses during the maintenance and titration periods and during each 4 weeks of the maintenance period will be produced. Patients with no corresponding seizures, for a particular seizure type, during the baseline period will be excluded from the analysis for that seizure type.

Open-label Extension:
Descriptive summaries described above for the blinded phase will be repeated for OLE periods.

5.5.4.3 Rescue Medication Use

Blinded Phase:

The number of days that rescue medication (RM) was taken since the previous visit will be collected throughout the trial at scheduled visits and safety telephone calls.

To standardize between patients, the total number of days RM was taken will be calculated as the sum of all reported records within a period. Hence, the average number of days RM was taken per 28 days within a period will be calculated as follows:

\[
\text{Average days RM taken per 28 days} = \frac{\text{Total number of days RM was taken during the period}}{\text{Number of days in the period}} \times 28
\]

This will be calculated for both the baseline period and treatment period. The number of days in a period will be calculated as the number of days from the visit prior to the first recorded value in the period to the day of the last recorded value in the period. The baseline period refers to the period between Visit 2 and Visit 3. The treatment period refers to the period between Visit 3 and Visit 10.

The number of days RM was taken per 28 days will be summarized by period and treatment arm. The change from the baseline period will also be included.

The change from the baseline period to the treatment period will be analyzed using an ANCOVA approach. The model will include the baseline period and stratified age group as covariates and treatment arm as fixed factor.

The estimated least squares means, treatment difference, together with the 95% CIs and p-value will be presented.

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for the OLE period. The OLE period refers to the period between Visit B1 and the last available visit in the OLE phase.

5.5.4.4 Status EPILEPTICUS

The number of episodes of status epilepticus will be collected daily via IVRS for the blinded phase and weekly via IVRS for the open-label extension.

The number of patients with status epilepticus will be presented for the baseline, treatment and OLE periods.

5.5.4.5 Subject/Caregiver Global Impression of Change in Seizure Duration

Blinded Phase:

The SGICSD and CGICSD comprise the following questions to be rated on a 3-point scale for each seizure type:

CGICSD:

- Since the patient started treatment, please assess the average duration of the patient’s seizures (comparing their condition now to their condition before treatment) using the scale below.

SGICSD:
• Since you started treatment, please assess the average duration of your seizures (comparing your condition now to your condition before treatment) using the scale below.

The 3 possible responses are:
- Decrease in average duration.
- No change in average duration.
- Increase in average duration.

The patient/caregiver will be asked to assess the average duration of seizures at Visit 3 (prior to commencement of IMP) as a memory aid for assessment further visits.

Each response will be coded with a score from 1 to 3, where 1 = Decrease in average duration, and 3 = Increase in average duration.

For each seizure type, the SGICSD and CGICSD will be summarized separately by treatment arm.

It is anticipated that only a small percentage of patients will complete the subject version of the questionnaire. Hence, no analyses will be performed for the SGICSD.

A combined score will be used as the primary analysis for this endpoint. The combined score will be defined as follows:
- If both a CGICSD and SGICSD are completed then the CGICSD will be used.
- If only a CGICSD is completed then the CGICSD will be used.
- If only a SGICSD is completed then the SGICSD will be used.

Proportional odd modelling will be carried out by including treatment arm and age group as factors. The estimated odds ratio (GWP42003-P vs. placebo), 95% CI for the odds ratio, and the p-value testing the null hypothesis that the odds ratio is equal to 1, will be presented.

Since this analysis uses a combination of caregiver and subject ratings, a sensitivity analysis will be performed using only the CGICSD score and using the same analyses as above.

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for OLE visits.

5.5.4.6 Vineland Adaptive Behavior Scales, Second Edition

Blinded Phase:

The Vineland-II is an individually administered instrument for assessing adaptive behaviors and consists of 4 adaptive behavior domains and a maladaptive behavior domain. The details of each domain are presented in Table 5.
## Table 5  Content Description of the Vineland-II

<table>
<thead>
<tr>
<th>Domains and Subdomains</th>
<th>Number of Items</th>
<th>Age Range (Years)</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adaptive Behavior Domains</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Communication Domain</td>
<td>99</td>
<td>≥0</td>
<td></td>
</tr>
<tr>
<td>Receptive</td>
<td>20</td>
<td>≥0</td>
<td>How the individual listens and pays attention, and what he or she understands</td>
</tr>
<tr>
<td>Expressive</td>
<td>54</td>
<td>≥0</td>
<td>What the individual says, how he or she uses words and sentences to gather and provide information</td>
</tr>
<tr>
<td>Written</td>
<td>25</td>
<td>≥3</td>
<td>What the individual understands about how letters make words, and what he or she reads and writes</td>
</tr>
<tr>
<td><strong>Daily Living Skills Domain</strong></td>
<td>109</td>
<td>≥0</td>
<td></td>
</tr>
<tr>
<td>Personal</td>
<td>41</td>
<td>≥0</td>
<td>How the individual eats, dresses and practices personal hygiene</td>
</tr>
<tr>
<td>Domestic</td>
<td>24</td>
<td>≥1</td>
<td>What household tasks the individual performs</td>
</tr>
<tr>
<td>Community</td>
<td>44</td>
<td>≥1</td>
<td>How the individual uses time, money, the telephone, the computer and job skills</td>
</tr>
<tr>
<td><strong>Socialization Domain</strong></td>
<td>99</td>
<td>≥0</td>
<td></td>
</tr>
<tr>
<td>Interpersonal Relationships</td>
<td>38</td>
<td>≥0</td>
<td>How the individual interacts with others</td>
</tr>
<tr>
<td>Play and Leisure Time</td>
<td>31</td>
<td>≥0</td>
<td>How the individual plays and uses leisure time</td>
</tr>
<tr>
<td>Coping Skills</td>
<td>30</td>
<td>≥1</td>
<td>How the individual demonstrates responsibility and sensitivity to others</td>
</tr>
<tr>
<td><strong>Motor Skills Domain</strong></td>
<td>76</td>
<td>≥0 to &lt;7</td>
<td>How the individual uses arms and legs for movement and coordination</td>
</tr>
<tr>
<td>Gross</td>
<td>40</td>
<td>≥0 to &lt;7</td>
<td>How the individual uses hands and fingers to manipulate objects</td>
</tr>
<tr>
<td>Fine</td>
<td>36</td>
<td>≥0 to &lt;7</td>
<td></td>
</tr>
<tr>
<td><strong>Maladaptive Behavior Domain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Maladaptive Behavior Index</strong></td>
<td>36</td>
<td>≥3</td>
<td>A composite of Internalizing, Externalizing, and Other types of undesirable behavior that may interfere with the individual’s adaptive functioning</td>
</tr>
<tr>
<td>Internalizing (Section A)</td>
<td>11</td>
<td>≥3</td>
<td></td>
</tr>
<tr>
<td>Externalizing (Section B)</td>
<td>10</td>
<td>≥3</td>
<td></td>
</tr>
<tr>
<td>Other (Section C)</td>
<td>15</td>
<td>≥3</td>
<td></td>
</tr>
<tr>
<td><strong>Maladaptive Behavior Critical Items</strong></td>
<td>14</td>
<td>≥3</td>
<td>More severe maladaptive behaviors that may provide clinically important information</td>
</tr>
</tbody>
</table>

For each subdomain, a raw score is calculated based on the responses to the individual items within the subdomain. For the maladaptive behavior index, the raw score is the sum of the 3 subdomain raw scores. Using the raw score and the patients' age the following are obtained:

- **v-Scale Score**: a type of standard score scale (standardized by age) to describe an individual's relative level of functioning. Ranging from a score of 1 to 24.
- **90% CI for the v-Scale Score**: a range of scores that has a certain likelihood of including the individual’s true score.
- Adaptive Level: a means to describe an individual's performance using terms that are nearly universal (Low, Moderately Low, Adequate, Moderately High, High).
  - For the maladaptive behavior index and maladaptive behavior subdomains the adaptive levels are: Average, Elevated or Clinically Significant.
- Age Equivalent: the age at which the raw score is average. Not applicable for the maladaptive behavior index and maladaptive behavior subdomains.

For each adaptive behavior domain, the sum of the v-scale scores of the subdomains is used along with the patients' age to obtain the following:
- Standard Score (standardized by age). Ranging from a score of 20 to 160.
- 90% CI for the domain standard score.
- Percentile Rank: the percentage of people whom the individual outperformed in his or her age group.
- Adaptive Level (Low, Moderately Low, Adequate, Moderately High, High).
- Stanine: whole number score ranging from 1 to 9 and representing a specific range of percentile ranks.

An adaptive behavior composite can then be obtained using the sum of the adaptive behavior domain standard scores (excluding the motor skills domain for patients ≥ 7 years of age). The same derived information as the adaptive behavior domain is obtained for the adaptive behavior composite.

For the maladaptive behavior index, all items within each section must be answered for a raw score to be calculated. If any of the items are missing then the maladaptive behavior index score will be missing.

For the adaptive behavior subdomains, the derivation of the raw score allows for up to 2 missing values or answers of “Don’t Know” within the items used for scoring. If there are more than 2 missing values or answers of “Don’t Know” then the raw score will not be calculated and the subdomain score, domain score and adaptive behavior composite score will be missing.

The adaptive levels corresponding to the v-scale scores and standard scores are presented in Table 6.

**Table 6  Adaptive Levels by v-Scale Scores and Standard Scores**

<table>
<thead>
<tr>
<th>Adaptive Level</th>
<th>v-Scale Score for Subdomains and Maladaptive Behavior Index</th>
<th>Standard Score for Domains and Adaptive Behavior Composite</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adaptive Behavior Domains</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1 to 9</td>
<td>20 to 70</td>
</tr>
<tr>
<td>Moderately Low</td>
<td>10 to 12</td>
<td>71 to 85</td>
</tr>
<tr>
<td>Adequate</td>
<td>13 to 17</td>
<td>86 to 114</td>
</tr>
<tr>
<td>Moderately High</td>
<td>18 to 20</td>
<td>115 to 129</td>
</tr>
<tr>
<td>High</td>
<td>21 to 24</td>
<td>130 to 160</td>
</tr>
<tr>
<td><strong>Maladaptive Behavior Domain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically Significant</td>
<td>21 to 24</td>
<td></td>
</tr>
<tr>
<td>Elevated</td>
<td>18 to 20</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>1 to 17</td>
<td></td>
</tr>
</tbody>
</table>

GWEP1521 Page 38 of 93 Confidential
The v-scale score from the 11 adaptive behavior subdomains, 3 maladaptive behavior subdomains and the maladaptive behavior index, and the standard score from the 4 adaptive behavior domains and the adaptive behavior composite, recorded at each visit, will be summarized, on a continuous scale, by treatment arm. The change from baseline will also be included.

The change from baseline to the end of treatment visit, for the 4 adaptive behavior domains, the adaptive behavior composite and the maladaptive behavior index only, will be analyzed using the same ANCOVA approach as specified in Section 5.5.3.2.4.

The adaptive level from the 11 adaptive behavior subdomains, 4 adaptive behavior domains, the adaptive behavior composite, the 3 maladaptive behavior subdomains and the maladaptive behavior index, recorded at each visit, will be summarized, on a categorical scale, by treatment arm.

The adaptive level from the 4 adaptive behavior domains, the adaptive behavior composite and the maladaptive behavior index only will be analyzed using ordinal logistic regression. Factors for treatment and age group will be included along with the baseline adaptive level as a covariate. The estimated odds ratios (GWP42003-P arms vs. placebo), 95% CI for the odds ratios, and the p-values testing the null hypothesis that the odds ratio is equal to 1, will be presented.

Each adaptive level for adaptive behavior will be coded with a score from 1 to 5, where 1 = Low, and 5 = High. Each adaptive level for the maladaptive behavior index will be coded with a score from 1 to 3, where 1 = Clinically Significant, and 3 = Average.

The individual responses within each domain will not be listed, only the derived information for each subdomain and domain will be listed.

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for OLE visits.

5.5.4.7 Wechsler Tests

Blinded Phase:

The Wechsler tests are age specific and will only be administered at a sub-group of centers that have the expertise to conduct the assessments. The age of the patient at entry is used when choosing the items to be administered. The following Wechsler Subtests will be used:

Age 2–6:

- Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition (WPPSI-4) Vocabulary and Matrix Reasoning

Age 6–Adult:

- Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-2) Vocabulary and Matrix Reasoning

The T scores (Vocabulary and Matrix Reasoning), scaled scores (Coding) and forward, backward, longest forward and longest backward scores (Digit Span) will be summarized by visit including the change from baseline.
The change from baseline will be analyzed using an ANCOVA approach. The model will include baseline and stratified age group as covariates and treatment arm as fixed factor. The estimated least squares means, treatment difference, together with the 95% CIs and p-value will be presented.

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for OLE visits.

5.5.4.8 Achenbach Child Behavior Checklists and Adult Behavior Checklist

Blinded Phase:

The Achenbach CBCL is a caregiver questionnaire assessing both behavioral and emotional symptoms in children. Depending on the patients’ age, 1 of 2 versions of the Achenbach CBCL is used. The CBCL/1½-5 is used for children 18 months old to 5 years and 11 months old. For patients ≥6 and ≤17 years old the CBDL/6-18 is used. An adult version of the checklist, the Achenbach ABCL (ABCL/18-59), is used for patients ≥18 and ≤59 years old.

The CBCL/1½-5 comprises of 100 items, the CBCL/6-18 comprises of 113 items and the ABCL/18-59 comprises of 123 items. Response options are 0=not true; 1=somewhat or sometimes true; 2=very true or often true. Similar items are grouped and summed to produce syndrome scale scores, which are further grouped into problem scales as specified in Table 7. Other scales for CBDL/6-18 and ABCL/18-59 are also derived.

Derivation instructions for the Achenbach scales are given in Appendix 5. For each questionnaire, the individual item responses will not be listed, only the raw scores for the scales given in Table 7 and Table 8 will be listed. For the Achenbach CBCL/1½-5, no scoring will be performed for the language development survey. For the Achenbach ABCL/18-59, no scoring will be performed for the spouse/partner functioning scale or the tobacco, alcohol and drugs substance use scales.

The derived raw scores for the syndrome scales and problem scales as indicated in Table 7, recorded at each visit, will be summarized, on a continuous scale, by questionnaire version and treatment arm. The change from baseline will also be included.

The change from baseline to the end of treatment visit, for the internalizing, externalizing and total problems scales only, will be analyzed for each of the questionnaire versions using the same ANCOVA approach as specified in Section 5.5.3.2.4.

The raw scores for other scales as indicated in Table 8 will also be summarized.

<table>
<thead>
<tr>
<th>Table 7</th>
<th>Achenbach CBCL and ABCL Syndrome and Problem Scales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Questionnaire Version</td>
<td>Problem Scales</td>
</tr>
<tr>
<td>CBCL/1½-5</td>
<td>Internalizing</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Externalizing</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>Anxious/Depressed</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>CBDL/6-18</td>
<td></td>
</tr>
<tr>
<td>Internalizing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Withdrawn/Depressed</td>
</tr>
<tr>
<td></td>
<td>Somatic Complaints</td>
</tr>
<tr>
<td>Externalizing</td>
<td>Rule-breaking Behavior</td>
</tr>
<tr>
<td></td>
<td>Aggressive Behavior</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Social Problems</td>
</tr>
<tr>
<td></td>
<td>Thought Problems</td>
</tr>
<tr>
<td></td>
<td>Attention Problems</td>
</tr>
<tr>
<td></td>
<td>Other Problems</td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>ABCL/18-59</td>
<td></td>
</tr>
<tr>
<td>Internalizing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anxious/Depressed</td>
</tr>
<tr>
<td></td>
<td>Withdraw</td>
</tr>
<tr>
<td></td>
<td>Somatic Complaints</td>
</tr>
<tr>
<td>Externalizing</td>
<td>Aggressive Behavior</td>
</tr>
<tr>
<td></td>
<td>Rule-breaking Behavior</td>
</tr>
<tr>
<td></td>
<td>Intrusive</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thought Problems</td>
</tr>
<tr>
<td></td>
<td>Attention Problems</td>
</tr>
<tr>
<td></td>
<td>Other Problems</td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
</tbody>
</table>

Table 8  Achenbach CBCL and ABCL Other Scales

<table>
<thead>
<tr>
<th>Questionnaire Version</th>
<th>Other Scales</th>
<th>Other Sub-Scales</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBDL/6-18</td>
<td>Total Competence</td>
<td>Activities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Social</td>
</tr>
<tr>
<td></td>
<td></td>
<td>School</td>
</tr>
<tr>
<td>ABCL/18-59</td>
<td>Friends</td>
<td>Critical Items</td>
</tr>
</tbody>
</table>

**Open-label Extension:**

Descriptive summaries described above for the blinded phase will be repeated for OLE visits.

**5.5.4.9  Social Communication Questionnaire**

**Blinded Phase:**

The current version of the SCQ will be completed by the caregiver for all patients above the age of 4 years with a mental age of at least 2 years. The scale assesses behavior over the most recent three month period using 40 questions, each to be answered ‘yes’ or ‘no’.

The answer to Item 1 ‘Is she/he now able to talk using short phrases or sentences?’ is not scored and is instead used to determine which of the remaining items relating to abnormal language will contribute to the total score. If the answer to Item 1 is ‘yes’, then the six items relating to abnormal language will be used and the total score will range from 0 to 39 points from items 2 to 40. If the answer to Item 1 is ‘no’ then the six items relating to abnormal language will not be used and the total score will range from 0 to 33 points from items 8 to 40 only.
For Items 2, 9, 19 and 20–40, ‘yes’ will be assigned a score of 0 and ‘no’ a score of 1. For all other items, ‘yes’ will be assigned a score of 1 and ‘no’ a score of 0. The total score is calculated by taking the sum of the scores for each item.

In addition to the total score, the following domain scores will be derived:

- Reciprocal Social Interaction: Items 9, 10, 19, 26-33, 36, 37, 39 and 40.
- Communication: Items 2-6, 20-25, 34 and 35.
- Restricted, Repetitive and Stereotyped Patterns of Behavior: Items 7, 8 and 11-16.

The total score and domain scores will be summarized by visit including the change from baseline. The change from baseline for each score will be analyzed using an ANCOVA approach. The model will include baseline and stratified age group as covariates and treatment arm as fixed factor. Sex will also be included as a covariate in the model only if the p-value of the estimate is <0.05.

The estimated least squares means, treatment difference, together with the 95% CIs and p-values will be presented.

The individual responses will not be listed, only the derived information for each derived score will be listed.

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for OLE visits.

5.5.4.10 Time to Baseline TSC-associated Seizure Frequency

Blinded Phase only:

Time to baseline TSC-associated seizure frequency is defined as the number of reported days in IVRS, from Day 1, that it takes for the cumulative number of TSC-associated seizures experienced to be greater than or equal to the number of seizures (per 28 days) experienced during the baseline period and will be calculated as:

\[
\text{Date criterion was achieved} - \text{Date of Day 1} - \text{Number of unreported days in IVRS between Day 1 and date criterion was achieved} + 1
\]

Patients who complete the trial without experiencing greater than or equal to the number of seizures (per 28 days) experienced during the baseline period, or who withdraw from the trial, will be censored at the earliest of:

- Day 99.
- The date of last dose as recorded on the ‘End of Treatment Study Outcome’ CRF page.

The exact day used for censoring will be the day obtained from above minus the number of unreported days in IVRS between Day 1 and the day obtained from above.

Time to baseline TSC-associated seizure frequency will be summarized on a continuous scale, by treatment arm, for patients in the ITT analysis set. The lower and upper quartiles will also be presented. The Kaplan-Meier estimates for the median time to baseline TSC-associated seizure frequency will be presented along with 95% CIs for the median and p-values from log-rank tests comparing each GWP42003-P arm with placebo. A Kaplan-Meier plot will also be produced.
The above will be repeated using Day 29 instead of Day 1 as the start day for counting the cumulative number of TSC-associated seizures.

5.5.5 Subgroup Analyses

To assess the degree of effect heterogeneity, effect modifier analyses are proposed, on the ITT analysis set, for the primary efficacy endpoint and the key secondary efficacy endpoint of ≥50% reduction in TSC-associated seizure frequency.

For the primary efficacy endpoint, the effect modifier analysis will be performed using the negative binomial regression analysis as described in Section 5.5.2. The model will be updated to include covariates for each level of the effect being tested (excluding a reference level), individually and with interactions with time, interactions with treatment arm and interactions with time and treatment. A separate model will be used for testing each effect. The treatment ratios (GWP42003-P vs. placebo), percent reduction and 95% confidence intervals will be presented for each level of the effect. In addition, the effect by time by treatment arm interaction p-value, testing the hypothesis that the effect level treatment ratios are homogeneous, will be presented.

For the key secondary efficacy endpoint of ≥50% reduction in TSC-associated seizure frequency, patients with a ≥50% reduction in seizure frequency will be modelled using logistic regression, including stratified age group and treatment arm as covariates. The model will also include covariates for each level of the effect being tested (excluding a reference level), individually and with interactions with treatment arm. A separate model will be used for testing each effect. The number and percent of responders, and odds ratios and 95% confidence intervals will be presented for each level of the effect. In addition, the effect by treatment arm interaction p-value, testing the hypothesis that the effect level odds ratios are homogeneous, will be presented.

The following effects will be tested:

- Age group (1-6 years, 7-11 years, 12-17 years and 18-65 years). Note: stratified age group will be removed as a covariate for this model.
- Sex (Male, Female).
- Region (US, Rest of the World).
- Clobazam use (Yes, No).
- Valproic acid use (Yes, No).
- Levitiracetam use (Yes, No).
- Vigabatrin use (Yes, No).
- Baseline average TSC-associated seizures per 28 days (≤ observed Tertile 1, > observed Tertile 1 to ≤ observed Tertile 2, > observed Tertile 2). The observed tertile values will be rounded to the nearest whole number.
- Number of concurrent AEDs (<3, ≥3).
- Number of prior AEDs (<5, ≥5).
- Number of prior and concurrent AEDs (<8, ≥8).

Effects of patients taking other AED types will also be tested if the overall frequency of patients taking the AED is >25%.

5.6 Safety Evaluation

5.6.1 Exposure to IMP

Blinded Phase:
Patients are required to take IMP twice daily (morning and evening). The first dose will be taken in the clinic on Day 1. The date of final dose in the treatment phase will be recorded on the CRF. The date of final dose, for patients who enter the taper period, will be recorded on the CRF at the end of taper visit.

The total number of dosing days in the treatment phase will be calculated as:

\[(\text{Date of last dose in the treatment phase} - \text{Date of Day 1}) + 1\]

The date of last dose in the treatment phase will be obtained from the CRF at the end of treatment visit.

Any missed doses during treatment should be recorded on the ‘IMP Missed Doses Log’ CRF page. The number of days with any missed doses and the number of days where trial medication was not taken in the AM nor PM will be summarized based on data in the treatment phase (Day 1 to end of treatment visit).

In addition, the number of days in which trial medication was taken at least once (AM or PM) will be summarized and calculated as:

Total number of dosing days – the number of days where trial medication was not taken in the AM nor PM

The number of days in which trial medication was taken both AM and PM will be summarized and calculated as:

Total number of dosing days – the number of days with any missed doses

The above summaries will be presented for all patients and repeated for patients who completed the treatment phase.

In addition, the expected daily volume of IMP to be administered during the treatment phase, once a patient has titrated to target dose, will be summarized by treatment.

The expected daily volume of IMP will be calculated as:

\[2 \times \left[ \frac{\text{Weight (kg) at Day 1}}{8} \right] \text{ and rounded to the nearest 0.1} \]

for patients randomized to the 25 mg/kg/day dose level and:

\[2 \times \left[ \frac{\text{Weight (kg) at Day 1}}{4} \right] \text{ and rounded to the nearest 0.1} \]

for patients randomized to the 50 mg/kg/day dose level.

Finally, IMP compliance will be summarized by treatment and calculated as:

\[100 \times \left( \frac{\text{Number of days IMP taken at least once} + \text{number of days IMP taken both AM and PM}}{2 \times \text{day of completion or withdrawal during the treatment period}} \right)\]

Open-label Extension:

The total number of dosing days will be calculated for the OLE and presented along with a categorical summary of patients whose largest dose was 25 mg/kg/day or less and patients whose largest dose was over 25 mg/kg/day during the OLE treatment phase.

5.6.2 Adverse Events

All reported AEs will be classified by system organ class (SOC), preferred term and lower level term using Version 19.1 of MedDRA.

Summaries will be presented by treatment arm as well as SOC and preferred term.
A blinded phase treatment emergent AE (TEAE) is defined as an AE with a start date on or after the first dose of IMP during the blinded phase up to and including the date of first dose of the OLE phase (OLE Day 1). An OLE phase TEAE is defined as an AE with a start date on or after the OLE Day 1. If an AE has a partial start date and it is unclear from the partial date (or the stop date) whether the AE started prior to or post first dose of IMP then the AE will be considered treatment emergent and if it is unclear which phase the event started, it will be assigned to both phases. If the start date of the AE is the same as the date of first dose of IMP from the blinded phase and the plausible relationship to IMP is marked on the CRF as “Prior to study medication” then the AE will not be considered treatment emergent.

An AE will be considered treatment-related if the plausibility relationship to trial medication is recorded on the CRF as ‘yes’. If the data on plausibility relationship to trial medication is missing then the AE will be considered treatment-related.

An AE will be considered leading to permanent discontinuation of IMP if the action taken with IMP is recorded on the CRF as ‘study medication stopped’ or the outcome is recorded on the CRF as ‘patient died’.

An AE will be considered leading to IMP dose reduction excluding permanent discontinuation if the action taken with IMP is recorded on the CRF as ‘dose reduced’, ‘dose reduced temporarily’ or ‘study medication interrupted’.

An AE will be considered leading to temporary IMP dose reduction if the action taken with IMP is recorded on the CRF as ‘dose reduced temporarily’.

An AE will be considered leading to permanent IMP dose reduction excluding permanent discontinuation if the action taken with IMP is recorded on the CRF as ‘dose reduced’.

An AE will be considered fatal if the outcome is recorded on the CRF as ‘patient died’.

The following summaries will be generated separately for the blinded and OLE phase (counts are by patient unless specified otherwise):

- Overall summary of AEs, including number of patients reporting each of: TEAEs, treatment related TEAEs, TEAEs leading to withdrawal, treatment related TEAEs leading to withdrawal, serious TEAEs, treatment related serious TEAEs.
- Summary of TEAEs.
- Summary of TEAEs by event.
- Summary of treatment-related TEAEs.
- Summary of treatment-related TEAEs by event.
- Summary of TEAEs by maximal severity.
- Summary of TEAEs by sex.
- Summary of serious TEAEs.
- Summary of serious TEAEs by event.
- Summary of non-serious TEAEs.
- Summary of non-serious TEAEs by event.
- Summary of treatment-related serious TEAEs.
- Summary of treatment-related serious TEAEs by event.
- Summary of TEAEs leading to permanent discontinuation of IMP.
• Summary of treatment-related TEAEs leading to permanent discontinuation of IMP.
• Summary of TEAEs leading to IMP dose reduction excluding permanent discontinuation (by resolution and overall).
• Summary of treatment-related TEAEs leading to IMP dose reduction excluding permanent discontinuation (by resolution and overall).
• Summary of TEAEs leading to temporary IMP dose reduction (by resolution and overall).
• Summary of treatment-related TEAEs leading to temporary IMP dose reduction (by resolution and overall).
• Summary of TEAEs leading to permanent IMP dose reduction excluding permanent discontinuation (by resolution and overall).
• Summary of treatment-related TEAEs leading to permanent IMP dose reduction excluding permanent discontinuation (by resolution and overall).
• Summary of fatal TEAEs.
• Summary of TEAEs by time of first onset of AE.
• Summary of TEAEs by time to AE resolution.
• Summary of TEAEs reported in ≥2% of patients (after rounding) in the GWP42003-P treatment arms and where the incidence is greater than the placebo treatment arm.
• List of patients experiencing TEAEs by SOC and preferred term.
• Summary of pre-treatment AEs (blinded phase only).

For the summary of TEAEs by maximal severity, for each patient, the worst severity recorded by preferred term, SOC and overall will be used for summary purposes. If severity is missing, the worst case (severe) will be assumed.

For summaries by resolution, AEs with an outcome of ‘recovered’ or ‘recovered with sequelae’ will be summarized as ‘Resolved’ and AEs with an outcome of ‘continuing’, ‘patient died’ or those with a missing outcome will be summarized as ‘Not resolved’.

For the summary of TEAEs by time of first onset of AE, data will be summarized under the following categories:

• Weeks 1 to 2 (Day 1 to 14).
• Weeks 3 to 4 (Day 15 to 28).
• Weeks 5 to 8 (Day 29 to 56).
• Weeks 9 to 12 (Day 57 to 84).
• >12 weeks (> Day 84).

The time to first onset of AE will be calculated for TEAEs as:

\[ \text{Start date of AE} - \text{Date of first dose of IMP} + 1 \]

If patients have multiple occurrences of an AE then the AE will be counted once for the first occurrence only. Percentages will be based on the number of patients in the safety analysis set who have a visit or follow-up call within each time period above.
For the summary of TEAEs by time to AE resolution, data will be summarized under the following categories:

- 1 week (≤7 days).
- 2 weeks (8 to 14 days).
- 3 weeks (15 to 21 days).
- 4 weeks (22 to 28 days).
- >4 weeks (>28 days).
- Ongoing (for AEs not resolved).

The time to AE resolution will be calculated for TEAEs as:

\[
\text{Stop date of AE} - \text{Start date of AE} + 1
\]

If patients have multiple occurrences of an AE then the AE will be counted once for the occurrence with the longest time to AE resolution. However, if any of the AEs are not resolved then the AE will be counted once within the ‘Ongoing’ category.

The start and stop day of the AE relative to the first dose of IMP (as recorded on the CRF) will be calculated as per Section 5.1.2. For partial dates, if it is clear from the partial date that the start/stop day was prior to the first dose of IMP, then ‘pre’ will be listed, similarly if it is clear that the event was post the first dose of IMP then ‘post’ will be listed as the start/stop day as appropriate.

All AEs will be listed. Listings will include the start and stop day of the AE, a flag for treatment emergence, and limited demographic information about the patient (age, sex, race and weight at screening). A separate listing will be provided for pre-treatment AEs, serious AEs and events of special interest (see Appendix 1).

### 5.6.3 Clinical Laboratory Evaluation

#### 5.6.3.1 Hematology and Biochemistry

Summaries will be presented by treatment arm for each laboratory parameter at each visit. Change from baseline to each post-baseline visit will also be presented.

If values for any of the parameters are below or above the limit of quantification of the assay (BLQ or ALQ), then they will be included in the summary tables at the BLQ or ALQ thresholds. However, for estimated creatinine clearance, results >60 are reported only as ‘>60’. Hence, estimated glomerular filtration rate (eGFR) will be calculated as:

For patients who are ≥18 years at screening, the Cockcroft-Gault equation will be used:

\[
eGFR \text{ (mL/min)} = \frac{[(140 - \text{age}) \times \text{weight} \times k]}{\text{serum creatinine}}
\]

where age is measured in years, weight is measured in kg, \(k = 1.23\) if male, \(k = 1.04\) if female and serum creatinine is measured in μmol/L. eGFR will be indexed to body surface area (BSA) using the following formula:

\[
eGFR \text{ (mL/min/1.73m2)} = eGFR \text{ (mL/min)} \times 1.73/\text{BSA}
\]

where BSA is based on the Du Bois and Du Bois formula:

\[
\text{weight} 0.425 \times \text{height} 0.725 \times 0.007184
\]

where weight is measured in kg and height is measured in cm.
For patients who are <18 years at screening, the revised Schwartz estimate will be used:

\[
(36.2 \times \text{height}) / \text{serum creatinine}
\]

where height is measured in cm and serum creatinine is measured in μmol/L. When available, enzymatic serum creatinine will be used. Otherwise, the Jaffe serum creatinine will be used. If height or weight is missing at the collection date, then the closest value to the sample date will be used. If there is more than one height or weight value on the same day or 2 height or weight values equally distant from the collection date, then the mean will be used. The eGFR will be summarized separately for each method.

Where laboratory samples are repeated, the baseline value is defined as the final recorded value prior to the first dose of IMP.

Shift tables for hematology and biochemistry parameters will be constructed, based upon normal ranges and GW toxicity limits (See Section 8), to determine the categorical shifts from baseline to each post-baseline visit. Values will be categorized as ‘Normal’, ‘Low’ or ‘High’ based on normal ranges and ‘Toxically Low’, ‘Toxically Normal’ or ‘Toxically High’ based on GW toxicity limits.

For eGFR, results will be assigned to the following grades:

- Normal: >60 ml/min/1.73 m²
- Grade 1: 60 ml/min/1.73 m²
- Grade 2: ≥30 and <60 ml/min/1.73 m²
- Grade 3: ≥15 and <30 ml/min/1.73 m²
- Grade 4: <15 ml/min/1.73 m²

A separate shift table will be produced for eGFR based upon the above grades to determine the categorical shifts from baseline to each post-baseline visit.

For the blinded phase, scatter plots will be produced for each laboratory parameter presenting the maximum post baseline result divided by the upper limit of normal (ULN) on the Y-axis, and the baseline result divided by the ULN on the X-axis. However, for prothrombin international normalized ratio (INR), both axes will present the raw results rather than dividing by ULN.

An additional table will be produced for the blinded phase only, summarizing the number of patients meeting the following criteria:

- Alanine aminotransferase (ALT) > 1×ULN at baseline
- Aspartate aminotransferase (AST) > 1×ULN at baseline
- AT > 1×ULN at baseline
- Treatment emergent ALT > 3×ULN, > 5×ULN and > 8×ULN
- Treatment emergent AST > 3×ULN, > 5×ULN and > 8×ULN
- Treatment emergent AT > 3×ULN, > 5×ULN and > 8×ULN
- Treatment emergent AT > 3×ULN and either bilirubin > 2×ULN or INR > 1.5

where AT is AST or ALT, and treatment emergent is defined as criteria not met at baseline but met at any time post-baseline. The above will be summarized overall and for the following subgroups:

- Sex (Male, Female).
- Valproic acid use (Yes, No).
- Clobazam use (Yes, No).
- Valproic acid use and Clobazam use (Yes/Yes, Yes/No, No/Yes, No/No).
- Patients taking 3 or more current AEDs.
- Patients taking 4 or more current AEDs.

A separate table will be produced, by treatment arm and visit, presenting the incidence of patients with urinalysis or blood results indicative of a medical condition at Visit 1 and indicative of an adverse event after Visit 1.

All laboratory data will be listed; listings will include limited demographic information about the patient (age, sex, race and weight at baseline). Abnormal laboratory values will be listed separately.

5.6.3.2 Urinalysis

Urinalysis is assessed, using dipsticks, at the same visits as biochemistry and hematology. Urinalysis results will be listed only.

5.6.3.3 Pregnancy Test and Urine THC Screen

Serum pregnancy test results and urine THC screen results will be summarized by treatment arm and visit.

5.6.4 Vital Signs, Other Physical Findings and Other Safety Data

5.6.4.1 Vital Signs

At Visit 1, 3 and B3, systolic and diastolic blood pressure are collected in the sitting, supine and standing positions. At all other visits, systolic and diastolic blood pressure are collected in the sitting position only.

Summaries will be presented by treatment arm for each vital sign parameter at each visit. Change from baseline to each post-baseline visit will also be presented.

Body mass index will be calculated, for each visit in which height and weight are recorded, as:

\[
\text{Weight (kg)} \div \text{height (m)}^2
\]

A separate table will be produced, by treatment arm and visit, presenting the incidence of patients with vital signs indicative of a medical condition at Visit 1 and indicative of an adverse event after Visit 1.

Based on the criteria presented in Section 8, clinically significant changes from baseline in vital signs measurements and other defined flagged values will be identified at each visit. The number of patients with a clinically significant change from baseline will be summarized by parameter, visit and treatment arm. The number of patients with at least one post-baseline flagged vital sign parameter value will be summarized by parameter, flagged criteria and treatment arm for the blinded phase and repeated for the OLE phase.
5.6.4.2 Electrocardiogram

Summaries will be presented by treatment arm for ventricular rate, PR interval, QRS duration, QT interval and QTcB, at each visit. Change from baseline to each post-baseline visit will also be presented.

A separate table will be produced, by treatment arm and visit, presenting the incidence of patients with an ECG indicative of a medical condition at Visit 1 and indicative of an adverse event after Visit 1.

Based on the criteria presented in Section 8, defined flagged values will be identified at each visit. The number of patients with at least one post-baseline flagged ECG parameter value will be summarized by parameter, flagged criteria and treatment arm for the blinded phase and repeated for the OLE phase.

5.6.4.3 Physical Examination

Any relevant findings at screening are included as part of the patient's medical history. Any changes seen after screening that are indicative of an AE are to be recorded as such on the AE form and included as part of the AE summaries.

Additionally, height and weight are recorded as part of the physical examination. Height and weight will be summarized and listed together with the vital signs parameters.

Incidence of patients with a physical examination indicative of a medical condition at Visit 1 and indicative of an adverse event after Visit 1 will be summarized by treatment arm and visit.

5.6.4.4 Columbia-Suicide Severity Rating Scale

The C-SSRS is completed for patients who are 6 years and older and capable of understanding and answering the questions, in the investigator's opinion. Questions are asked on suicidal behavior, suicidal ideation and intensity of ideation. At the screening visit, questions are in relation to lifetime experiences and all subsequent questioning in relation to the last assessment.
The following C-SSRS data will be summarized by treatment arm at each visit for patients in the safety analysis set:

- Incidence of the following suicidal ideation:
  - Wish to be dead.
  - Non-specific active suicidal thoughts.
  - Active suicidal ideation with any methods (not plan) without intent to act.
  - Active suicidal ideation with some intent to act, without specific plan.
  - Active suicidal ideation with specific plan and intent.

- Incidence of the following suicidal behavior:
  - Actual attempt.
  - Interrupted attempt.
  - Aborted attempt.
  - Preparatory acts or behavior.
  - Suicidal behavior.
  - Completed suicide.

5.6.4.5 Inpatient Hospitalizations due to Epilepsy

The number of inpatient epilepsy-related hospitalizations since the previous visit are recorded at every visit starting from Visit 2.

The number of patients with inpatient epilepsy-related hospitalizations will be presented by visit, including OLE visits.

5.6.4.6 Growth and Development

IGF-1 levels will be analyzed as part of the clinical laboratory testing. IGF-1 levels will be summarized on a continuous scale, including change from baseline, by treatment arm.

For the blinded phase only, change from baseline to the end of treatment visit for IGF-1 levels will also be plotted against the Tanner Stages, weight, and height recorded at baseline.

The pubic hair growth (both sexes), genital (males only) and breast (females only) development of all adolescent patients (i.e., 10 to less than 18 years of age at the time of signing the informed consent form, or earlier if clinically indicated by onset of menarche or other signs of precocious puberty) will be assessed using Tanner Staging. The patients will undergo a discreet physical examination and be assigned a value under each category of Pubic Hair Growth (both sexes), Genitals (male patients only), and Breasts (female patients only).

Tanner Stages will be summarized on a categorical scale, by treatment arm.

5.6.4.7 Menstruation

Menstruation details will be summarized as appropriate, including any changes in normal cycles, by treatment arm.

5.7 Other Measures

5.7.1 Concomitant Medication

A medication will be considered concomitant for each phase if it has a start date on or after the first dose of IMP for the corresponding phase or if it was started prior to the first dose of IMP and was ongoing. If a medication has a partial or missing start/stop date and it is unclear from the date whether the medication was taken after the first dose of IMP then it will be considered concomitant.

For summaries and listings of medications the following approach will be used to determine the Anatomical Therapeutic Chemical (ATC) term to be presented:

- If coded to level 4 then the level 4 coded term will be presented.
- If coding is not performed at level 4 but level 3 coding is present, then level 3 coded term will be presented.
- If coding is not performed at level 3 but level 2 coding is present, then the level 2 coded term will be presented.
- If coding is not performed at level 2 but level 1 coding is present, then the level 1 coded term will be presented.

Summaries of each of the following by ATC term and preferred term will be summarized by absolute counts (n) and percentages (%), separately for the blinded and OLE phase (unless stated otherwise):

- History of AEDs (blinded phase only);
- Concomitant AEDs;
- Concomitant rescue medications; and
- Other concomitant medications.

The ATC term, preferred term, reported generic name and reported brand name will be listed.

An additional summary table will be produced for concomitant antiepileptic therapies, displaying the number and percentage of patients with a vagus nerve stimulation device or on a ketogenic diet.

The start day and stop day will be included in the listing according to Section 5.1.2. If the date is partial and the exact day is unknown then the text ‘pre’ or ‘post’ will replace the start or stop day if it is clear from the partial date that the medication started or stopped prior to or after the first dose of IMP.

### 5.7.2 Pharmacokinetics of CBD and its Major Metabolites

Samples for PK analysis are taken on Visit 3 (first dose, Day 1) and Visit 10 (last maintenance dose of the blinded phase, Day 113) for patients weighing more than 20 kg. For patients recruited under Protocol Version 2, PK samples were taken at the following time-points:

- Prior to administration of IMP, ≤0.0 hours pre-dose on Visit 3 or C\text{trough} at steady state (Visit 10).
- ≥4.0 hours to ≤5.0 hours.
- ≥6.0 hours to ≤7.0 hours.
- ≥8.0 hours to ≤10.0 hours, for patients 18 years or older.
Patients recruited under Protocol Version 3 onwards, PK samples were taken at the following time-points:

- Prior to administration of IMP, ≤ 0.0 hours pre-dose on Visit 3 or C_{\text{trough}} at steady state (Visit 10).
- ≥ 2.0 hours to ≤ 3.0 hours.
- ≥ 4.0 hours to ≤ 6.0 hours.
- ≥ 8.0 hours to ≤ 10.0 hours, for patients 18 years or older.

The nominal mid-point time of 0, 2.5, 4.5, 5, 6.5 and 9 hours will be used for summaries of plasma concentrations. Plasma concentrations and PK parameters will be summarized showing the number of non-missing values (n), arithmetic mean, standard deviation, coefficient of variation (%), median, minimum and maximum. Where samples are reported as BLQ, a value of zero will be used in the summaries. Summary statistics will be presented to 3 significant figures.

Where data allow, the PK parameter AUC_{0-t}, will be derived at each visit by the PK vendor. A dose-normalized AUC_{0-t} will be calculated as AUC_{0-t} divided by the randomized dose per administration (12.5 or 25 mg/kg). This will include Visit 3, for consistency, where the first dose of IMP will be 2.5 mg/kg.

Plasma concentrations of CBD and its major metabolites 7-hydroxy-CBD (7-OH-CBD) and 7-carboxy-CBD (7-COOH-CBD) will be summarized by nominal mid-point time, visit and GWP42003-P arm. In addition, a dot plot of plasma concentrations for each patient, by nominal mid-point time will be created for each visit and GWP42003-P arm. The arithmetic mean will be highlighted on the plot. Additionally, a line plot of the arithmetic mean plasma concentration will be created with standard error bars by nominal mid-point time for each visit and GWP42003-P arm. These plots will be presented both a linear and semi-logarithmic scale for plasma concentration.

AUC_{0-t} and dose normalized AUC_{0-t}, for CBD and its major metabolites 7-OH-CBD and 7-COOH-CBD, will be summarized by visit and GWP42003-P arm. In addition, the ratio of 7-OH-CBD AUC_{0-t} to CBD AUC_{0-t} and the ratio of 7-COOH-CBD AUC_{0-t} to CBD AUC_{0-t} will be summarized. Box plots of AUC_{0-t} will be produced comparing visit on the x-axis, by parent and metabolite, and GWP42003-P arm. This will be repeated with parent and metabolite on the x-axis, by visit and GWP42003-P arm. Summaries and plots of AUC_{0-t} will be repeated by stratified age group.

Plasma concentration and AUC_{0-t} summaries may exclude individual time-points or visits for patients deemed to meet certain criteria that could affect exposure. These criteria include:

- Patients vomiting on or 1 day prior to the PK visit.
- Missed doses prior to the PK visit.
- IMP dose reduction.
- Cases of severe diarrhoea.
- Use of disallowed concomitant medication.

All exclusion will be detailed in a separate document finalized prior to unblinding. All data will be listed with data excluded from summaries flagged along with the reason for exclusion.
5.7.3 Plasma Concentrations of Concomitant AEDs

Blood sampling for AEDs will be performed at Visit 3 (Day 1), Visit 5, Visit 7, Visit 9 and Visit 10 (end of treatment) of the blinded phase. For each AED, plasma concentrations will be summarized by treatment arm at each visit for patients in the safety analysis set.

5.7.4 Study Medication Use and Behavior Survey

This form consists of 18 questions regarding the use of the IMP. The trained investigator or trial coordinator will complete this survey as an interview with the patient/caregiver at the final dosing visit.

The form will be completed for all patients 12 years of age and older in the trial.

Each question will be summarized, on a categorical scale, by treatment arm. Percentages will be based on the number of patients completing the survey, in each treatment arm. The summary will be presented separately for all patients with a completed form and patients 12 years of age and older.

5.7.5 Supplemental Drug Accountability Form

This form consists of 7 questions regarding various aspects of drug accountability and patient usage. It is completed as part of an interview with the patient/caregiver when a triggering drug accountability discrepancy is identified.

The triggering drug accountability discrepancies are as follows:

- Missing bottle(s).
- Compliance issues where one or more bottles are used compared to what was the expected use, according to the IVRS report and paper diary.
- Returned IMP supply with evidence of tampering.
- Greater than the target daily dose as recorded in the IVRS report and paper diary.

The number of patients with a completed form will be summarized separately for the blinded phase and OLE phase. The summary will be presented separately for all patients with a completed form and patients 12 years of age and older.

5.7.6 Supplemental Adverse Event Form

This form consists of 15 questions regarding the AE and use of IMP. It is completed as part of an interview with the patient/caregiver when a triggering AE of interest is reported.

The categories for triggering AEs of interest are:

- Euphoria or inappropriate elation.
- Inappropriate laughter or exhilaration.
- Mood changes.
- Drunk, high or intoxicated.
- Hallucinations (visual or auditory), dissociations, disorientation, agitation.
- Disturbance in cognition, memory, or attention.
- Drug abuse.
- Drug withdrawal or drug withdrawal syndrome.
- Addiction.
- Overdose.
- Misuse of IMP.
- Thoughts of suicide, attempted suicide or suicide.
The number of patients with a completed form will be summarized separately for the blinded phase and OLE phase. The summary will be presented separately for all patients with a completed form and patients 12 years of age and older.

5.7.7 Site Classification Form

The investigator reviews the applicable Supplemental Adverse Event Form or Supplemental Drug Accountability Form, and then completes a Site Classification Form. For each Supplemental Adverse Event Form or Supplemental Drug Accountability Form completed, there should be an associated Site Classification Form.

The Site Classification Form requires the investigator to assign the finding to an appropriate classification and then to also assign the possible relationship to the IMP. The investigator is also required to indicate the level of the certainty of the classification.

The number of patients with a completed form a will be summarized, along with the form associated to, separately for the blinded phase and OLE phase. The summary will be presented separately for all patients with a completed form and patients 12 years of age and older.

5.7.8 IVRS Compliance

For the blinded phase only, the number of unreported days in IVRS, during the baseline and treatment periods, will be summarized, on a continuous and categorical scale, by treatment arm for patients in the ITT analysis set. For the summary on a continuous scale, the lower and upper quartiles will also be presented.

The percentage IVRS compliance, during the baseline and treatment periods, will also be summarized, on a continuous and categorical scale, and calculated as:

\[
\left( \frac{\text{Number of reported days in IVRS}}{\text{Number of reported days in IVRS} + \text{Number of unreported days in IVRS}} \right) \times 100
\]
5.8 Changes in the Conduct of the Trial or Planned Analysis

During the OLE, seizure counts are collected every 7 days rather than daily. Hence, the endpoint of TSC-associated seizure free days has been defined for the blinded phase only. The endpoint of number of patients experiencing a >25% worsening, –25 to +25% no change, 25–50% improvement, 50–75% improvement or >75% improvement in convulsive seizures from baseline has been updated to the following:

- Number of patients experiencing a >25% increase, ≥0 to ≤25% increase, >0 to <25% reduction, ≥25 to <50% reduction, ≥50 to <75% reduction or ≥75% reduction in convulsive seizures from baseline.

6. REFERENCES


2 QOLIE Development Group. Scoring Manual for the QOLIE-31-P: Patient-Weighted Quality of Life in Epilepsy (v2).

7. AMENDMENTS

Notable changes to the SAP that were completed prior to unblinding, are given below. Minor changes, clarifications and corrections are not listed.

<table>
<thead>
<tr>
<th>Date</th>
<th>Section</th>
<th>Description of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>24Apr2019</td>
<td>5.5.1</td>
<td>The hierarchy for analysis was updated to be consistent with protocol version 8, dated 23rd April 2019.</td>
</tr>
</tbody>
</table>
8. ATTACHMENTS AND APPENDICES

Appendix 1  Adverse Events of Special Interest – Abuse Liability

<table>
<thead>
<tr>
<th>Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug withdrawal convulsions</td>
</tr>
<tr>
<td>Drug withdrawal headache</td>
</tr>
<tr>
<td>Drug withdrawal maintenance therapy</td>
</tr>
<tr>
<td>Drug withdrawal syndrome</td>
</tr>
<tr>
<td>Drug withdrawal syndrome neonatal</td>
</tr>
<tr>
<td>Drug rehabilitation</td>
</tr>
<tr>
<td>Rebound effect</td>
</tr>
<tr>
<td>Steroid withdrawal syndrome</td>
</tr>
<tr>
<td>Withdrawal arrhythmia</td>
</tr>
<tr>
<td>Withdrawal syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug abuse and dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine dysregulation syndrome</td>
</tr>
<tr>
<td>Drug abuse</td>
</tr>
<tr>
<td>Drug abuser</td>
</tr>
<tr>
<td>Drug dependence</td>
</tr>
<tr>
<td>Drug dependence, antepartum</td>
</tr>
<tr>
<td>Drug dependence, postpartum</td>
</tr>
<tr>
<td>Intentional drug misuse</td>
</tr>
<tr>
<td>Intentional overdose</td>
</tr>
<tr>
<td>Maternal use of illicit drugs</td>
</tr>
<tr>
<td>Neonatal complications of substance abuse</td>
</tr>
<tr>
<td>Polysubstance dependence</td>
</tr>
<tr>
<td>Substance abuse</td>
</tr>
<tr>
<td>Substance abuser</td>
</tr>
<tr>
<td>Accidental overdose</td>
</tr>
<tr>
<td>Dependence</td>
</tr>
<tr>
<td>Disturbance in social behaviour</td>
</tr>
<tr>
<td>Drug administered at inappropriate site</td>
</tr>
<tr>
<td>Drug detoxification</td>
</tr>
<tr>
<td>Drug diversion</td>
</tr>
<tr>
<td>Drug level above therapeutic</td>
</tr>
<tr>
<td>Drug level increased</td>
</tr>
<tr>
<td>Drug screen</td>
</tr>
<tr>
<td>Drug screen positive</td>
</tr>
<tr>
<td>Drug tolerance</td>
</tr>
<tr>
<td>Drug tolerance decreased</td>
</tr>
<tr>
<td>Drug tolerance increased</td>
</tr>
<tr>
<td>Medication overuse headache</td>
</tr>
<tr>
<td>Narcotic bowel syndrome</td>
</tr>
<tr>
<td>Needle track marks</td>
</tr>
<tr>
<td>Overdose</td>
</tr>
<tr>
<td>Prescribed overdose</td>
</tr>
<tr>
<td>Prescription form tampering</td>
</tr>
<tr>
<td>Substance use</td>
</tr>
<tr>
<td>Substance-induced mood disorder</td>
</tr>
<tr>
<td>Substance-induced psychotic disorder</td>
</tr>
<tr>
<td>Toxicity to various agents</td>
</tr>
</tbody>
</table>
Appendix 2  Ranges for Clinically Significant Changes and Other Defined Flagged Values in Vital Signs

The range of values that will be used to identify clinically significant changes in vital signs parameters (See Section 5.6.4.1) are presented in Table 9.

Table 9  Ranges for Clinically Significant Changes in Vital Signs

<table>
<thead>
<tr>
<th>Vital Sign</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting Systolic BP</td>
<td>Change: &lt; -20, &gt; 20</td>
</tr>
<tr>
<td>Sitting Diastolic BP</td>
<td>Change: &lt; -10, &gt; 10</td>
</tr>
<tr>
<td>Pulse Rate</td>
<td>Change: &lt; -10, &gt; 10</td>
</tr>
<tr>
<td>Weight</td>
<td>Percent Change: ≤ -7, ≥ 7</td>
</tr>
</tbody>
</table>

Defined flagged values that will be used to identify low or high vital signs parameters (See Section 5.6.4.1) are presented in Table 10.

Table 10  Other Defined Flagged Values for Vital Signs

<table>
<thead>
<tr>
<th>Vital Sign</th>
<th>Flag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting Systolic BP</td>
<td>&lt; 90, &gt; 140, &gt; 160</td>
</tr>
<tr>
<td>Sitting Diastolic BP</td>
<td>&lt; 50, &gt; 90, &gt; 100</td>
</tr>
<tr>
<td>Pulse Rate</td>
<td>&lt; 60, &gt; 100</td>
</tr>
<tr>
<td>Temperature</td>
<td>&gt; 38.0, &lt; 36.0</td>
</tr>
<tr>
<td>Respiratory Rate</td>
<td>&lt; 12, &gt; 20</td>
</tr>
</tbody>
</table>
Appendix 3  Defined Flagged Values in ECG Parameters

Defined flagged values that will be used to identify low or high ECG parameters (See Section 5.6.4.2) are presented in Table 11.

Table 11  Defined Flagged Values for ECG Parameters

<table>
<thead>
<tr>
<th>ECG Parameter</th>
<th>Flag</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc</td>
<td>&gt; 450, &gt; 480, &gt; 500</td>
</tr>
</tbody>
</table>
Appendix 4 Toxicity Criteria for Laboratory Parameters

The toxicity criteria that will be used to identify abnormal laboratory parameters are presented in Table 12 and
Table 13.

**Table 12  Toxicity Criteria for Biochemistry Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Toxicity Decrease</th>
<th>Toxicity Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloride</td>
<td>( \leq 0.96xLL )</td>
<td>( \geq 1.04xUL )</td>
</tr>
<tr>
<td>Calcium</td>
<td>( \leq 0.89xLL )</td>
<td>( \geq 1.16xUL )</td>
</tr>
<tr>
<td>Sodium</td>
<td>( \leq 0.96xLL )</td>
<td>( \geq 1.04xUL )</td>
</tr>
<tr>
<td>Potassium</td>
<td>( \leq 0.90xLL )</td>
<td>( \geq 1.10xUL )</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>( \leq 3.2 )</td>
<td>( \geq 16 )</td>
</tr>
<tr>
<td>Phosphate</td>
<td>( \leq 0.79xLL )</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>( \leq 0.85xLL )</td>
<td>( \geq 1.6xUL )</td>
</tr>
<tr>
<td>AST</td>
<td></td>
<td>( \geq 3xUL )</td>
</tr>
<tr>
<td>ALT</td>
<td></td>
<td>( \geq 3xUL )</td>
</tr>
<tr>
<td>Lactate Dehydrogenase</td>
<td></td>
<td>( \geq 2.6xUL )</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td></td>
<td>( \geq 2xUL )</td>
</tr>
<tr>
<td>Gamma GT</td>
<td></td>
<td>( \geq 2.6xUL )</td>
</tr>
<tr>
<td>Bilirubin</td>
<td></td>
<td>( &gt;2xUL )</td>
</tr>
<tr>
<td>Albumin</td>
<td>( \leq 0.84xLL )</td>
<td></td>
</tr>
<tr>
<td>Total protein</td>
<td>( \leq 0.84xLL )</td>
<td>( \geq 1.16xUL )</td>
</tr>
<tr>
<td>Urea</td>
<td></td>
<td>( \geq 2.6xUL )</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td></td>
<td>( \geq 2.6xUL )</td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
<td>( \geq 2.6xUL )</td>
</tr>
<tr>
<td>Uric acid</td>
<td></td>
<td>( \geq 1.16xUL )</td>
</tr>
</tbody>
</table>

UL = upper limit of reference range  
LL = lower limit of reference range
### Table 13  Toxicity Criteria for Hematology Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Toxicity Decrease</th>
<th>Toxicity Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>≤ 9.4</td>
<td></td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>≤ 28</td>
<td></td>
</tr>
<tr>
<td>Red cell count</td>
<td>≤ 0.84xLL</td>
<td></td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>≤ 0.84xLL</td>
<td>≥ 1.11xUL</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin</td>
<td>≤ 0.84xLL</td>
<td></td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin concentration</td>
<td>≤ 0.84xLL</td>
<td></td>
</tr>
<tr>
<td>Platelets (x10⁹/L)</td>
<td>≤ 74</td>
<td></td>
</tr>
<tr>
<td>Prothrombin time</td>
<td></td>
<td>&gt; 1.5xUL</td>
</tr>
<tr>
<td>Prothrombin international normalized ratio</td>
<td></td>
<td>&gt; 1.5</td>
</tr>
<tr>
<td>Total white blood cell count (x10⁹/L)</td>
<td>≤ 2.9</td>
<td>≥ 21</td>
</tr>
<tr>
<td>Total neutrophil count (x10⁹/L)</td>
<td>≤ 1.36</td>
<td>≥ 14.7</td>
</tr>
<tr>
<td>Segmented neutrophil count (x10⁹/L)</td>
<td>≤ 0.75</td>
<td>≥ 12.3</td>
</tr>
<tr>
<td>Eosinophils (x10⁹/L)</td>
<td></td>
<td>≥ 1.5</td>
</tr>
<tr>
<td>Basophils (x10⁹/L)</td>
<td></td>
<td>≥ 0.31</td>
</tr>
<tr>
<td>Monocytes (x10⁹/L)</td>
<td></td>
<td>≥ 2.1</td>
</tr>
<tr>
<td>Lymphocytes (x10⁹/L) for patients &lt; 18 years (auto hematology)</td>
<td>≤ 1.0</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes (x10⁹/L) for patients &lt; 18 years (manual hematology)</td>
<td>≤ 0.2</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes (x10⁹/L) for patients ≥ 18 years</td>
<td>≤ 0.2</td>
<td></td>
</tr>
</tbody>
</table>

**UL** = upper limit of reference range  
**LL** = lower limit of reference range
Appendix 5  Derivation Instructions for Achenbach Child Behavior Checklists and Adult Behavior Checklist

CBCL/1½–5

The syndrome scale and problem scale grouping of items is shown in Table 14. If data are missing for more than 8 items (not counting item 100) then the syndrome and problem scales will not be calculated.

Each of the items is scored 0, 1 or 2 as indicated on the questionnaire. The individual items associated with each syndrome scale are presented in Table 14.

The syndrome scale scores will be calculated as the sum of the individual items associated with that scale. The problem scale scores will then be calculated as the sum of the corresponding syndrome scale scores as per Table 7 in Section 5.5.4.8. The total problem scale score will be calculated as the sum of the internalizing, externalizing and other problem scales.

Table 14  Syndrome Scale Items for Achenbach CBCL/1½–5

<table>
<thead>
<tr>
<th>Problem Scales</th>
<th>Syndrome Scales</th>
<th>Items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internalizing</td>
<td>Emotionally Reactive</td>
<td>21, 46, 51, 79, 82, 83, 92, 97, 99</td>
</tr>
<tr>
<td></td>
<td>Anxious/Depressed</td>
<td>10, 33, 37, 43, 47, 68, 87, 90</td>
</tr>
<tr>
<td></td>
<td>Somatic Complaints</td>
<td>1, 7, 12, 19, 24, 39, 45, 52, 78, 86, 93</td>
</tr>
<tr>
<td></td>
<td>Withdrawn</td>
<td>2, 4, 23, 62, 67, 70, 71, 98</td>
</tr>
<tr>
<td>Externalizing</td>
<td>Attention Problems</td>
<td>5, 6, 56, 59, 95</td>
</tr>
<tr>
<td></td>
<td>Aggressive Behavior</td>
<td>8, 15, 16, 18, 20, 27, 29, 35, 40, 42, 44, 53, 58, 66, 69, 81, 85, 88, 96</td>
</tr>
<tr>
<td>Other</td>
<td>Other Problems</td>
<td>3, 9, 11, 13, 14, 17, 25, 26, 28, 30, 31, 32, 34, 36, 41, 49, 50, 54, 55, 57, 60, 61, 63, 65, 72, 73, 75, 76, 77, 80, 89, 91, 100</td>
</tr>
<tr>
<td>Sleep Problems</td>
<td></td>
<td>22, 38, 48, 64, 74, 84, 94</td>
</tr>
</tbody>
</table>

CBCL/6–18

The syndrome scale and problem scale grouping of items is shown in Table 15. If data are missing for more than 8 items (not counting items 56h or 113) then the syndrome and problem scales will not be calculated.

Each of the items is scored 0, 1 or 2 as indicated on the questionnaire. The individual items associated with each syndrome scale are presented in Table 15.

The syndrome scale scores will be calculated as the sum of the individual items associated with that scale. The problem scale scores will then be calculated as the sum of the corresponding syndrome scale scores as per Table 7 in Section 5.5.4.8. The total problem scale score will be calculated as the sum of the internalizing, externalizing and other problem scales.
Table 15  Syndrome Scale Items for Achenbach CBCL/6–18

<table>
<thead>
<tr>
<th>Problem Scales</th>
<th>Syndrome Scales</th>
<th>Items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internalizing</td>
<td>Anxious/Depressed</td>
<td>14, 29, 30, 31, 32, 33, 35, 45, 50, 52, 71, 91, 112</td>
</tr>
<tr>
<td></td>
<td>Withdrawn/Depressed</td>
<td>5, 42, 65, 69, 75, 102, 103, 111</td>
</tr>
<tr>
<td></td>
<td>Somatic Complaints</td>
<td>47, 49, 51, 54, 56a-g</td>
</tr>
<tr>
<td>Externalizing</td>
<td>Rule-breaking Behavior</td>
<td>2, 26, 28, 39, 43, 63, 67, 72, 73, 81, 82, 90, 96, 99, 101, 105, 106</td>
</tr>
<tr>
<td></td>
<td>Aggressive Behavior</td>
<td>3, 16, 19, 20, 21, 22, 37, 57, 68, 86, 87, 88, 89, 94, 95, 97, 104</td>
</tr>
<tr>
<td>Other</td>
<td>Social Problems</td>
<td>11, 12, 25, 27, 34, 36, 38, 48, 62, 64, 79</td>
</tr>
<tr>
<td></td>
<td>Thought Problems</td>
<td>9, 18, 40, 46, 58, 59, 60, 66, 70, 76, 83, 84, 85, 92, 100</td>
</tr>
<tr>
<td></td>
<td>Attention Problems</td>
<td>1, 4, 8, 10, 13, 17, 41, 61, 78, 80</td>
</tr>
<tr>
<td></td>
<td>Other Problems</td>
<td>6, 7, 15, 24, 44, 53, 55, 56h, 74, 77, 93, 98, 107, 108, 109, 110, 113</td>
</tr>
</tbody>
</table>

The activities scale is made up of 6 scores and the total score for the activities scale is the sum of these 6 scores. If more than 1 of the 6 scores is missing then the total score for the activities scale will not be calculated. If 1 score is missing, then the mean of the other 5 scores will be used for the missing score in calculating the total. However, if the missing score is an answer for question IB, IIB or IVB (see below) and the mean of the other 5 scores is greater than 2, then the missing score will be set to 2. The total activities score should be rounded to the nearest 0.5. The 6 scores used for the total score for the activities scale are derived as follows:

- **Question I, IA:**
  - 0 if ‘None’ is ticked.
  - 1 if 1 sport is listed under a, b or c.
  - 2 if 2 sports are listed under a, b or c.
  - 3 if 3 or more sports are listed under a, b and c.

- **Question I, IB:**
  - 0 if ‘None’ is ticked for IA.
  - Otherwise, for each sport under a, b and c, and for both time and skill the below scores will be assigned and then the mean of these scores (excluding “Don’t know” or blank responses) will be the score for IB:
    - 0 for “Less than average” or “below average”.
    - 1 for “Average”.
    - 2 for “More than average” or “above average”.

- **Question II, IIA:**
  - 0 if ‘None’ is ticked.
  - 1 if 1 activity is listed under a, b or c.
  - 2 if 2 activities are listed under a, b or c.
  - 3 if 3 or more activities are listed under a, b and c.

- **Question II, IIB:**
  - Calculated as per IB.

- **Question IV, IVA:**
  - 0 if ‘None’ is ticked.
  - 1 if 1 job is listed under a, b or c.
The social scale is made up of 6 scores and the total score for the social scale is the sum of these 6 scores. If more than 1 of the 6 scores is missing then the total score for the social scale will not be calculated. If 1 score is missing, then the mean of the other 5 scores will be used for the missing score in calculating the total. However, if the missing score is IIIB, V2, VIA or VIB (see below) and the mean of the other 5 scores is greater than 2, then the missing score will be set to 2. The total activities score should be rounded to the nearest 0.5. The 6 scores used for the total score for the social scale are derived as follows:

- **Question III, IIIA:**
  - 0 if ‘None’ is ticked.
  - 1 if 1 organization is listed under a, b or c.
  - 2 if 2 organizations are listed under a, b or c.
  - 3 if 3 or more organizations are listed under a, b and c.

- **Question III, IIIB**
  - Calculated as per IB for the activities scale.

- **Question V, V1:**
  - 0 if ‘None’ is ticked.
  - 1 if ‘1’ is ticked.
  - 2 if ‘2 or 3’ is ticked.
  - 3 if ‘4 or more’ is ticked.

- **Question V, V2:**
  - 0 if ‘less than 1’ is ticked.
  - 1 if ‘1 or 2’ is ticked.
  - 2 if ‘3 or more’ is ticked.

- **Question VI, VIA:**
  - For a to c, the below scores will be assigned and then the mean of these scores (excluding blank responses) will be the score for VIA:
    - 0 for “Worse”.
    - 1 for “Average”.
    - 2 for “Better”.

- **Question VI, VIB:**
  - For item d:
    - 0 if ‘Worse’ is ticked.
    - 1 if ‘Average’ is ticked.
    - 2 if ‘Better’ is ticked.

The school scale is made up of 4 scores and the total score for the school scale is the sum of these 4 scores. If any of the 4 scores are missing or the child does not attend school then the total score for the school scale will not be calculated. The total school score should be rounded to the nearest 0.5. The 4 scores used for the total score for the school scale are derived as follows:

- **Question VII, VII1:**
  - For a to g, the below scores will be assigned and then the mean of these scores (excluding blank responses) will be the score for VII1:
    - 0 for “Failing”.
    - 1 for “Below Average”.
    - 2 for “Average”.
- 3 for “Above Average”.
- Question VII, VII2:
  - 0 if ‘Yes’ is ticked.
  - 1 if ‘No’ is ticked.
- Question VII, VII3:
  - 0 if ‘Yes’ is ticked.
  - 1 if ‘No’ is ticked.
- Question VII, VII4:
  - 0 if ‘Yes’ is ticked for any academic or other problems in school.
  - 1 if ‘No’ is ticked for any academic or other problems in school.

The total competence score will be calculated as the sum of the activities, social and school scale scores. However, if any of these 3 scales are missing then the total competence score will be set to missing.

**ABCL/18–59**

The syndrome scale and problem scale grouping of items is shown in Table 16. If data are missing for more than 8 items (not counting items 2, 4, 15, 49, 73, 80, 88, 98, 106, 109, 110 and 123) then the syndrome and problem scales will not be calculated. If items 56a to 56g are missing then they will be scored as 0.

Each of the items is scored 0, 1 or 2 as indicated on the questionnaire. The individual items associated with each syndrome scale are presented in Table 16.

The syndrome scale scores will be calculated as the sum of the individual items associated with that scale. The problem scale scores will then be calculated as the sum of the corresponding syndrome scale scores as per Table 7 in Section 5.5.4.8. The total problem scale score will be calculated as the sum of the internalizing, externalizing and other problem scales.

**Table 16 Syndrome Scale Items for Achenbach ABCL/18–59**

<table>
<thead>
<tr>
<th>Problem Scales</th>
<th>Syndrome Scales</th>
<th>Items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internalizing</td>
<td>Anxious/Depressed</td>
<td>12, 13, 14, 22, 31, 33, 34, 35, 45, 47, 50, 52, 71, 91, 103, 107, 112, 113</td>
</tr>
<tr>
<td></td>
<td>Withdrawn</td>
<td>25, 30, 42, 48, 60, 65, 67, 69, 111</td>
</tr>
<tr>
<td></td>
<td>Somatic Complaints</td>
<td>51, 54, 56a-i, 100</td>
</tr>
<tr>
<td>Externalizing</td>
<td>Aggressive Behavior</td>
<td>3, 5, 16, 28, 37, 55, 57, 68, 81, 86, 87, 95, 97, 116, 118</td>
</tr>
<tr>
<td></td>
<td>Rule-breaking Behavior</td>
<td>6, 20, 23, 26, 39, 41, 43, 76, 82, 90, 92, 114, 117, 122</td>
</tr>
<tr>
<td></td>
<td>Intrusive</td>
<td>7, 19, 74, 93, 94, 104</td>
</tr>
<tr>
<td>Other</td>
<td>Thought Problems</td>
<td>9, 18, 36, 40, 46, 63, 66, 70, 84, 85</td>
</tr>
<tr>
<td></td>
<td>Attention Problems</td>
<td>1, 8, 17, 53, 59, 61, 64, 78, 101, 102, 105, 108, 119, 121</td>
</tr>
<tr>
<td></td>
<td>Other Problems</td>
<td>10, 21, 24, 27, 29, 32, 38, 44, 58, 62, 72, 75, 77, 79, 83, 89, 96, 99, 110, 115, 120</td>
</tr>
</tbody>
</table>

The critical items scale score will be calculated as the sum of the following 19 problem items scores:
• 6, 8, 9, 10, 14, 16, 18, 21, 40, 55, 57, 66, 70, 84, 90, 91, 92, 97, 103.

The friends scale is made up of 4 scores and the total score for the friends scale is the sum of these 4 scores. If any of the 4 scores are missing then the total score for the friends scale will not be calculated. The 4 scores used for the total score for the friends scale are derived as follows:

• If ‘None’ is ticked for item IA then 0 will be used for IB and IC.
• Question I, IA:
  o 0 if ‘None’ is ticked.
  o 1 if ‘1’ is ticked.
  o 2 if ‘2 or 3’ is ticked.
  o 3 if ‘4 or more’ is ticked.
• Question I, IB:
  o 0 if ‘Less than 1’ is ticked.
  o 1 if ‘1 or 2’ is ticked.
  o 2 if ‘3 or 4’ is ticked.
  o 3 if ‘5 or more’ is ticked.
• Question I, IC:
  o 0 if ‘Not well’ is ticked.
  o 1 if ‘Average’ is ticked.
  o 2 if ‘Above average’ is ticked.
  o 3 if ‘Far above average’ is ticked.
• Question I, ID:
  o 0 if ‘Less than 1’ is ticked.
  o 1 if ‘1 or 2’ is ticked.
  o 2 if ‘3 or 4’ is ticked.
  o 3 if ‘5 or more’ is ticked.
## Appendix 6  List of Tables, Listings and Figures

### Table 17  List of Blinded Phase Tables

<table>
<thead>
<tr>
<th>Table Number</th>
<th>Title</th>
<th>Analysis Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 1.1.1</td>
<td>Summary of Patient Disposition – Number of Patients Screened and Randomized by Site</td>
<td>All Screened Patients</td>
</tr>
<tr>
<td>Table 1.1.2</td>
<td>Summary of Patient Disposition – Number of Patients Screened and Randomized by Country</td>
<td>All Screened Patients</td>
</tr>
<tr>
<td>Table 1.2</td>
<td>Summary of Patient Disposition – Reasons for Screen Failure</td>
<td>All Screened Patients</td>
</tr>
<tr>
<td>Table 1.3.1</td>
<td>Summary of Patient Disposition by Site</td>
<td>All Randomized Patients</td>
</tr>
<tr>
<td>Table 1.3.2</td>
<td>Summary of Patient Disposition by Country</td>
<td>All Randomized Patients</td>
</tr>
<tr>
<td>Table 1.4</td>
<td>Summary of Overall Patient Disposition</td>
<td>All Randomized Patients</td>
</tr>
<tr>
<td>Table 2.1</td>
<td>Summary of Important Protocol Deviations</td>
<td>All Randomized Patients</td>
</tr>
<tr>
<td>Table 2.2</td>
<td>Summary of Analysis Sets</td>
<td>All Randomized Patients</td>
</tr>
<tr>
<td>Table 3.1.1</td>
<td>Summary of Demographic Data</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 3.1.2</td>
<td>Summary of Demographic Data</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 3.1.3</td>
<td>Summary of Demographic Data</td>
<td>PP Analysis Set</td>
</tr>
<tr>
<td>Table 3.2.1</td>
<td>Summary of Baseline Characteristics</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 3.2.2</td>
<td>Summary of Baseline Characteristics</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 3.2.3</td>
<td>Summary of Baseline Characteristics</td>
<td>PP Analysis Set</td>
</tr>
<tr>
<td>Table 4.1.1</td>
<td>Summary of Seizure Types No Longer Occurring</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 4.1.2</td>
<td>Summary of Current Seizure Types</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 5.1</td>
<td>Summary of Previous Significant Non-Epilepsy Medical or Surgical History Now Resolved</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 5.2</td>
<td>Summary of Significant Non-Epilepsy Medical or Surgical History – Current Conditions</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 6.1</td>
<td>Summary of History of Antiepileptic Drugs</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 6.2</td>
<td>Summary of Concomitant Antiepileptic Therapies</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 6.3</td>
<td>Summary of Concomitant Antiepileptic Drugs</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 6.4</td>
<td>Summary of Concomitant Rescue Medications</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 6.5</td>
<td>Summary of Other Concomitant Medications</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 7.1</td>
<td>Summary of Treatment Compliance</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 7.2</td>
<td>Summary of IVRS Compliance</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 8.1.1</td>
<td>Summary of TSC-associated Seizure Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 8.1.2</td>
<td>Negative Binomial Regression Analysis of TSC-associated Seizure Count During Baseline and Treatment Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 8.2.1.1</td>
<td>Summary of TSC-associated Seizure Frequency</td>
<td>PP Analysis Set</td>
</tr>
<tr>
<td>Table 8.2.1.2</td>
<td>Negative Binomial Regression Analysis of TSC-associated Seizure Count During Baseline and Treatment Periods</td>
<td>PP Analysis Set</td>
</tr>
<tr>
<td>Table Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Table 8.2.2</td>
<td>Analysis of Percentage Change from Baseline in TSC-associated Seizure</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td></td>
<td>Frequency During the Treatment Period – Wilcoxon Rank-Sum Test</td>
<td></td>
</tr>
<tr>
<td>Table 8.2.3</td>
<td>Analysis of Percentage Change from Baseline in TSC-associated Seizure</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td></td>
<td>Frequency During the Treatment Period – Rank ANCOVA</td>
<td></td>
</tr>
<tr>
<td>Table 8.2.4</td>
<td>Analysis of TSC-associated Seizure Frequency During the Treatment</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td></td>
<td>Period – Log-transformed ANCOVA</td>
<td></td>
</tr>
<tr>
<td>Table 8.2.5</td>
<td>Analysis of Percentage Change from Baseline in TSC-associated Seizure</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td></td>
<td>Frequency During the Treatment Period – ANCOVA</td>
<td></td>
</tr>
<tr>
<td>Table 8.2.6</td>
<td>Negative Binomial Regression Analysis of TSC-associated Seizure</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td></td>
<td>Count During Baseline and Titration and Maintenance Periods</td>
<td></td>
</tr>
<tr>
<td>Table 8.2.7</td>
<td>Negative Binomial Regression Analysis of TSC-associated Seizure</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td></td>
<td>Count During Baseline and Treatment Periods After Imputing Unreported</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Days in IVRS</td>
<td></td>
</tr>
<tr>
<td>Table 8.2.8</td>
<td>Negative Binomial Regression Analysis of TSC-associated Seizure</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td></td>
<td>Count During Baseline and Treatment Periods After Multiple Imputation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>to Account for MNAR</td>
<td></td>
</tr>
<tr>
<td>Table 9.1.1</td>
<td>Summary and Analysis of TSC-associated Seizure Treatment Responders</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td></td>
<td>and TSC-associated Seizure Freedom During the Treatment Period</td>
<td></td>
</tr>
<tr>
<td>Table 9.1.2</td>
<td>Summary and Analysis of TSC-associated Seizure Treatment Responders</td>
<td>PP Analysis Set</td>
</tr>
<tr>
<td></td>
<td>and TSC-associated Seizure Freedom During the Treatment Period</td>
<td></td>
</tr>
<tr>
<td>Table 9.1.3</td>
<td>Summary and Analysis of TSC-associated Seizure Treatment Responders</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td></td>
<td>and TSC-associated Seizure Freedom During the Titration and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maintenance Periods</td>
<td></td>
</tr>
<tr>
<td>Table 9.2.1.1</td>
<td>Summary of the Subject/Caregiver Global Impression of Change</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.2.1.2</td>
<td>Analysis of the Subject/Caregiver Global Impression of Change</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.2.2.1</td>
<td>Summary of the Subject/Caregiver Global Impression of Change</td>
<td>PP Analysis Set</td>
</tr>
<tr>
<td>Table 9.2.2.2</td>
<td>Analysis of the Subject/Caregiver Global Impression of Change</td>
<td>PP Analysis Set</td>
</tr>
<tr>
<td>Table 9.3.1.1</td>
<td>Summary of Total Seizure Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.3.1.2</td>
<td>Negative Binomial Regression Analysis of Total Seizure Count</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td></td>
<td>During Baseline and Treatment Periods</td>
<td></td>
</tr>
<tr>
<td>Table 9.3.2.1</td>
<td>Summary of Total Seizure Frequency</td>
<td>PP Analysis Set</td>
</tr>
<tr>
<td>Table 9.3.2.2</td>
<td>Negative Binomial Regression Analysis of Total Seizure Count</td>
<td>PP Analysis Set</td>
</tr>
<tr>
<td>Table Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Table 9.3.3</td>
<td>Negative Binomial Regression Analysis of Total Seizure Count During Baseline and Titration and Maintenance Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.4.1</td>
<td>Analysis of Change from Baseline in TSC-associated Seizure Free Days Per 28 Days During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.4.2</td>
<td>Analysis of Change from Baseline in TSC-associated Seizure Free Days Per 28 Days During the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.5.1.1</td>
<td>Summary of Other Seizure Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.5.1.2</td>
<td>Negative Binomial Regression Analysis of Other Seizure Count During Baseline and Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.5.2</td>
<td>Summary and Analysis of Other Seizure Treatment Responders and Other Seizure Freedom During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.6.1</td>
<td>Summary and Analysis of Total Seizure Treatment Responders and Total Seizure Freedom During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.6.2</td>
<td>Summary and Analysis of Total Seizure Treatment Responders and Total Seizure Freedom During the Titration and Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.7.1.1</td>
<td>Summary of Quality of Life in Childhood Epilepsy Scores (2-18 Years)</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.7.1.2</td>
<td>Analysis of Change from Baseline in Quality of Life in Childhood Epilepsy Scores (2-18 Years)</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.7.2.1</td>
<td>Summary of Quality of Life in Epilepsy Scores (19 Years and Above)</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.7.2.2</td>
<td>Analysis of Change from Baseline in the Quality of Life in Epilepsy Total Score (19 Years and Above)</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.8.1</td>
<td>Summary of the Physician Global Impression of Change</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.8.2</td>
<td>Analysis of the Physician Global Impression of Change</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.9.1</td>
<td>Summary of Composite Focal Seizure Score</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.9.2</td>
<td>Negative Binomial Regression Analysis of Composite Focal Seizure Score During Baseline and Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.1.1.1</td>
<td>Summary of Type 1 Focal Seizure Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.1.1.2</td>
<td>Negative Binomial Regression Analysis of Type 1 Focal Seizure Count During Baseline and Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.1.2</td>
<td>Negative Binomial Regression Analysis of Type 1 Focal Seizure Count During Baseline and Titration and Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.1.3</td>
<td>Summary and Analysis of Type 1 Focal Seizure Treatment Responders and Type 1 Focal Seizure Freedom During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Table 9.10.1.4</td>
<td>Summary and Analysis of Type 1 Focal Seizure Treatment Responders and Type 1 Focal Seizure Freedom During the Titration and Maintenance Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.2.1.1</td>
<td>Summary of Type 2 Focal Seizure Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.2.1.2</td>
<td>Negative Binomial Regression Analysis of Type 2 Focal Seizure Count During Baseline and Treatment Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.2.2</td>
<td>Negative Binomial Regression Analysis of Type 2 Focal Seizure Count During Baseline and Titration and Maintenance Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.2.3</td>
<td>Summary and Analysis of Type 2 Focal Seizure Treatment Responders and Type 2 Focal Seizure Freedom During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.2.4</td>
<td>Summary and Analysis of Type 2 Focal Seizure Treatment Responders and Type 2 Focal Seizure Freedom During the Titration and Maintenance Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.3.1.1</td>
<td>Summary of Type 3 Focal Seizure Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.3.1.2</td>
<td>Negative Binomial Regression Analysis of Type 3 Focal Seizure Count During Baseline and Treatment Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.3.2</td>
<td>Negative Binomial Regression Analysis of Type 3 Focal Seizure Count During Baseline and Titration and Maintenance Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.3.3</td>
<td>Summary and Analysis of Type 3 Focal Seizure Treatment Responders and Type 3 Focal Seizure Freedom During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.3.4</td>
<td>Summary and Analysis of Type 3 Focal Seizure Treatment Responders and Type 3 Focal Seizure Freedom During the Titration and Maintenance Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.4.1.1</td>
<td>Summary of Tonic-Clonic Seizure Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.4.1.2</td>
<td>Negative Binomial Regression Analysis of Tonic-Clonic Seizure Count During Baseline and Treatment Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.4.2</td>
<td>Negative Binomial Regression Analysis of Tonic-Clonic Seizure Count During Baseline and Titration and Maintenance Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.4.3</td>
<td>Summary and Analysis of Tonic-Clonic Seizure Treatment Responders and Tonic-Clonic Seizure Freedom During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.4.4</td>
<td>Summary and Analysis of Tonic-Clonic Seizure Treatment Responders and Tonic-Clonic Seizure Freedom During the Titration and Maintenance Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.5.1.1</td>
<td>Summary of Tonic Seizure Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.5.1.2</td>
<td>Negative Binomial Regression Analysis of Tonic Seizure Count During Baseline and Treatment Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Table 9.10.5.2</td>
<td>Negative Binomial Regression Analysis of Tonic Seizure Count During Baseline and Titration and Maintenance Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.5.3</td>
<td>Summary and Analysis of Tonic Seizure Treatment Responders and Tonic Seizure Freedom During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.5.4</td>
<td>Summary and Analysis of Tonic Seizure Treatment Responders and Tonic Seizure Freedom During the Titration and Maintenance Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.6</td>
<td>Summary of Clonic Seizure Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.7</td>
<td>Summary of Atonic Seizure Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.8</td>
<td>Summary of Absence Seizure Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.9</td>
<td>Summary of Myoclonic Seizure Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.10</td>
<td>Summary of Partial Sensory Seizure Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.10.11</td>
<td>Summary of Infantile or Epileptic Spasm Frequency</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.11.1</td>
<td>Summary of Number of Days of Rescue Medication Use</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.11.2</td>
<td>Analysis of Change from Baseline in the Number of Days of Rescue Medication Use</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.12</td>
<td>Summary of Patients with Status Epilepticus</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.13.1</td>
<td>Summary of Subject/Caregiver Global Impression of Change in Seizure Duration</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.13.2</td>
<td>Analysis of Subject/Caregiver Global Impression of Change in Seizure Duration</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.14.1.1</td>
<td>Summary of the Vineland-II Adaptive Behavior Subdomain, Domain and Composite Scores</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.14.1.2</td>
<td>Summary of the Vineland-II Adaptive Behavior Subdomain, Domain and Composite Adaptive Levels</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.14.1.3</td>
<td>Analysis of Change from Baseline in the Vineland-II Adaptive Behavior Domain and Composite Scores</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.14.1.4</td>
<td>Analysis of the Vineland-II Adaptive Behavior Domain and Composite Adaptive Levels</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.14.2.1</td>
<td>Summary of the Vineland-II Maladaptive Behavior Subdomain and Index Scores</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.14.2.2</td>
<td>Summary of the Vineland-II Maladaptive Behavior Subdomain and Index Adaptive Levels</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.14.2.3</td>
<td>Analysis of Change from Baseline in the Vineland-II Maladaptive Behavior Index Score</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.14.2.4</td>
<td>Analysis of the Vineland-II Maladaptive Behavior Index Adaptive Level</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.15.1</td>
<td>Summary of Wechsler Tests</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.15.2</td>
<td>Analysis of Wechsler Tests</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.16.1.1</td>
<td>Summary of Achenbach Child Behavior Checklists</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.16.1.2</td>
<td>Analysis of Achenbach Child Behavior Checklists</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.16.2.1</td>
<td>Summary of Achenbach Adult Behavior Checklist</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.16.2.2</td>
<td>Analysis of Achenbach Adult Behavior Checklist</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.17.1</td>
<td>Summary of Social Communication Questionnaire</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.17.2</td>
<td>Analysis of Social Communication Questionnaire</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Table 9.18.1</td>
<td>Analysis of Time to Baseline TSC-associated Seizure Frequency from the Start of the Treatment Period (Day 1)</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.18.2</td>
<td>Analysis of Time to Baseline TSC-associated Seizure Frequency from the Start of the Maintenance Period (Day 29)</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.19.1</td>
<td>Negative Binomial Regression Effect Modification Analysis of TSC-associated Seizure Count during Baseline and Treatment Periods</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 9.19.2</td>
<td>Logistic Regression Effect Modification Analysis of TSC-associated Seizure Responders (&gt;=50% Reduction) During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table 10.1</td>
<td>Summary of Exposure</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 10.2</td>
<td>Summary of Expected Daily Volumes of IMP Taken Post-Titration</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.1</td>
<td>Overall Summary of Treatment Emergent Adverse Events</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.2</td>
<td>Summary of Treatment Emergent Adverse Events</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.3</td>
<td>Summary of Treatment-Related Treatment Emergent Adverse Events</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.4</td>
<td>Summary of Treatment Emergent Adverse Events by Maximal Severity</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.5</td>
<td>Summary of Treatment Emergent Adverse Events by Sex</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.6</td>
<td>Summary of TEAEs by Time of First Onset of AE</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.7</td>
<td>Summary of TEAEs by Time to AE Resolution</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.8</td>
<td>Summary of TEAEs Reported in &gt;=2% of Patients in the GWP42003-P Treatment Arms</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.9</td>
<td>Summary of Non-Serious Treatment Emergent Adverse Events</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.10</td>
<td>List of Patients Experiencing Treatment Emergent Adverse Events by System Organ Class and Preferred term</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.11</td>
<td>Summary of Pre-Treatment Adverse Events</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.12</td>
<td>Summary of Treatment Emergent Adverse Events by Event</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.13</td>
<td>Summary of Treatment-Related Treatment Emergent Adverse Events by Event</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 11.14</td>
<td>Summary of Non-Serious Treatment Emergent Adverse Events by Event</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 12.1</td>
<td>Summary of Serious Treatment Emergent Adverse Events</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 12.2</td>
<td>Summary of Treatment-Related Serious Treatment Emergent Adverse Events</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 12.3</td>
<td>Summary of Treatment Emergent Adverse Events Leading to Permanent Discontinuation of IMP</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 12.4</td>
<td>Summary of Treatment-Related Treatment Emergent Adverse Events Leading to Permanent Discontinuation of IMP</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Table 12.5</td>
<td>Summary of Treatment Emergent Adverse Events Leading to IMP Dose Reduction Excluding Permanent Discontinuation and by Resolution and Overall</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 12.6</td>
<td>Summary of Treatment-Related Treatment Emergent Adverse Events Leading to IMP Dose Reduction Excluding Permanent Discontinuation and by Resolution and Overall</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 12.7</td>
<td>Summary of Treatment Emergent Adverse Events Leading to Temporary IMP Dose Reduction by Resolution and Overall</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 12.8</td>
<td>Summary of Treatment-Related Treatment Emergent Adverse Events Leading to Temporary IMP Dose Reduction by Resolution and Overall</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 12.9</td>
<td>Summary of Treatment Emergent Adverse Events Leading to Permanent IMP Dose Reduction Excluding Permanent Discontinuation and by Resolution and Overall</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 12.10</td>
<td>Summary of Treatment-Related Treatment Emergent Adverse Events Leading to Permanent IMP Dose Reduction Excluding Permanent Discontinuation and by Resolution and Overall</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 12.11</td>
<td>Summary of Fatal Treatment Emergent Adverse Events</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 12.12</td>
<td>Summary of Serious Treatment Emergent Adverse Events by Event</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 12.13</td>
<td>Summary of Treatment-Related Serious Treatment Emergent Adverse Events by Event</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 13.1.1</td>
<td>Summary of Laboratory Safety Parameters – Hematology</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 13.1.2</td>
<td>Summary of Laboratory Safety Parameters – Biochemistry</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 13.2.1</td>
<td>Shift Table for Hematology Laboratory Parameters – Based on Reference Ranges</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 13.2.2</td>
<td>Shift Table for Biochemistry Laboratory Parameters – Based on Reference Ranges</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 13.3.1</td>
<td>Shift Table for Hematology Laboratory Parameters – Based on Toxicity Limits</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 13.3.2</td>
<td>Shift Table for Biochemistry Laboratory Parameters – Based on Toxicity Limits</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 13.3.3</td>
<td>Shift Table for eGFR – Based on Derived Grades</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 13.4</td>
<td>Summary of Liver Parameter Flags</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 13.5</td>
<td>Incidence of Laboratory Abnormalities</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 13.6</td>
<td>Summary of Pregnancy Test and Urine THC Screen Results</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 14.1.1</td>
<td>Summary of Vital Signs</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 14.1.2</td>
<td>Incidence of Clinically Significant Changes from Baseline for Vital Signs</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 14.1.3</td>
<td>Incidence of Defined Flagged Vital Signs</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Table 14.1.4</td>
<td>Incidence of Vital Signs Abnormalities</td>
<td>Safety Analysis Set</td>
</tr>
</tbody>
</table>
### Table Number | Title | Analysis Set
--- | --- | ---
Table 14.2.1 | Summary of ECG Parameters | Safety Analysis Set
Table 14.2.2 | Incidence of Defined Flagged ECG Parameter Values | Safety Analysis Set
Table 14.2.3 | Incidence of ECG Abnormalities | Safety Analysis Set
Table 14.3 | Summary of Columbia-Suicide Severity Rating Scale by Type | Safety Analysis Set
Table 14.4 | Incidence of Physical Examination Abnormalities | Safety Analysis Set
Table 14.5 | Summary of Tanner Stages | Safety Analysis Set
Table 14.6 | Summary of Menstruation Details | Safety Analysis Set
Table 14.7 | Summary of Patients with Inpatient Hospitalizations due to Epilepsy | Safety Analysis Set
Table 14.8.1 | Summary of Plasma Concentrations | Safety Analysis Set
Table 14.8.2.1 | Summary of PK Parameters (Overall and by Age Group) | Safety Analysis Set
Table 14.8.2.2 | Summary of PK Parameter Metabolite to Parent Ratio (Overall and by Age Group) | Safety Analysis Set
Table 14.9 | Summary of Plasma Concentrations of Concomitant Antiepileptic Drugs | Safety Analysis Set
Table 14.10 | Summary of Study Medication Use and Behavior Survey | Safety Analysis Set
Table 14.11.1 | Summary of Supplemental Drug Accountability Form | Safety Analysis Set
Table 14.11.2 | Summary of Supplemental Adverse Event Form | Safety Analysis Set
Table 14.11.3 | Summary of Site Classification Form | Safety Analysis Set

### Table 18 | List of OLE Phase Tables

<table>
<thead>
<tr>
<th>Table Number</th>
<th>Title</th>
<th>Analysis Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLE Table 1.1.1</td>
<td>Summary of Patient Disposition by Site</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 1.1.2</td>
<td>Summary of Patient Disposition During by Country</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 1.2</td>
<td>Summary of Overall Patient Disposition</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 2</td>
<td>Summary of Important Protocol Deviations</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 3.1</td>
<td>Summary of Demographic Data</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 3.2</td>
<td>Summary of Baseline Characteristics</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 6.1</td>
<td>Summary of Concomitant Antiepileptic Therapies</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 6.2</td>
<td>Summary of Concomitant Antiepileptic Drugs</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 6.3</td>
<td>Summary of Concomitant Rescue Medications</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 6.4</td>
<td>Summary of Other Concomitant Medications</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>Table Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>OLE Table 9.1.1.1</td>
<td>Summary of TSC-associated Seizure Frequency</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.1.1.2</td>
<td>Summary of TSC-associated Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.1.1.3</td>
<td>Summary of TSC-associated Seizure Frequency (Patients with Data in OLE Week 37 to 48)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.1.2.1</td>
<td>Summary of TSC-associated Seizure Treatment Responders and TSC-associated Seizure Freedom</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.1.2.2</td>
<td>Summary of TSC-associated Seizure Treatment Responders and TSC-associated Seizure Freedom (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.1.2.3</td>
<td>Summary of TSC-associated Seizure Treatment Responders and TSC-associated Seizure Freedom (Patients with Data in OLE Week 37 to 48)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.2</td>
<td>Summary of the Subject/Caregiver Global Impression of Change</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.3.1.1</td>
<td>Summary of Total Seizure Frequency</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.3.1.2</td>
<td>Summary of Total Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.3.1.3</td>
<td>Summary of Total Seizure Frequency (Patients with Data in OLE Week 37 to 48)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.3.2.1</td>
<td>Summary of Total Seizure Treatment Responders and Total Seizure Freedom</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.3.2.2</td>
<td>Summary of Total Seizure Treatment Responders and Total Seizure Freedom (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.3.2.3</td>
<td>Summary of Total Seizure Treatment Responders and Total Seizure Freedom (Patients with Data in OLE Week 37 to 48)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.4.1.1</td>
<td>Summary of Other Seizure Frequency</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.4.1.2</td>
<td>Summary of Other Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.4.2.1</td>
<td>Summary of Other Seizure Treatment Responders and Other Seizure Freedom</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.4.2.2</td>
<td>Summary of Other Seizure Treatment Responders and Other Seizure Freedom (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.5</td>
<td>Summary of Quality of Life in Childhood Epilepsy Scores (2-18 Years)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.6</td>
<td>Summary of Quality of Life in Epilepsy Scores (19 Years and Above)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.7</td>
<td>Summary of the Physician Global Impression of Change</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.8.1</td>
<td>Summary of Composite Focal Seizure Score</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.8.2</td>
<td>Summary of Composite Focal Seizure Score (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.1.1.1</td>
<td>Summary of Type 1 Focal Seizure Frequency</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>Table Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>OLE Table 9.9.1.1.2</td>
<td>Summary of Type 1 Focal Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.1.2.1</td>
<td>Summary of Type 1 Focal Seizure Treatment Responders and Type 1 Focal Seizure Freedom</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.1.2.2</td>
<td>Summary of Type 1 Focal Seizure Treatment Responders and Type 1 Focal Seizure Freedom (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.2.1.1</td>
<td>Summary of Type 2 Focal Seizure Frequency</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.2.1.2</td>
<td>Summary of Type 2 Focal Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.2.2.1</td>
<td>Summary of Type 2 Focal Seizure Treatment Responders and Type 2 Focal Seizure Freedom</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.2.2.2</td>
<td>Summary of Type 2 Focal Seizure Treatment Responders and Type 2 Focal Seizure Freedom (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.3.1.1</td>
<td>Summary of Type 3 Focal Seizure Frequency</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.3.1.2</td>
<td>Summary of Type 3 Focal Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.3.2.1</td>
<td>Summary of Type 3 Focal Seizure Treatment Responders and Type 3 Focal Seizure Freedom</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.3.2.2</td>
<td>Summary of Type 3 Focal Seizure Treatment Responders and Type 3 Focal Seizure Freedom (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.4.1.1</td>
<td>Summary of Tonic-Clonic Seizure Frequency</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.4.1.2</td>
<td>Summary of Tonic-Clonic Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.4.2.1</td>
<td>Summary of Tonic-Clonic Seizure Treatment Responders and Tonic-Clonic Seizure Freedom</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.4.2.2</td>
<td>Summary of Tonic-Clonic Seizure Treatment Responders and Tonic-Clonic Seizure Freedom (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.5.1.1</td>
<td>Summary of Tonic Seizure Frequency</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.5.1.2</td>
<td>Summary of Tonic Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.5.2.1</td>
<td>Summary of Tonic Seizure Treatment Responders and Tonic Seizure Freedom</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.5.2.2</td>
<td>Summary of Tonic Seizure Treatment Responders and Tonic Seizure Freedom (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.6.1</td>
<td>Summary of Clonic Seizure Frequency</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.6.2</td>
<td>Summary of Clonic Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.7.1</td>
<td>Summary of Atonic Seizure Frequency</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.7.2</td>
<td>Summary of Atonic Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>Table Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------------------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>OLE Table 9.9.8.1</td>
<td>Summary of Absence Seizure Frequency</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.8.2</td>
<td>Summary of Absence Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.9.1</td>
<td>Summary of Myoclonic Seizure Frequency</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.9.2</td>
<td>Summary of Myoclonic Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.10.1</td>
<td>Summary of Partial Sensory Seizure Frequency</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.10.2</td>
<td>Summary of Partial Sensory Seizure Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.11.1</td>
<td>Summary of Infantile or Epileptic Spasm Frequency</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.9.11.2</td>
<td>Summary of Infantile or Epileptic Spasm Frequency (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.10.1</td>
<td>Summary of Number of Days of Rescue Medication Use</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.11</td>
<td>Summary of Patients with Status Epilepticus</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.12.1</td>
<td>Summary of Subject/Caregiver Global Impression of Change in Seizure Duration</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.13.1.1</td>
<td>Summary of the Vineland-II Adaptive Behavior Subdomain, Domain and Composite Scores</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.13.1.2</td>
<td>Summary of the Vineland-II Adaptive Behavior Subdomain, Domain and Composite Adaptive Levels</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.13.2.1</td>
<td>Summary of the Vineland-II Maladaptive Behavior Subdomain and Index Scores</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.13.2.2</td>
<td>Summary of the Vineland-II Maladaptive Behavior Subdomain and Index Adaptive Levels</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.14</td>
<td>Summary of Wechsler Tests</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.15.1.1</td>
<td>Summary of Achenbach Child Behavior Checklists</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.15.2.1</td>
<td>Summary of Achenbach Adult Behavior Checklist</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 9.16.1</td>
<td>Summary of Social Communication Questionnaire</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 10</td>
<td>Summary of Exposure</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 11.1</td>
<td>Overall Summary of Treatment Emergent Adverse Events</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 11.2</td>
<td>Summary of Treatment Emergent Adverse Events</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 11.3</td>
<td>Summary of Treatment-Related Treatment Emergent Adverse Events</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 11.4</td>
<td>Summary of Treatment Emergent Adverse Events by Maximal Severity</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>Table Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>OLE Table 11.5</td>
<td>Summary of Treatment Emergent Adverse Events by Sex</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 11.6</td>
<td>Summary of TEAEs by Time of First Onset of AE</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 11.7</td>
<td>Summary of TEAEs by Time to AE Resolution</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 11.8</td>
<td>Summary of TEAEs Reported in &gt;=2% of Patients in the GWP42003-P Treatment Arms</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 11.9</td>
<td>Summary of Non-Serious Treatment Emergent Adverse Events</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 11.10</td>
<td>List of Patients Experiencing Treatment Emergent Adverse Events by System Organ Class and Preferred term</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 11.11</td>
<td>Summary of Treatment Emergent Adverse Events by Event</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 11.12</td>
<td>Summary of Treatment-Related Treatment Emergent Adverse Events by Event</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 11.13</td>
<td>Summary of Non-Serious Treatment Emergent Adverse Events by Event</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 12.1</td>
<td>Summary of Serious Treatment Emergent Adverse Events</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 12.2</td>
<td>Summary of Treatment-Related Serious Treatment Emergent Adverse Events</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 12.3</td>
<td>Summary of Treatment Emergent Adverse Events Leading to Permanent Discontinuation of IMP</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 12.4</td>
<td>Summary of Treatment-Related Treatment Emergent Adverse Events Leading to Permanent Discontinuation of IMP</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 12.5</td>
<td>Summary of Treatment Emergent Adverse Events Leading to IMP Dose Reduction Excluding Permanent Discontinuation and by Resolution and Overall</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 12.6</td>
<td>Summary of Treatment-Related Treatment Emergent Adverse Events Leading to IMP Dose Reduction Excluding Permanent Discontinuation and by Resolution and Overall</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 12.7</td>
<td>Summary of Treatment Emergent Adverse Events Leading to Temporary IMP Dose Reduction by Resolution and Overall</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 12.8</td>
<td>Summary of Treatment-Related Treatment Emergent Adverse Events Leading to Temporary IMP Dose Reduction by Resolution and Overall</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 12.9</td>
<td>Summary of Treatment Emergent Adverse Events Leading to Permanent IMP Dose Reduction Excluding Permanent Discontinuation and by Resolution and Overall</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 12.10</td>
<td>Summary of Treatment-Related Treatment Emergent Adverse Events Leading to Permanent IMP Dose Reduction Excluding Permanent Discontinuation and by Resolution and Overall</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>Table Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>OLE Table</td>
<td>Summary of Fatal Treatment Emergent Adverse Events</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>12.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLE Table</td>
<td>Summary of Serious Treatment Emergent Adverse Events by Event</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>12.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLE Table</td>
<td>Summary of Treatment-Related Serious Treatment Emergent Adverse Events by Event</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>12.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLE Table</td>
<td>Summary of Laboratory Safety Parameters – Hematology</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>13.1.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLE Table</td>
<td>Summary of Laboratory Safety Parameters – Biochemistry</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>13.1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLE Table</td>
<td>Shift Table for Hematology Laboratory Parameters – Based on Reference Ranges</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>13.2.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLE Table</td>
<td>Shift Table for Biochemistry Laboratory Parameters – Based on Reference Ranges</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>13.2.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLE Table</td>
<td>Shift Table for Hematology Laboratory Parameters – Based on Toxicity Limits</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>13.3.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLE Table</td>
<td>Shift Table for Biochemistry Laboratory Parameters – Based on Toxicity Limits</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>13.3.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLE Table</td>
<td>Shift Table for eGFR – Based on Derived Grades</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>13.3.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLE Table</td>
<td>Summary of Liver Parameter Flags</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>13.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLE Table</td>
<td>Incidence of Laboratory Abnormalities</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>13.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLE Table</td>
<td>Summary of Pregnancy Test and Urine THC Screen Results</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>13.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLE Table</td>
<td>Summary of Vital Signs</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>14.1.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLE Table</td>
<td>Incidence of Clinically Significant Changes from Baseline for Vital Signs</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>14.1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLE Table</td>
<td>Incidence of Defined Flagged Vital Signs</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>14.1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLE Table</td>
<td>Incidence of Vital Signs Abnormalities</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>14.1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLE Table</td>
<td>Summary of ECG Parameters</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>14.2.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLE Table</td>
<td>Incidence of Defined Flagged ECG Parameter Values</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>14.2.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLE Table</td>
<td>Incidence of ECG Abnormalities</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>14.2.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLE Table</td>
<td>Summary of Columbia-Suicide Severity Rating Scale by Type</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>14.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLE Table</td>
<td>Incidence of Physical Examination Abnormalities</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>14.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLE Table</td>
<td>Summary of Tanner Stages</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>14.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLE Table</td>
<td>Summary of Menstruation Details</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>14.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLE Table</td>
<td>Summary of Patients with Inpatient Hospitalizations due to Epilepsy</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>14.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Table Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>---------------</td>
<td>------------------------------------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>OLE Table 14.8</td>
<td>Summary of Study Medication Use and Behavior Survey</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 14.9.1</td>
<td>Summary of Supplemental Drug Accountability Form</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 14.9.2</td>
<td>Summary of Supplemental Adverse Event Form</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Table 14.9.3</td>
<td>Summary of Site Classification Form</td>
<td>OLE Safety Analysis Set</td>
</tr>
</tbody>
</table>
### Table 19  List of Blinded Phase Listings

<table>
<thead>
<tr>
<th>Listing Number</th>
<th>Title</th>
<th>Analysis Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>Listing 1.1</td>
<td>Screen Failures</td>
<td>All Screen Failure Patients</td>
</tr>
<tr>
<td>Listing 1.2.1</td>
<td>Patient Disposition – End of Treatment</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 1.2.2</td>
<td>Patient Disposition – End of Taper</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 1.3</td>
<td>Inclusion/Exclusion Criteria Not Met</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 1.4</td>
<td>Visit Dates</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 2.1.1</td>
<td>Important Protocol Deviations</td>
<td>All Randomized Patients</td>
</tr>
<tr>
<td>Listing 2.1.2</td>
<td>All Protocol Deviations</td>
<td>All Randomized Patients</td>
</tr>
<tr>
<td>Listing 2.2</td>
<td>Analysis Sets</td>
<td>All Randomized Patients</td>
</tr>
<tr>
<td>Listing 3.1</td>
<td>Demography</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 3.2</td>
<td>Baseline Characteristics</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 4.1.1</td>
<td>Genetic Testing History</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 4.2.1</td>
<td>History of Seizures No Longer Occurring</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 4.2.2</td>
<td>History of Current Seizures</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 4.3</td>
<td>Neuroimaging History</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 5</td>
<td>Significant Non-Epilepsy Medical or Surgical History</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 6.1</td>
<td>History of Antiepileptic Drugs</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 6.2</td>
<td>Prior and Concomitant Antiepileptic Therapies</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 6.3</td>
<td>Prior and Concomitant Antiepileptic Drugs</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 6.4</td>
<td>Prior and Concomitant Rescue Medications</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 6.5</td>
<td>Other Prior and Concomitant Medications</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 7</td>
<td>IVRS Compliance</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 8.1.1</td>
<td>IVRS Diary Data – Part 1</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 8.1.2</td>
<td>IVRS Diary Data – Part 2</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 8.2.1</td>
<td>Derived TSC-associated, Other and Total Seizure Data</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 8.2.2</td>
<td>Derived Type 1, 3 and 3 Focal Seizure Data and Composite Focal Seizure Score</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 8.2.3</td>
<td>Derived Tonic-Clonic, Tonic, Clonic, and Atonic Seizure Data</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 8.2.4</td>
<td>Derived Absence, Myoclonic, Partial Sensory Seizure and Infantile or Epileptic Spasm Data</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 8.2.5</td>
<td>Derived Status Epilepticus Data</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 9.1</td>
<td>Subject/Caregiver/Physician Global Impression of Change</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 9.2</td>
<td>TSC-associated Seizure Free Days Per 28 Days</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 9.3</td>
<td>Quality of Life in Childhood Epilepsy (2-18 Years) – Derived Scores</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 9.4</td>
<td>Quality of Life in Epilepsy (19 Years and Above) – Derived Scores</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 9.5</td>
<td>Number of Days of Rescue Medication Use</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>----------------</td>
<td>------------------------------------------------------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Listing 9.6</td>
<td>Subject/Caregiver Global Impression of Change in Seizure Duration</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 9.7.1</td>
<td>Vineland-II Adaptive Behavior – Derived Data</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 9.7.2</td>
<td>Vineland-II Maladaptive Behavior – Derived Data</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 9.8</td>
<td>Wechsler Tests</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 9.9.1</td>
<td>Achenbach Child and Adult Behavior Checklist – Problem Scale Scores</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 9.9.2</td>
<td>Achenbach Child and Adult Behavior Checklist – Syndrome Scale Scores</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 9.9.3</td>
<td>Achenbach Child and Adult Behavior Checklist – Other Scale Scores</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 9.10</td>
<td>Social Communication Questionnaire – Derived Data</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 9.11</td>
<td>Time to Baseline TSC-associated Seizure Frequency</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 10.1</td>
<td>Exposure and Compliance</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 10.2</td>
<td>Exposure by Time</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 10.3</td>
<td>IMP Accountability</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 11.1.1</td>
<td>Treatment Emergent Adverse Events</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 11.1.2</td>
<td>Treatment Emergent Adverse Events of Special Interest</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 11.2</td>
<td>Pre-Treatment Adverse Events</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 12</td>
<td>Serious Adverse Events</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 13.1.1</td>
<td>Laboratory Parameters</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 13.1.2.1</td>
<td>Abnormal Laboratory Parameters by Patient</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 13.1.2.2</td>
<td>Abnormal Laboratory Parameters by Parameter</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 13.1.3</td>
<td>Laboratory Comments</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 13.1.4</td>
<td>Laboratory Liver Parameters</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.1.1</td>
<td>Vital Signs – Blood Pressures</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.1.2</td>
<td>Vital Signs – Pulse Rate, Respiratory Rate and Temperature</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.1.3</td>
<td>Vital Signs – Height, Weight and BMI</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.2</td>
<td>Clinically Significant Changes from Baseline for Vital Signs</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.3.1</td>
<td>ECG Data – Part 1</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.3.2</td>
<td>ECG Data – Part 2</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.4.1</td>
<td>Columbia-Suicide Severity Rating Scale (C-SSRS) – Suicidal Ideation and Intensity</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.4.2</td>
<td>Columbia-Suicide Severity Rating Scale (C-SSRS) – Suicidal Behavior</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.4.3</td>
<td>Columbia-Suicide Severity Rating Scale (C-SSRS) – Actual Attempts</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.5</td>
<td>Physical Examination</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.6</td>
<td>Tanner Stages</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.7</td>
<td>Menstruation Details</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.8</td>
<td>Inpatient Hospitalizations due to Epilepsy</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.9.1</td>
<td>Plasma Concentrations</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Listing 14.9.2</td>
<td>PK Parameters</td>
<td>Safety Analysis Set</td>
</tr>
</tbody>
</table>
### Listing Number | Title | Analysis Set
---|---|---
Listing 14.10 | Plasma Concentrations of Concomitant Antiepileptic Drugs | Safety Analysis Set
Listing 14.11.1 | Study Medication Use and Behavior Survey – Part 1 | Safety Analysis Set
Listing 14.11.2 | Study Medication Use and Behavior Survey – Part 2 | Safety Analysis Set
Listing 14.12.1 | Supplemental Drug Accountability Form | Safety Analysis Set
Listing 14.12.2 | Supplemental Adverse Events Form | Safety Analysis Set
Listing 14.12.3 | Site Classification Form | Safety Analysis Set
Listing 15 | Investigators' General Comments | Safety Analysis Set

### Table 20 List of OLE Phase Listings

<table>
<thead>
<tr>
<th>Listing Number</th>
<th>Title</th>
<th>Analysis Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLE Listing 1.1.1</td>
<td>Patient Disposition – End of Treatment</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 1.1.2</td>
<td>Patient Disposition – End of Taper</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 1.2</td>
<td>Visit Dates</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 2.1</td>
<td>Important Protocol Deviations</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 6.1</td>
<td>Prior and Concomitant Antiepileptic Therapies</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 6.2</td>
<td>Prior and Concomitant Antiepileptic Drugs</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 6.3</td>
<td>Prior and Concomitant Rescue Medications</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 6.4</td>
<td>Other Prior and Concomitant Medications</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 8.1.1</td>
<td>IVRS Diary Data – Part 1</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 8.1.2</td>
<td>IVRS Diary Data – Part 2</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 8.2.1</td>
<td>Derived TSC-associated, Other and Total Seizure Data</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 8.2.2</td>
<td>Derived Type 1, 3 and 3 Focal Seizure Data and Composite Focal Seizure Score</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 8.2.3</td>
<td>Derived Tonic-Clonic, Tonic, Clonic, and Atonic Seizure Data</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 8.2.4</td>
<td>Derived Absence, Myoclonic, Partial Sensory Seizure and Infantile or Epileptic Spasm Data</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 8.2.5</td>
<td>Derived Status Epilepticus Data</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 9.1</td>
<td>Subject/Caregiver/Physician Global Impression of Change</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 9.2</td>
<td>Quality of Life in Childhood Epilepsy (2-18 Years) – Derived Scores</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>Listing Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------------------------------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>OLE Listing 9.3</td>
<td>Quality of Life in Epilepsy (19 Years and Above) – Derived Scores</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 9.4</td>
<td>Number of Days of Rescue Medication Use</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 9.5</td>
<td>Subject/Caregiver Global Impression of Change in Seizure Duration</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 9.6.1</td>
<td>Vineland-II Adaptive Behavior – Derived Data</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 9.6.2</td>
<td>Vineland-II Maladaptive Behavior – Derived Data</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 9.7</td>
<td>Wechsler Tests</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 9.8.1</td>
<td>Achenbach Child and Adult Behavior Checklist – Problem Scale Scores</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 9.8.2</td>
<td>Achenbach Child and Adult Behavior Checklist – Syndrome Scale Scores</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 9.8.3</td>
<td>Achenbach Child and Adult Behavior Checklist – Other Scale Scores</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 9.9</td>
<td>Social Communication Questionnaire – Derived Data</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 10.1</td>
<td>Exposure</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 10.2</td>
<td>Exposure by Time</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 10.3</td>
<td>IMP Accountability</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 11.1.1</td>
<td>Treatment Emergent Adverse Events</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 11.1.2</td>
<td>Treatment Emergent Adverse Events of Special Interest</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 12</td>
<td>Serious Adverse Events</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 13.1.1</td>
<td>Laboratory Parameters</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 13.1.2.1</td>
<td>Abnormal Laboratory Parameters by Patient</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 13.1.2.2</td>
<td>Abnormal Laboratory Parameters by Parameter</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 13.1.3</td>
<td>Laboratory Comments</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 13.1.4</td>
<td>Laboratory Liver Parameters</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.1.1</td>
<td>Vital Signs – Blood Pressures</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.1.2</td>
<td>Vital Signs – Pulse Rate, Respiratory Rate and Temperature</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.1.3</td>
<td>Vital Signs – Height, Weight and BMI</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>Listing Number</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------------------------------------------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>OLE Listing 14.2</td>
<td>Clinically Significant Changes from Baseline for Vital Signs</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.3.1</td>
<td>ECG Data – Part 1</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.3.2</td>
<td>ECG Data – Part 2</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.4.1</td>
<td>Columbia-Suicide Severity Rating Scale (C-SSRS) – Suicidal Ideation and Intensity</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.4.2</td>
<td>Columbia-Suicide Severity Rating Scale (C-SSRS) – Suicidal Behavior</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.4.3</td>
<td>Columbia-Suicide Severity Rating Scale (C-SSRS) – Actual Attempts</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.5</td>
<td>Physical Examination</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.6</td>
<td>Tanner Stages</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.7</td>
<td>Menstruation Details</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.8</td>
<td>Inpatient Hospitalizations due to Epilepsy</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.9.1</td>
<td>Study Medication Use and Behavior Survey – Part 1</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.9.2</td>
<td>Study Medication Use and Behavior Survey – Part 2</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.10.1</td>
<td>Supplemental Drug Accountability Form</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.10.2</td>
<td>Supplemental Adverse Events Form</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 14.10.3</td>
<td>Site Classification Form</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Listing 15</td>
<td>Investigators’ General Comments</td>
<td>OLE Safety Analysis Set</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Figure Number</th>
<th>Title</th>
<th>Analysis Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 9.1.1.1.1</td>
<td>Cumulative Distribution Function for TSC-associated Seizures During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.1.1.2</td>
<td>Cumulative Distribution Function for TSC-associated Seizures During the Treatment Period</td>
<td>PP Analysis Set</td>
</tr>
<tr>
<td>Figure 9.1.2</td>
<td>Cumulative Distribution Function for TSC-associated Seizures During the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.1.3</td>
<td>Cumulative Distribution Function for TSC-associated Seizures During the Titration Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.1.4</td>
<td>Cumulative Distribution Function for TSC-associated Seizures During Weeks 1 to 4 of the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>9.1.5</td>
<td>Cumulative Distribution Function for TSC-associated Seizures During Weeks 5 to 8 of the Maintenance Period</td>
<td></td>
</tr>
<tr>
<td>9.1.6</td>
<td>Cumulative Distribution Function for TSC-associated Seizures During Weeks 9 to 12 of the Maintenance Period</td>
<td></td>
</tr>
<tr>
<td>9.2.1</td>
<td>Cumulative Distribution Function for Total Seizures During the Treatment Period</td>
<td></td>
</tr>
<tr>
<td>9.2.2</td>
<td>Cumulative Distribution Function for Total Seizures During the Maintenance Period</td>
<td></td>
</tr>
<tr>
<td>9.2.3</td>
<td>Cumulative Distribution Function for Total Seizures During the Titration Period</td>
<td></td>
</tr>
<tr>
<td>9.2.4</td>
<td>Cumulative Distribution Function for Total Seizures During Weeks 1 to 4 of the Maintenance Period</td>
<td></td>
</tr>
<tr>
<td>9.2.5</td>
<td>Cumulative Distribution Function for Total Seizures During Weeks 5 to 8 of the Maintenance Period</td>
<td></td>
</tr>
<tr>
<td>9.2.6</td>
<td>Cumulative Distribution Function for Total Seizures During Weeks 9 to 12 of the Maintenance Period</td>
<td></td>
</tr>
<tr>
<td>9.3</td>
<td>Cumulative Distribution Function for Other Seizures During the Treatment Period</td>
<td></td>
</tr>
<tr>
<td>9.4</td>
<td>Cumulative Distribution Function for Composite Focal Seizure Score During the Treatment Period</td>
<td></td>
</tr>
<tr>
<td>9.5.1</td>
<td>Cumulative Distribution Function for Type 1 Focal Seizures During the Treatment Period</td>
<td></td>
</tr>
<tr>
<td>9.5.2</td>
<td>Cumulative Distribution Function for Type 1 Focal Seizures During the Maintenance Period</td>
<td></td>
</tr>
<tr>
<td>9.5.3</td>
<td>Cumulative Distribution Function for Type 1 Focal Seizures During the Titration Period</td>
<td></td>
</tr>
<tr>
<td>9.5.4</td>
<td>Cumulative Distribution Function for Type 1 Focal Seizures During Weeks 1 to 4 of the Maintenance Period</td>
<td></td>
</tr>
<tr>
<td>9.5.5</td>
<td>Cumulative Distribution Function for Type 1 Focal Seizures During Weeks 5 to 8 of the Maintenance Period</td>
<td></td>
</tr>
<tr>
<td>9.5.6</td>
<td>Cumulative Distribution Function for Type 1 Focal Seizures During Weeks 9 to 12 of the Maintenance Period</td>
<td></td>
</tr>
<tr>
<td>9.6.1</td>
<td>Cumulative Distribution Function for Type 2 Focal Seizures During the Treatment Period</td>
<td></td>
</tr>
<tr>
<td>9.6.2</td>
<td>Cumulative Distribution Function for Type 2 Focal Seizures During the Maintenance Period</td>
<td></td>
</tr>
<tr>
<td>9.6.3</td>
<td>Cumulative Distribution Function for Type 2 Focal Seizures During the Titration Period</td>
<td></td>
</tr>
<tr>
<td>9.6.4</td>
<td>Cumulative Distribution Function for Type 2 Focal Seizures During Weeks 1 to 4 of the Maintenance Period</td>
<td></td>
</tr>
<tr>
<td>9.6.5</td>
<td>Cumulative Distribution Function for Type 2 Focal Seizures During Weeks 5 to 8 of the Maintenance Period</td>
<td></td>
</tr>
<tr>
<td>9.6.6</td>
<td>Cumulative Distribution Function for Type 2 Focal Seizures During Weeks 9 to 12 of the Maintenance Period</td>
<td></td>
</tr>
<tr>
<td>Period</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Figure 9.7.1</td>
<td>Cumulative Distribution Function for Type 3 Focal Seizures During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.7.2</td>
<td>Cumulative Distribution Function for Type 3 Focal Seizures During the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.7.3</td>
<td>Cumulative Distribution Function for Type 3 Focal Seizures During the Titration Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.7.4</td>
<td>Cumulative Distribution Function for Type 3 Focal Seizures During Weeks 1 to 4 of the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.7.5</td>
<td>Cumulative Distribution Function for Type 3 Focal Seizures During Weeks 5 to 8 of the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.7.6</td>
<td>Cumulative Distribution Function for Type 3 Focal Seizures During Weeks 9 to 12 of the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.8.1</td>
<td>Cumulative Distribution Function for Tonic-Clonic Seizures During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.8.2</td>
<td>Cumulative Distribution Function for Tonic-Clonic Seizures During the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.8.3</td>
<td>Cumulative Distribution Function for Tonic-Clonic Seizures During the Titration Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.8.4</td>
<td>Cumulative Distribution Function for Tonic-Clonic Seizures During Weeks 1 to 4 of the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.8.5</td>
<td>Cumulative Distribution Function for Tonic-Clonic Seizures During Weeks 5 to 8 of the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.8.6</td>
<td>Cumulative Distribution Function for Tonic-Clonic Seizures During Weeks 9 to 12 of the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.9.1</td>
<td>Cumulative Distribution Function for Tonic Seizures During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.9.2</td>
<td>Cumulative Distribution Function for Tonic Seizures During the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.9.3</td>
<td>Cumulative Distribution Function for Tonic Seizures During the Titration Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.9.4</td>
<td>Cumulative Distribution Function for Tonic Seizures During Weeks 1 to 4 of the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.9.5</td>
<td>Cumulative Distribution Function for Tonic Seizures During Weeks 5 to 8 of the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.9.6</td>
<td>Cumulative Distribution Function for Tonic Seizures During Weeks 9 to 12 of the Maintenance Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.10</td>
<td>Cumulative Distribution Function for Clonic Seizures During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.11</td>
<td>Cumulative Distribution Function for Atonic Seizures During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.12</td>
<td>Cumulative Distribution Function for Absence Seizures During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.13</td>
<td>Cumulative Distribution Function for Myoclonic Seizures During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------------------------------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Figure 9.14</td>
<td>Cumulative Distribution Function for Partial Sensory Seizures During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.15</td>
<td>Cumulative Distribution Function for Infantile or Epileptic Spasms During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.16.1</td>
<td>Kaplan-Meier Plot of Time to Baseline TSC-associated Seizure Frequency from the Start of the Treatment Period (Day 1)</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 9.16.2</td>
<td>Kaplan-Meier Plot of Time to Baseline TSC-associated Seizure Frequency from the Start of the Maintenance Period (Day 29)</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Figure 14.1.1</td>
<td>Box Plot of Change from Baseline to the End of Treatment Visit in IGF-1 Levels by Tanner Stages at Baseline</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.1.2</td>
<td>Scatter Plot of Change from Baseline to the End of Treatment Visit in IGF-1 Levels Against Weight at Baseline</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.1.3</td>
<td>Scatter Plot of Change from Baseline to the End of Treatment Visit in IGF-1 Levels Against Height at Baseline</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.1.4.1.X</td>
<td>Scatter Plot of Shift from Baseline to Maximum Post First Dose Laboratory Result - Hematology</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.1.4.2.X</td>
<td>Scatter Plot of Shift from Baseline to Maximum Post First Dose Laboratory Result - Biochemistry</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.1.1.1</td>
<td>Dot Plot of Individual CBD Plasma Concentration vs. Time Profiles, Visit 3, 25 and 50 mg/kg/day (Linear Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.1.1.2</td>
<td>Dot Plot of Individual CBD Plasma Concentration vs. Time Profiles, Visit 3, 25 and 50 mg/kg/day (Semi-Log Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.1.2.1</td>
<td>Dot Plot of Individual 7-OH-CBD Plasma Concentration vs. Time Profiles, Visit 3, 25 and 50 mg/kg/day (Linear Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.1.2.2</td>
<td>Dot Plot of Individual 7-OH-CBD Plasma Concentration vs. Time Profiles, Visit 3, 25 and 50 mg/kg/day (Semi-Log Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.1.3.1</td>
<td>Dot Plot of Individual 7-COOH-CBD Plasma Concentration vs. Time Profiles, Visit 3, 25 and 50 mg/kg/day (Linear Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.1.3.2</td>
<td>Dot Plot of Individual 7-COOH-CBD Plasma Concentration vs. Time Profiles, Visit 3, 25 and 50 mg/kg/day (Semi-Log Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.1.4.1</td>
<td>Dot Plot of Individual CBD Plasma Concentration vs. Time Profiles, Visit 10, 25 and 50 mg/kg/day (Linear Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.1.4.2</td>
<td>Dot Plot of Individual CBD Plasma Concentration vs. Time Profiles, Visit 10, 25 and 50 mg/kg/day (Semi-Log Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.1.5.1</td>
<td>Dot Plot of Individual 7-OH-CBD Plasma Concentration vs. Time Profiles, Visit 10, 25 and 50 mg/kg/day (Linear Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure</td>
<td>Dot Plot of Individual 7-OH-CBD Plasma</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Section</td>
<td>Title</td>
<td>Analysis Set</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------------------------------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>14.2.1.5.2</td>
<td>Concentration vs. Time Profiles, Visit 10, 25 and 50 mg/kg/day (Semi-Log Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.1.6.1</td>
<td>Dot Plot of Individual 7-COOH-CBD Plasma Concentration vs. Time Profiles, Visit 10, 25 and 50 mg/kg/day (Linear Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.1.6.2</td>
<td>Dot Plot of Individual 7-COOH-CBD Plasma Concentration vs. Time Profiles, Visit 10, 25 and 50 mg/kg/day (Semi-Log Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.2.1.1</td>
<td>Line Plot of Mean CBD Plasma Concentration vs. Time Profiles, Visit 3, 25 and 50 mg/kg/day (Linear Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.2.1.2</td>
<td>Line Plot of Mean CBD Plasma Concentration vs. Time Profiles, Visit 3, 25 and 50 mg/kg/day (Semi-Log Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.2.2.1</td>
<td>Line Plot of Mean 7-OH-CBD Plasma Concentration vs. Time Profiles, Visit 3, 25 and 50 mg/kg/day (Linear Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.2.2.2</td>
<td>Line Plot of Mean 7-OH-CBD Plasma Concentration vs. Time Profiles, Visit 3, 25 and 50 mg/kg/day (Semi-Log Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.2.3.1</td>
<td>Line Plot of Mean 7-COOH-CBD Plasma Concentration vs. Time Profiles, Visit 3, 25 and 50 mg/kg/day (Linear Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.2.3.2</td>
<td>Line Plot of Mean 7-COOH-CBD Plasma Concentration vs. Time Profiles, Visit 3, 25 and 50 mg/kg/day (Semi-Log Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.2.4.1</td>
<td>Line Plot of Mean CBD Plasma Concentration vs. Time Profiles, Visit 10, 25 and 50 mg/kg/day (Linear Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.2.4.2</td>
<td>Line Plot of Mean CBD Plasma Concentration vs. Time Profiles, Visit 10, 25 and 50 mg/kg/day (Semi-Log Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.2.5.1</td>
<td>Line Plot of Mean 7-OH-CBD Plasma Concentration vs. Time Profiles, Visit 10, 25 and 50 mg/kg/day (Linear Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.2.5.2</td>
<td>Line Plot of Mean 7-OH-CBD Plasma Concentration vs. Time Profiles, Visit 10, 25 and 50 mg/kg/day (Semi-Log Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.2.6.1</td>
<td>Line Plot of Mean 7-COOH-CBD Plasma Concentration vs. Time Profiles, Visit 10, 125 and 50 mg/kg/day (Linear Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.2.6.2</td>
<td>Line Plot of Mean 7-COOH-CBD Plasma Concentration vs. Time Profiles, Visit 10, 25 and 50 mg/kg/day (Semi-Log Scale)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.1.1.1</td>
<td>Box Plot of AUC0-t by Visit for CBD (25 mg/kg/day)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.1.1.2</td>
<td>Box Plot of AUC0-t by Visit for CBD (25 mg/kg/day), Age 1 to 6 Years</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.1.1.3</td>
<td>Box Plot of AUC0-t by Visit for CBD (25 mg/kg/day), Age 7 to 11 Years</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure</td>
<td>Box Plot of AUC0-t by Visit for CBD (25 mg/kg/day)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>14.2.3.1.1.4</td>
<td>mg/kg/day), Age 12 to 17 Years</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Figure 14.2.3.1.1.5</td>
<td>Box Plot of AUC0-t by Visit for CBD (25 mg/kg/day), Age 16 to 65 Years</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.1.2.1</td>
<td>Box Plot of AUC0-t by Visit for 7-OH-CBD (25 mg/kg/day)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.1.2.2</td>
<td>Box Plot of AUC0-t by Visit for 7-OH-CBD (25 mg/kg/day), Age 1 to 6 Years</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.1.2.3</td>
<td>Box Plot of AUC0-t by Visit for 7-OH-CBD (25 mg/kg/day), Age 7 to 11 Years</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.1.2.4</td>
<td>Box Plot of AUC0-t by Visit for 7-OH-CBD (25 mg/kg/day), Age 12 to 17 Years</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.1.2.5</td>
<td>Box Plot of AUC0-t by Visit for 7-OH-CBD (25 mg/kg/day), Age 18 to 65 Years</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.1.3.1</td>
<td>Box Plot of AUC0-t by Visit for 7-COOH-CBD (25 mg/kg/day)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.1.3.2</td>
<td>Box Plot of AUC0-t by Visit for 7-COOH-CBD (25 mg/kg/day), Age 1 to 6 Years</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.1.3.3</td>
<td>Box Plot of AUC0-t by Visit for 7-COOH-CBD (25 mg/kg/day), Age 7 to 11 Years</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.1.3.4</td>
<td>Box Plot of AUC0-t by Visit for 7-COOH-CBD (25 mg/kg/day), Age 12 to 17 Years</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.1.3.5</td>
<td>Box Plot of AUC0-t by Visit for 7-COOH-CBD (25 mg/kg/day), Age 18 to 65 Years</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.2.1.1</td>
<td>Box Plot of AUC0-t by Visit for CBD (50 mg/kg/day)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.2.1.2</td>
<td>Box Plot of AUC0-t by Visit for CBD (50 mg/kg/day), Age 1 to 6 Years</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.2.1.3</td>
<td>Box Plot of AUC0-t by Visit for CBD (50 mg/kg/day), Age 7 to 11 Years</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.2.1.4</td>
<td>Box Plot of AUC0-t by Visit for CBD (50 mg/kg/day), Age 12 to 17 Years</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.2.1.5</td>
<td>Box Plot of AUC0-t by Visit for CBD (50 mg/kg/day), Age 18 to 65 Years</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.2.2.1</td>
<td>Box Plot of AUC0-t by Visit for 7-OH-CBD (50 mg/kg/day)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.2.2.2</td>
<td>Box Plot of AUC0-t by Visit for 7-OH-CBD (50 mg/kg/day), Age 1 to 6 Years</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.2.2.3</td>
<td>Box Plot of AUC0-t by Visit for 7-OH-CBD (50 mg/kg/day), Age 7 to 11 Years</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.2.2.4</td>
<td>Box Plot of AUC0-t by Visit for 7-OH-CBD (50 mg/kg/day), Age 12 to 17 Years</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.2.2.5</td>
<td>Box Plot of AUC0-t by Visit for 7-OH-CBD (50 mg/kg/day), Age 18 to 65 Years</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.2.3.1</td>
<td>Box Plot of AUC0-t by Visit for 7-COOH-CBD (50 mg/kg/day)</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.2.3.2</td>
<td>Box Plot of AUC0-t by Visit for 7-COOH-CBD (50 mg/kg/day), Age 1 to 6 Years</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.2.3.3</td>
<td>Box Plot of AUC0-t by Visit for 7-COOH-CBD (50 mg/kg/day), Age 7 to 11 Years</td>
<td>Safety Analysis Set</td>
</tr>
<tr>
<td>Figure 14.2.3.2.3.4</td>
<td>Box Plot of AUC0-t by Visit for 7-COOH-CBD (50 mg/kg/day), Age 12 to 17 Years</td>
<td>Safety Analysis Set</td>
</tr>
</tbody>
</table>
Table 22  List of OLE Phase Figures

<table>
<thead>
<tr>
<th>Figure Number</th>
<th>Title</th>
<th>Analysis Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLE Figure 9.1.1</td>
<td>Percentage Change in TSC-associated Seizure Frequency Over Time</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Figure 9.1.2</td>
<td>Percentage Change in TSC-associated Seizure Frequency Over Time (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Figure 9.1.3</td>
<td>Percentage Change in TSC-associated Seizure Frequency Over Time (Patients with Data in OLE Week 37 to 48)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>------------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>OLE Figure 9.2.1</td>
<td>Percentage Change in Total Seizure Frequency Over Time</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Figure 9.2.2</td>
<td>Percentage Change in Total Seizure Frequency Over Time (LOCF)</td>
<td>OLE Safety Analysis Set</td>
</tr>
<tr>
<td>OLE Figure 9.2.3</td>
<td>Percentage Change in Total Seizure Frequency Over Time (Patients with Data in OLE Week 37 to 48)</td>
<td>OLE Safety Analysis Set</td>
</tr>
</tbody>
</table>
GW Research Ltd.

Trial Code: GWEP1521

A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF CANNABIDIOL (GWP42003-P, CBD) AS ADD-ON THERAPY IN PATIENTS WITH TUBEROUS SCLEROSIS COMPLEX WHO EXPERIENCE INADEQUATELY-CONTROLLED SEIZURES

Statistical Analysis Plan Addendum

28th November 2019
CONTENTS

1. INTRODUCTION 4
2. STATISTICAL METHODS 4
   2.1 General Considerations 4
   2.2 Analysis Sets 4
   2.3 Efficacy Analysis 4
      2.3.1 General Approach 4
      2.3.2 Cumulative Distribution Function Plots of Percent Reduction in Seizure Frequency 4
      2.3.3 Robustness to Withdrawn Patients 4
      2.3.4 Onset of Efficacy 5
   2.4 Safety Evaluation 6
      2.4.1 IMP Doses 6
3. AMENDMENTS 6
4. ATTACHMENTS AND APPENDICES 7
## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>Intention to Treat</td>
</tr>
<tr>
<td>NBR</td>
<td>Negative Binomial Regression</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
</tr>
</tbody>
</table>
1. INTRODUCTION

This document is an addendum to the statistical analysis plan (SAP) for trial GWEP1521, Version 2 dated 24th April 2019 (hereinafter referred to as the main SAP). This addendum consists of descriptions for a number of post-hoc analyses to support a summary of clinical efficacy.

2. STATISTICAL METHODS

2.1 General Considerations

Unless otherwise stated, the statistical reporting definitions and considerations as stated in the main SAP will also apply to this addendum.

All analyses and summaries will be produced using SAS® Version 9.4.

2.2 Analysis Sets

The intention to treat (ITT) analysis set as defined in the main SAP will be the primary analysis set for all endpoints.

2.3 Efficacy Analysis

2.3.1 General Approach

Statistical hypothesis testing will be performed as appropriate. However, no formal adjustment of statistical significance for multiple testing will be performed, although the multiplicity should be allowed for when interpreting the results.

All statistical tests will be 2-sided and use the 5% significance level.

2.3.2 Cumulative Distribution Function Plots of Percent Reduction in Seizure Frequency

Cumulative distribution plots plotting the percent reduction against the cumulative proportion of patients achieving that level of reduction, as described in the main SAP, will be generated for the following:

- Patients taking clobazam.
- Patients not taking clobazam.

The above will be generated for TSC-associated seizures during the blinded phase treatment period.

2.3.3 Robustness to Withdrawn Patients

There were higher proportions of patients in each treatment arm that withdrew during the blinded phase treatment period when compared with placebo. In order to assess the robustness of the results, 2 analyses in the following sections are proposed.
2.3.3.1 Time to 10th and 20th Seizure

Time from Day 1 to a patient experiencing their 10th and 20th or more seizure will be calculated as follows:

Date criterion was achieved – Date of Day 1 – Number of unreported days in IVRS between Day 1 and date criterion was achieved + 1

Patients who complete the blinded phase without experiencing greater than or equal to the corresponding number of seizures, or who withdraw from the blinded phase, will be censored at the earliest of:

- Day 113.
- The last recorded seizure day during the blinded phase treatment period.

The exact day used for censoring will be the day obtained from above minus the number of unreported days in IVRS between Day 1 and the day obtained from above.

The advantage of this proposed time to event analysis is that it is distinctly less sensitive to early withdrawals.

The time to corresponding event will be summarized on a continuous scale, by treatment arm. The lower and upper quartiles will also be presented along with the number of events and number of patients censored. In addition, the hazard ratio and 95% confidence interval, from a Cox proportional hazards model including treatment arm and stratified age group as covariates, will be presented along with a p-value from a log-rank test. A corresponding Kaplan-Meier plot will also be produced for both TSC-associated seizures and total seizures.

2.3.3.2 Analysis using Worst Case of No Change or Observed Worsening

The negative binomial regression (NBR) primary analysis will be repeated penalizing patients in the 25 mg/kg/day or 50 mg/kg/day treatment arms who withdrew during the blinded phase treatment period. The following will be used as the analysis value for withdrawn patients in the active arms:

- Patients with a reduction (improvement) in percentage change from baseline during the blinded phase treatment period will be imputed by setting the treatment period denominator, used in the NBR offset, to 113 days and the seizure count set to a value giving the same daily average observed during the baseline period.
- Patients with an increase (worsening) in percentage change from baseline during the blinded phase treatment period will be imputed by setting the treatment period denominator, used in the NBR offset, to 113 days and the seizure count set to a value giving the same daily average observed during the treatment period.

The primary endpoint analysis will be repeated using the above imputation.

2.3.4 Onset of Efficacy

To estimate the time to onset of efficacy, the NBR primary analysis and the first key secondary endpoint of ≥50% reduction in seizure frequency will be repeated by each cumulative day (e.g. Day 1, Day 1 and 2, Day 1, 2 and 3, etc.) of the blinded phase treatment period for TSC-associated seizures. In addition, the 25 mg/kg/day and 50 mg/kg/day treatment arms will be pooled and the above repeated for the first 10 days only.
2.4 Safety Evaluation

2.4.1 IMP Doses

For patients randomized to the 25 mg/kg/day or 50 mg/kg/day treatment arms, the following will be calculated for the blinded phase treatment period:

- Maximum dose achieved.
- Dose at the end of the period or time of withdrawal.
- Modal dose.

Unless missed doses or a dose reduction is recorded during the titration period, it will be assumed that patients were titrated according to the titration schedule stated in the protocol. The blinded phase treatment period will be defined as Day 1 to earliest of the day of last blinded phase dose or Day 113. The following will be summarized for patients randomized to the 25 mg/kg/day or 50 mg/kg/day treatment arms:

- Proportion of patients achieving the target maintenance dose.
- Proportion of patients at the target maintenance dose at the end of the blinded phase treatment period or time of withdrawal.
- Maximum dose achieved (mg/kg/day).
- Dose at the end of the blinded phase treatment period or time of withdrawal (mg/kg/day).
- Modal dose during the blinded phase treatment period (mg/kg/day).

3. AMENDMENTS

Notable changes to the SAP addendum between approved versions are given below. Minor changes, clarifications and corrections are not listed.

<table>
<thead>
<tr>
<th>Date</th>
<th>Section</th>
<th>Description of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 1  
List of Tables and Figures

Lists of the tables, figures and listings to be provided are given below in Table 1 Table 2 and Table 3, respectively.

Table 1  
List of Tables

<table>
<thead>
<tr>
<th>Table Number</th>
<th>Title</th>
<th>Analysis Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table A1.1</td>
<td>Analysis of Time to TSC-associated Seizures from the Start of the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table A1.2</td>
<td>Analysis of Time to Total Seizures from the Start of the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table A2</td>
<td>Negative Binomial Regression Analysis of TSC-associated Seizure Count During Baseline and Treatment Periods Using Worst Case of No Change or Observed Worsening for 25 mg/kg/day or 50 mg/kg/day Patients who Withdrew During the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table A3.1.1</td>
<td>Negative Binomial Regression Analysis of TSC-associated Seizure Count During Baseline and by Cumulative Day in the Treatment Period</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table A3.1.2</td>
<td>Analysis of TSC-associated Seizure Treatment Responders During the Treatment Period by Cumulative Day</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table A3.2.1</td>
<td>Negative Binomial Regression Analysis of Convulsive Seizure Count During Baseline and by Cumulative Day in the Treatment Period - 25 mg/kg/day and 50 mg/kg/day Pooled</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table A3.2.2</td>
<td>Analysis of TSC-associated Seizure Treatment Responders During the Treatment Period by Cumulative Day - 25 mg/kg/day and 50 mg/kg/day Pooled</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td>Table A4</td>
<td>Summary of Dose During the Blinded Treatment Phase</td>
<td>Safety Analysis Set</td>
</tr>
</tbody>
</table>
Table 2  List of Figures

<table>
<thead>
<tr>
<th>Figure Number</th>
<th>Title</th>
<th>Analysis Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure A1.1</td>
<td>Cumulative Distribution Function for TSC-associated Seizures During</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td></td>
<td>the Treatment Period - Patients Taking Clobazam</td>
<td></td>
</tr>
<tr>
<td>Figure A1.2</td>
<td>Cumulative Distribution Function for TSC-associated Seizures During</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td></td>
<td>the Treatment Period - Patients Not Taking Clobazam</td>
<td></td>
</tr>
<tr>
<td>Figure A2.1.1</td>
<td>Kaplan-Meier Plot of Time to 10th TSC-associated Seizure from the</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td></td>
<td>Start of the Treatment Period (Day 1)</td>
<td></td>
</tr>
<tr>
<td>Figure A2.1.2</td>
<td>Kaplan-Meier Plot of Time to 20th TSC-associated Seizure from the</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td></td>
<td>Start of the Treatment Period (Day 1)</td>
<td></td>
</tr>
<tr>
<td>Figure A2.2.1</td>
<td>Kaplan-Meier Plot of Time to 10th Total Seizure from the Start of</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td></td>
<td>the Treatment Period (Day 1)</td>
<td></td>
</tr>
<tr>
<td>Figure A2.2.2</td>
<td>Kaplan-Meier Plot of Time to 20th Total Seizure from the Start of</td>
<td>ITT Analysis Set</td>
</tr>
<tr>
<td></td>
<td>the Treatment Period (Day 1)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3  List of Listings

| Figure Number | Title                                             | Analysis Set         |
|---------------|                                                  |                      |
| Listing A1    | Dose During the Blinded Treatment Phase          | Safety Analysis Set  |