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This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned this report, healthcare professionals should consult local prescribing information for the product approved in their country.

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## 1.0 TITLE PAGE

<table>
<thead>
<tr>
<th>Title</th>
<th>A Phase 3, 12-Week, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Preladenant in Subjects With Moderate to Severe Parkinson's Disease (Phase 3; Protocol No. P07037)</th>
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<td>Schering-Plough Research Institute, a Division of Schering Corporation</td>
</tr>
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<td>Phase</td>
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<td>20 OCT 2011 – Amendment No. 3</td>
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<td>20 JUL 2011 – Amendment No. 2  07 DEC 2010 – Amendment No. 1  24 MAY 2010 – INITIAL PROTOCOL</td>
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<td>Protocol Template Approval Date</td>
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Redacted
2.0 SYNOPSIS

**TITLE OF TRIAL:** A Phase 3, 12-Week, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Preladenant in Subjects With Moderate to Severe Parkinson’s Disease (Phase 3; Protocol No. P07037)

**OBJECTIVES:**

**Primary Efficacy Objective:** The Primary Efficacy Objective of this trial is to evaluate the efficacy of the preladenant doses 2 mg twice daily and 5 mg twice daily compared with placebo in subjects with moderate to severe Parkinson’s disease (PD) experiencing motor fluctuations and receiving a stable dose of levodopa (L-dopa), as measured by “off” time.

**Primary Safety Objective:** The Primary Safety Objective of this trial is to assess the safety and tolerability of preladenant compared with placebo in subjects with moderate to severe PD experiencing motor fluctuations and receiving a stable dose of L-dopa.

**Key Secondary Trial Objectives:** The Key Secondary Efficacy Objectives for this trial are to evaluate the efficacy of the preladenant doses 2 mg twice daily and 5 mg twice daily compared with placebo in subjects with moderate to severe PD experiencing motor fluctuations and receiving a stable dose of L-dopa as measured by the proportion of Responders and by “on” time without troublesome dyskinesia.

**Trial Design**

**Overview:** This is a randomized, placebo-controlled, parallel-group, multiple-center, double-blind trial of preladenant in adult subjects with moderate to severe PD.

**Number of Trial Centers:** Approximately 80.

**Duration of Participation:** Each subject will participate in the trial for approximately 15 to 18 weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of up to 5 weeks, each subject will be receiving assigned treatment for approximately 12 weeks. After the End of Treatment, the subject may choose to enroll in an extension trial (up until the maximum number of subjects for that extension trial has been reached) or return for a Follow-up Visit 2 weeks later.

**Duration of Trial:** The trial will require approximately 1.5 years from the beginning to the end of the overall trial (first subject signing informed consent to last contact with last subject).

**Inclusion/Exclusion Criteria:** Adult subjects with a diagnosis of moderate to severe idiopathic Parkinson’s disease will be selected to participate in the trial.

**Inclusion Criteria:**

- Each subject must have a diagnosis of idiopathic PD based on the United Kingdom Parkinson’s Disease Society Brain Bank Criteria and the inclusion/exclusion criteria for this protocol.
  - Each subject should have bradykinesia and at least one of the following symptoms:
    - Muscular rigidity
    - Resting tremor (4 to 6 Hz; Please note that for the purposes of this study, a diagnosis based solely on bradykinesia and postural instability is insufficient for diagnosis of idiopathic Parkinson’s Disease, and subjects diagnosed in this manner cannot be enrolled in the study)
  - Each subject must have received prior therapy with L-dopa for approximately 1 or more years immediately before Screening and must continue to have a beneficial clinical response to L-dopa at Screening.
  - Each subject must have been on a stable, optimal dopaminergic treatment regimen, defined as maximum therapeutic effect achieved with available anti-parkinsonian treatment, for at least the 5 weeks immediately before Randomization.
  - Subjects receiving the adjunct PD medications listed in the table below are permitted to enroll in this trial. Each subject who is receiving one or more of the adjunct PD medications listed below must have been on a stable regimen of treatment for at least the 5 weeks immediately before Randomization.
TITLE OF TRIAL: A Phase 3, 12-Week, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Preladenant in Subjects With Moderate to Severe Parkinson's Disease (Phase 3; Protocol No. P07037)

- Amantadine
- Anticholinergics
- Dopa decarboxylase inhibitors
- Dopamine agonists
- Entacapone
- L-dopa

• Each subject's Hoehn and Yahr stage must be ≥2.5 and ≤4 in the optimum “on” state at Screening.
• Each subject must be experiencing motor fluctuations with or without dyskinesia following optimum titration of treatment medications and within the 5 weeks immediately before Screening.
• Each subject must be experiencing a minimum of 2 hours/day of “off” time as estimated by the investigator and supported by the 3-day symptom diary (Daily Diary) at Randomization.
• Each subject, with or without the help of a caregiver, must be capable of maintaining an accurate and complete symptom diary (Daily Diary) as assessed at the Diary Training Visit.
• Each subject (or subject’s legal representative) must be willing and able to provide written informed consent for the trial. For a subject who is unable to provide independent consent, a legal representative may provide written informed consent. Subjects who are unwilling to provide written informed consent for exploratory pharmacogenetic testing may be included in the trial; however, exploratory pharmacogenetic samples must not be obtained.
• Each subject must be ≥30 to ≤85 years of age. A subject may be of either sex, any race/ethnicity.
• Each subject must have results of Screening clinical laboratory tests (hematology, blood chemistries, and urinalysis) drawn within 5 weeks prior to Randomization, clinically acceptable to the investigator, and not within the parameters specified for exclusion (below).
• Each subject must have results of a physical examination within normal limits or clinically acceptable limits to the investigator.
• Each subject must be able to adhere to dose and visit schedules.
• All subjects that are sexually active or plan to be sexually active agree to use a highly effective method of birth control while the subject is in the study and for 2 weeks after the last dose of study drug. A male subject must also not donate sperm within 2 weeks after the last dose of study drug. Complete details regarding contraceptive requirements are specified in protocol Section 7.7.2.7.
**Title of Trial:** A Phase 3, 12-Week, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Preladenant in Subjects With Moderate to Severe Parkinson's Disease (Phase 3; Protocol No. P07037)

**Exclusion Criteria**

- A subject must not have a form of drug-induced or atypical parkinsonism, cognitive impairment (i.e., Montreal Cognitive Assessment [MoCA] score <22, bipolar disorder, schizophrenia, or other psychotic disorder. (Subjects with non-troublesome hallucinations, stable on low dose quetiapine or clozapine are allowed to enroll.)

- A subject must not have a history of any of the following:
  - repeated strokes with stepwise progression of Parkinsonian features
  - repeated head injury
  - definitive encephalitis
  - oculogyric crises
  - neuroleptic treatment at onset of symptoms
  - more than one first degree relative affected
  - sustained remission
  - strictly unilateral features after 3 years
  - supranuclear gaze palsy
  - cerebellar signs
  - early severe autonomic involvement
  - severe symptomatic autonomic involvement unrelated to medications
  - early severe dementia with disturbances of memory, language, and praxis
  - Babinski sign with clear, clinically significant pyramidal tract involvement
  - presence of cerebral tumor or communicating hydrocephalus on neuroimaging (by history)
  - negative response to large doses of L-dopa (if malabsorption excluded)
  - MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) or known neurotoxin exposure
  - hallucinations unrelated to medications
  - stroke within 6 months of Screening or persistent neurological deficit that may interfere with study assessments
  - surgery for PD

- A subject must not have an untreated major depressive disorder meeting Diagnostic and Statistical Manual of Mental Disorders IV Text Revision (DSM-IV-TR) criteria or Beck Depression Inventory II (BDI II) score ≥19. A subject who is successfully treated (Beck Depression Inventory-II [BDI-II] score <19) with stable doses of allowed antidepressant medications for at least the 5 weeks immediately before Screening is eligible to enroll in the trial.

- A subject must not be at imminent risk of self-harm or harm to others, in the investigator's opinion based on clinical interview and responses provided on the Columbia - Suicide Severity Rating Scale (C-SSRS). Subjects must be excluded if they report suicidal ideation of Type 4 or 5 in the past 2 months or suicidal behavior in the past 6 months as measured by the C-SSRS during Screening or Randomization Visits.
**Title of Trial:** A Phase 3, 12-Week, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Preladenant in Subjects With Moderate to Severe Parkinson’s Disease (Phase 3; Protocol No. P07037)

- In the judgment of the investigator, a subject must not have sleep attacks or compulsive behavior that would interfere with the integrity of the trial or would pose a risk to the subject in participating in the trial.

- **Blood Pressure:** A subject must not have a systolic blood pressure (BP) ≥150 mm Hg OR diastolic BP ≥95 mm Hg at Screening and at a BP recheck prior to Randomization. Should the BP remain elevated, the subject may not enter the trial until the BP has been adequately controlled with antihypertensive medication as demonstrated by 2 BP measurements meeting this criterion at consecutive separate visits (scheduled or unscheduled) within 5 weeks prior to Randomization. If antihypertensive medications are used to control a subject’s BP, the subject’s BP and doses of antihypertensive medications must be stable for at least 2 weeks prior to Randomization. Note: during the course of the study antihypertensive medication may be initiated or increased to control a subject’s BP at any time during treatment in P07037 as needed.

- **Cardiovascular Disease:** A subject must not have had any clinically significant cardiovascular event or procedure for 6 months prior to Randomization, including, but not limited to, myocardial infarction, prolonged QTc interval [a subject must not have a QTcF result > 500 msec], angioplasty, unstable angina, or heart failure; and a subject must not have heart failure staged New York Heart Association Class III or IV.

- **Liver Enzymes:** A subject must not have an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3 x the upper limit of normal (ULN) or total bilirubin (T-BIL) ≥1.5 x ULN. Should a liver function test (LFT) be abnormal (AST/ALT >ULN but <3 x ULN, T-BIL >ULN but <1.5 x ULN) at Screening, the investigator should attempt to characterize at entry the reason(s) for elevation(s), eg, alcohol abuse (see next exclusion criterion), metabolic syndrome with fatty liver, etc. No repeat testing allowed. Subjects with suspected Gilbert’s Syndrome who have isolated T-BILI ≥ 1.5 x ULN may enter the study upon genetic confirmation (UGT1A1 assessment).

- **Liver Disease:** A subject must not have active serologically confirmed hepatic dysfunction (defined as viral infection [Hepatitis B, C, or E; Epstein-Barr virus (EBV); cytomegalovirus (CMV)]) or a history of diagnosis of drug- or alcohol-induced hepatic toxicity or frank hepatitis.

- If a subject has abnormal ALT or AST at Screening (>1.5 x ULN), the subject must have serology testing to rule out active viral hepatitis. A subject who has a history of serologically confirmed EBV or CMV may be enrolled in the trial as long as his/her viral infection was not associated with hepatitis in the past, and his/her ALT and AST are normal at Screening. Types of serology assays to be performed are specified in the table of Laboratory Tests in the section on Trial Procedures.

- A subject must not have a history within the past 5 years of a primary or recurrent malignant disease with the exception of adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or in situ prostate cancer with a normal prostate-specific antigen (PSA) post resection.

- A subject must not have received any treatment listed in the table below more recently than the indicated period before Randomization.

- A subject must not need to continue to receive any treatment listed in the table below during the trial. Note: Warnings and Contraindications detailed in the Prescribing Information for the allowed medications (listed in the inclusion criteria describing stable dopaminergic treatment) should be followed.
**PROHIBITED MEDICATIONS, SUPPLEMENTS, AND OTHER SUBSTANCES**

<table>
<thead>
<tr>
<th>Prohibited Medications, Supplements, and Other Substances</th>
<th>Period Before Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolcapone</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Irreversible MAO inhibitors, eg, rasagiline, selegiline, Zydus selegiline</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Reversible MAOB or MAOA inhibitor</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Centrally acting dopamine antagonist (including metoclopramide, sulpiride, tiapride, etc)</td>
<td>4 weeks</td>
</tr>
<tr>
<td>α-methyldopa</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Reserpine</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Flunarizine</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Cinnarizine</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Diphenhydramine used to treat parkinsonism</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Theophylline</td>
<td>4 weeks</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Other potentially hepatotoxic drugs (including amiodarone, azathioprine, felbamate, imatinib, isoniazid, isotretinoin,</td>
<td>4 weeks</td>
</tr>
<tr>
<td>lefluonamide, methotrexate, nevirapine, pioglitazone, rosiglitazone, pyrazinamide, valproic acid, and voriconazole)</td>
<td></td>
</tr>
<tr>
<td>Potent CYP3A4 inhibitors (eg, ritonavir, nelfinavir, indinavir); macrolide antibiotics (eg, erythromycin, clari...</td>
<td>4 weeks</td>
</tr>
<tr>
<td>telithromycin, azithromycin (azithromycin is allowed)); and systemically administered antifungal agents (eg, ketoconazole,</td>
<td></td>
</tr>
<tr>
<td>itraconazole)</td>
<td></td>
</tr>
<tr>
<td>CYP3A4 inducers (eg, phenytoin, phenobarbital, barbiturates, systemic glucocorticoids)</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

- A subject must not have an average daily consumption of more than three 4-ounce glasses (118 mL) of wine or the equivalent.
- A subject must not have poorly controlled diabetes (eg, HbA1c >8.5) or significantly abnormal renal function (eg, creatinine >2.0 mg/dL) in the opinion of the investigator.
- A subject must not have a severe or ongoing unstable medical condition (eg, any form of clinically significant cardiac disease, symptomatic orthostatic hypotension, seizures, or alcohol/drug dependence).
- A subject must not have participated in any studies using preladenant.
- A subject must not have allergy/sensitivity to the investigational products or their excipients.
- A female subject must not be breast-feeding or considering breast-feeding.
- A female subject must not be pregnant or intending to become pregnant.
- A subject must not have any clinically significant condition or situation, other than the condition being studied that, in the opinion of the investigator, would interfere with the trial evaluations or optimal participation in the trial.
TITLE OF TRIAL: A Phase 3, 12-Week, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Preladenant in Subjects With Moderate to Severe Parkinson’s Disease (Phase 3; Protocol No. P07037)

- A subject must not have used any investigational drugs within 90 days immediately before Screening.
- A subject must not have been participating in any other clinical trial within 90 days, inclusive, of signing the informed consent form of this trial.
- A subject must not be a member or a family member of the personnel of the investigational or sponsor staff directly involved with this trial.

INVESTIGATIONAL PRODUCT, REFERENCE PRODUCTS, DOSE, MODE OF ADMINISTRATION

Investigational Product: Preladenant (SCH 420814) will be supplied as 2- and 5-mg tablets. Subjects in the 2 mg and 5 mg treatment groups will receive one 2-mg tablet or one 5-mg tablet of preladenant orally twice daily for 12 weeks.

Reference Product: Subjects in the placebo treatment group will receive one matching placebo tablet orally twice daily for 12 weeks.

STATISTICAL METHODS:

Data Sets to be Analyzed:

Full Analysis Set (FAS): All randomized subjects with subjects excluded for the following reasons:

- Failure to receive at least one dose of study treatment.
- Lack of any post-Randomization endpoint data subsequent to at least one dose of study treatment.
- Lack of Baseline data for those analyses requiring Baseline data.

All Subjects as Treated (ASaT) Set: All subjects who received at least one dose of study drug.

Efficacy analyses will be conducted using the FAS. Randomization will be preserved in the efficacy analyses. Safety analyses will be conducted using the ASaT Set. In the safety analyses, subjects will be analyzed according to the treatment actually received.

Sample Size: Approximately 450 subjects will receive randomized treatment assignment in a 1:1:1 ratio so that approximately 150 subjects are assigned to each of the three treatment arms.

Primary Efficacy Analysis:

“On” time is when a PD subject’s symptoms are improved. “Off” time is when a subject’s PD symptoms return. Both measures are subject-reported on a Daily Diary for 3 days (24 hours/day) prior to given time points.

Hypothesis 1 (Primary Hypothesis): At least the 5 mg twice daily dose of preladenant is superior to placebo as measured by the change from Baseline to Week 12 in the mean “off” time.

The Primary Efficacy Endpoint for this trial is:

- The change from Baseline to End of Treatment (Week 12) in mean “off” time in hours per day.

The Primary Efficacy Endpoint will be analyzed using a constrained longitudinal data analysis (cLDA) approach with treatment, time, treatment-by-time interaction, Baseline value and subject effects in the model. The least squares mean (LSM) response and pairwise differences between preladenant doses and placebo along with 95% confidence intervals will be provided. P-values from tests of preladenant versus placebo for this endpoint constitute tests of the Primary Hypothesis.

Key Secondary Efficacy Analysis: There are two Key Secondary Hypotheses:

Hypothesis 2: At least the 5 mg twice daily dose of preladenant is superior to placebo as measured by the proportion of subjects with at least a 30% reduction in mean “off” time from Baseline to Week 12.

Hypothesis 3: At least the 5 mg twice daily dose of preladenant is superior to placebo as measured by the change from Baseline to Week 12 in mean “on” time without troublesome dyskinesia.

The Key Secondary Efficacy Endpoints are:
**TITLE OF TRIAL:** A Phase 3, 12-Week, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Preladenant in Subjects With Moderate to Severe Parkinson's Disease (Phase 3; Protocol No. P07037)

- The proportion of Responders, where a Responder is defined as a subject with at least a 30% reduction in mean "off" time from Baseline to Week 12.
- The change from Baseline to Week 12 in mean "on" time without troublesome dyskinesia in hours per day.

The proportion of Responders will be analyzed using a generalized linear mixed model with treatment effect and Baseline mean "off" time as a covariate. Responder rates for each treatment arm will be presented along with odds ratios and 95% confidence intervals for the odds ratios comparing preladenant dose groups with placebo. The change from Baseline in the mean "on" time without troublesome dyskinesia will be evaluated using the same cLDA model used for the Primary Endpoint. The LSM and pairwise differences between preladenant doses and placebo along with 95% confidence intervals will be provided. P-values from tests of preladenant versus placebo for these endpoints constitute tests of the Key Secondary Hypotheses.

Multiplicity for the preladenant versus placebo comparisons in the Primary and Key Secondary Endpoints will be controlled using a sequential testing procedure. Testing for the Primary and Key Secondary Endpoints will begin with comparisons of the highest dose of preladenant versus placebo (5 mg twice daily) for each endpoint beginning with the Primary endpoint, then the proportion of Responders and last, the "on" time without troublesome dyskinesias. If each of these comparisons is statistically significant (p ≤ 0.049) then testing will continue with comparisons of the lowest dose, 2 mg twice daily, versus placebo for the same three endpoints. Testing will continue until a non statistically significant difference is reached or all Primary and Key Secondary hypotheses have been tested.

**Safety Analysis:** Treatment comparisons for pre-specified (Tier 1) events (including the incidence of elevated BP [systolic ≥ 180 mm Hg and/or diastolic ≥ 105 mm Hg] and aminotransferase elevations [ALT and/or AST ≥ 3 x ULN] with ≥ a 10% increase from Baseline], and suicidality incidence) will be performed using the Miettinen and Nurminen method. The 95% confidence intervals on the pairwise differences between preladenant doses versus placebo will be provided. Between-treatment group differences in the Epworth Sleepiness Scale score change from Baseline will be evaluated using the same cLDA model as for the Primary Endpoint.

Commonly Occurring Adverse Events will be summarized by dose group using frequency counts, as well as incidence rates with 95% confidence intervals. Suicidal behavior and suicidal ideation will be summarized by treatment group. Adverse events, vital signs, laboratory data, 12-lead electrocardiogram (ECG) parameters, and QUIP-RS score and Sleep Attack Questionnaire results will be listed and summarized by treatment group and time point; where applicable, values outside the normal range will be flagged. Assessments of interest, LFTs and BP, will be analyzed using descriptive statistics and graphs.

**Interim Analysis:** No formal interim efficacy analysis is planned. However, an external Data Monitoring Committee will be reviewing safety data and may ask to review efficacy data if deemed necessary. Therefore, an alpha adjustment of 0.001 (Haybittle Peto method) will be made to account for this, and the final analysis will use a 0.049 alpha-level.

**Data Monitoring Committee (DMC):** Safety will be monitored by an external DMC on an ongoing basis and the DMC will make recommendations to the sponsor as appropriate. Details will be provided in the DMC Charter. ALT/AST ≥ 3 x ULN and ≥ 10% increase from Baseline and vascular adverse events will be adjudicated by separate blinded independent expert committees and findings reported to the DMC.
2.1 Trial Design Diagram (P07037)

Screening Period (up to 5 weeks) →
- Preladenant 5 mg Twice Daily (n=150)
- Preladenant 2 mg Twice Daily (n=150)
- Placebo Twice Daily (n=150)

Double-Blind Treatment Period (12 weeks)

Safety Follow-Up Period (2 weeks)
- Subject Continues in Extension Trial
- Subject Does Not Continue to Extension Trial and Completes Safety Follow-Up Visit

Diary Training →
- CV1 → CV2 → CV3 → CV4 → CV5 → LV6 → CV7 → CV8 → CV9

Baseline Randomization (Day 1*)

End of Active Treatment

Safety Follow-Up Visit

3-Day Daily Diary Collection Period before each indicated visit.

CV = Clinic Visit; LV = Laboratory Visit

a The Daily Diary must be completed the 3 consecutive days immediately prior to the Baseline Visit and for all subsequent Clinic Visits (excluding the Lab Visit 6 and Follow-Up Visit).

b The timing of all visits after the Day 1 visit must be based on the day the first dose of study drug was administered to the subject. If study drug is not available at the study center at the time of the Day 1 visit, then the Day 1 visit must be postponed until drug has arrived at the study center.
### 2.2 Trial Flow Chart (P07037)

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Visit Window (Days)</th>
<th>Screening Period</th>
<th>Double-Blind Treatment Period</th>
<th>Follow-Up Period*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lab Visit (LV)(^2) or Clinic Visit (CV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Week</td>
<td>-5 to -2</td>
<td>-2 to (-1)^t</td>
<td>(Day 1(^{th}))</td>
<td>2</td>
</tr>
<tr>
<td>Procedures</td>
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<td></td>
</tr>
<tr>
<td>Informed Consent(^3)</td>
<td>X</td>
<td></td>
<td>±3</td>
<td>±7</td>
</tr>
<tr>
<td>Assign Screening Number</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacogenetic Testing Consent(^4)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Issue/Collect Subject Identification Card(^5)</td>
<td>X</td>
<td></td>
<td>±7</td>
<td>±7</td>
</tr>
<tr>
<td>Inclusion/Exclusion Criteria(^6)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assign Subject Number and Randomized Treatment</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History Including Duration of PD, Caffeine &amp; Alcohol Use &amp; Smoking, &amp; Family History of Premature Coronary Heart Disease(^7)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Prior Medications(^8)</td>
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<tr>
<td>Concomitant Medications(^9)</td>
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<td></td>
<td>±7</td>
<td>±7</td>
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<tr>
<td>Record Adverse Events</td>
<td>X</td>
<td></td>
<td>±7</td>
<td>±14</td>
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<td>Physical Exam Including Melanoma Exam (by a Board Certified Dermatologist)</td>
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<td>Hoehn and Yahr Stage (in the Optimal “On” State)</td>
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<tr>
<td>Montreal Cognitive Assessment (MoCA)</td>
<td>X</td>
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<td>±7</td>
<td>±7</td>
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<tr>
<td>Beck Depression Inventory (BDI-II)</td>
<td>X</td>
<td></td>
<td>±7</td>
<td>±7</td>
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<td>Epworth Sleepiness Scale</td>
<td>X</td>
<td></td>
<td>±7</td>
<td>±7</td>
</tr>
<tr>
<td>Procedures</td>
<td>Visit Window (Days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>---------------------</td>
<td></td>
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<tr>
<td>Questionnaire for Impulsive-Compulsive Disorders in PD – Rating Scale (QUIP-RS)</td>
<td>±3</td>
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<tr>
<td>Apathy Scale</td>
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</tr>
<tr>
<td>EuroQoL Five Dimension Questionnaire (EQ-5D)</td>
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<tr>
<td>Parkinson’s Disease Questionnaire PDQ-39</td>
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<td>** Pre Study Drug UPDRS Parts 1, 2, 3, and 4th</td>
<td>X&lt;sup&gt;th&lt;/sup&gt;</td>
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<tr>
<td>Blood Sample for Exploratory Pharmacogenetics&lt;sup&gt;h&lt;/sup&gt;</td>
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<tr>
<td>HLA and UGT1A1 Sample&lt;sup&gt;g&lt;/sup&gt;</td>
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<tr>
<td>Pre Study Drug Dose Blood Sample for Pharmacokinetics&lt;sup&gt;g&lt;/sup&gt;</td>
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<tr>
<td>Blood Samples for Hematology and Blood Chemistry</td>
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<td>Urinalysis (and as warranted)</td>
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<tr>
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** Table 1: Study Procedures and Visit Window **

- **Screening Period:**
  - 1 CV
  - 2 CV
  - 3 CV
  - 4 CV
  - 5 CV
  - 6 LV
  - 7 CV
  - 8 CV
  - 9 CV

- **Double-Blind Treatment Period:**
  - 2 to -1<sup>a</sup> (Day 1<sup>a</sup>)
  - 6
  - 8

- **Follow-Up Period:**
  - 12

- **Early Termination:**
  - 14
<table>
<thead>
<tr>
<th>Procedures</th>
<th>Visit Window (Days)</th>
<th>Screening Period</th>
<th>Double-Blind Treatment Period</th>
<th>Follow-Up Period</th>
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<tr>
<td>Lab Visit (LV) or Clinic Visit (CV)</td>
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<tr>
<td>Study Week</td>
<td>−5 to −2</td>
<td>1 CV</td>
<td>2 CV</td>
<td>3 CV</td>
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<tr>
<td></td>
<td>−2 to −1</td>
<td>4 CV</td>
<td>5 CV</td>
<td>6 LV CV</td>
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<td></td>
<td>(Day 1)</td>
<td>7 CV</td>
<td>8 CV</td>
<td>9 CV CV</td>
</tr>
<tr>
<td>Procedures</td>
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<tr>
<td>Medication Compliance/Drug Accountability</td>
<td>±3</td>
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<td>±7</td>
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<tr>
<td>Dispense Study Drug</td>
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<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>On-Site Administration of Study Drug</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>^1 ≥1 Hour after the 1st Dose UPDRS Part 3^3</td>
<td>x</td>
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<td>x</td>
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<tr>
<td>^2 ≥1 Hour after the AM Dose UPDRS Parts 1, 2, 3, &amp; 4^4</td>
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<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Post Study Drug Blood Sample for Pharmacokinetics</td>
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<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>ON/OFF and Diary Training</td>
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<td>x</td>
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<tr>
<td>Diary Dispensing</td>
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<td>x</td>
</tr>
<tr>
<td>Give Blank EQ-5D/PDQ-39</td>
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<tr>
<td>Diary Assessment</td>
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<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Register Visit in Interactive Voice Response System (IVRS)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

Note: With the exception of Day 1 and Week 8, on the days of lab visits and clinic visits and on the days in between them, subjects should take the first daily dose of study drug at home at their regular time. The second dose should be taken 8 hours later.

At all times during the study, including on clinic visit and lab visit days, each subject should continue taking his/her regular doses of L-dopa and adjunct PD medications, according to his/her individually prescribed, stable regimen. Doses of the permitted adjunct PD medications must remain constant (with exceptions for increases only as noted in Section 7.4.2.1.2).

At every clinic visit, each subject should be reminded to carry all his/her study drug AND any and all PD medications to the next CV.

∞ The C-SSRS and UPDRS should be assessed by the same experienced qualified rater for a given subject across clinic visits. Hoehn and Yahr staging also must be performed by an experienced qualified rater.
<table>
<thead>
<tr>
<th>Lab Visit (LV) or Clinic Visit (CV)</th>
<th>Screening</th>
<th>Diary Training(^b)</th>
<th>Baseline Randomization</th>
<th>Lab Only(^c)</th>
<th>End of Treatment</th>
<th>Safety Follow-Up(^d)</th>
<th>Early Termination(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Week</td>
<td>1 CV</td>
<td>2 CV</td>
<td>3 CV</td>
<td>4 CV</td>
<td>5 CV</td>
<td>6 LV</td>
<td>7 CV</td>
</tr>
<tr>
<td>Procedures</td>
<td>Visit Window (Days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>±3</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±7</td>
<td>±14</td>
<td>±7</td>
</tr>
</tbody>
</table>

\(^a\) Only for subjects who are not continuing into an extension trial.

\(^b\) Subject fills out Daily Diary for 3 consecutive days immediately before the clinic visit. Subject returns to site to have the Daily Diary assessed, to review recognition of ON and OFF states, and to receive reinforcement of Daily Diary training.

\(^c\) A Lab Visit is one in which the following laboratory safety bloodwork is collected: total serum bilirubin [T-BIL], serum aspartate aminotransferase [AST], serum alanine aminotransferase [ALT], serum alkaline phosphatase [ALK-P]. Each lab visit should be registered in IVRS.

\(^d\) The Safety Follow-Up Visit also applies to subjects who have been terminated early from the study. Following discontinuation of study drug, the patient will be followed by telephone contact at 48 hours and 7 days after the subject’s last dose of study drug as detailed in Section 7.7.2.2.3. Further, whenever a subject is discontinued from the trial because of elevated liver enzymes, the subject must be followed until there is evidence of recovery and resolution. Blood for a chemistry panel should be obtained at the Safety Follow-Up and any Early Termination Visit. Blood samples for hematology and/or serology must be drawn and/or urine collected at the Safety Follow-Up and any Early Termination Visit only if there were clinically relevant abnormal lab results at the subject’s previous visit.

\(^e\) There must be 3 days for the collection of Daily Diary data between the Screening Visit and the Diary Training Visit, and the Diary Training Visit and the Baseline Visit.

\(^f\) The timing of all visits after the Day 1 Visit must be based on the day the first dose of study drug was administered to the subject. If study drug is not available at the study center at the time of the Day 1 Visit, then the Day 1 visit must be postponed until drug has arrived at the study center. If a subject is unable to attend his/her scheduled visit, this must be documented in the subject’s file and the site should request that the subject return as close to the scheduled visit date as possible.

\(^g\) Subjects who sign the Informed Consent Form (ICF) for P07037 are also consenting to supply pharmacokinetic and HLA and UGT1A1 blood samples in P07037. At Clinic Visit 7 the subject must be provided with the ICF for, and counseled regarding specifics about, the extension study in order to provide sufficient time for an informed decision about whether or not to participate in the extension study. If a subject wishes to participate in the extension study (up until the maximum number of subjects for that extension study has been reached), he/she will be counseled on medications not allowed in the P06153 extension study at the Screening Visit for P07037 and will be asked to sign the ICF for the extension study at the End of Treatment Visit in P07037. Subjects who wish to participate in the P06153 extension study but are taking medications not allowed for entry into P06153 must washout of such medications for the appropriate period prior to entry into P07037 to be eligible for the extension study.

\(^h\) Informed consent for exploratory pharmacogenetic testing must be obtained before the DNA sample. DNA sample for analysis should be obtained before the first study drug dose on Day 1.
<table>
<thead>
<tr>
<th></th>
<th>Screening Period</th>
<th>Double-Blind Treatment Period</th>
<th>Follow-Up Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lab Visit (LV) or Clinic Visit (CV)</td>
<td>Screening 1 CV 2 CV 3 CV</td>
<td>Diary Training (Day 1&lt;sup&gt;a&lt;/sup&gt;) Baseline Randomization 4 CV 5 CV 6 LV 7 CV 8 CV 9 CV 10&lt;sup&gt;a&lt;/sup&gt;</td>
<td>End of Treatment 2 4 6 8 12 14</td>
</tr>
<tr>
<td>Study Week</td>
<td>-5 to -2</td>
<td>-2 to -1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Safety Follow-Up 14</td>
</tr>
<tr>
<td>Procedures</td>
<td>Visit Window (Days)</td>
<td>14</td>
<td>Early Termination CV</td>
</tr>
</tbody>
</table>

<sup>a</sup> Subject Identification Cards for P07037 will be issued to all subjects before dispensing study drug at the Baseline/Randomization Visit. At the End of Treatment Visit, Subject Identification Cards will be collected only from subjects continuing into the extension trial. For subjects not continuing into the extension trial, Subject Identification Cards will be collected at the Safety Follow Up or Early Termination Visit.

<sup>b</sup> For subjects who entered P07037 under the initial protocol, the investigator or qualified designee should contact the subjects and obtain the subjects’ family history of premature coronary heart disease. This information must be recorded in the subjects’ source documentation and on the Family History of Premature Coronary Heart Disease eCRF.

<sup>c</sup> When reviewing concomitant medications, also review drugs, foods, nutraceuticals and other substances prohibited for subjects to ingest during the trial. During this review, the subject will be instructed to take his/her stable L-dopa and adjunct PD medications as usual and to carry the L-dopa and adjunct PD medications to clinic visits. Doses of the permitted adjunct PD medications must remain constant (with exceptions only as noted in Section 7.4.2.1.2).

<sup>d</sup> The EQ-5D and PDQ-39 may be filled out by the subject at home on the day before or the morning of a clinic visit. If these tests are done by the subject at home, they do not need to be repeated in the clinic. However, site staff must review them for completeness before transcribing them to the eCRF.

<sup>e</sup> See Section 2.2.1 for full details regarding how the UPDRS is to be evaluated.

<sup>f</sup> See Section 7.6 Trial Procedures for details regarding BP methodology.

<sup>g</sup> At the Baseline Visit and the End of Treatment or Early Termination Visit, record three sets of 12-lead ECGs taken 5 to 10 minutes apart. Only a single set of 12-lead ECGs is required at Screening.

<sup>h</sup> The sample for HLA (human lymphocyte antigen) and UGT1A1 is mandatory. A single 6-mL sample (for both HLA and UGT1A1) must be drawn before the first dose of study drug and will be stored for potential analysis if liver safety findings need further clarification.

<sup>i</sup> At Week 8, blood for PK analysis will be drawn before the on-site administration of study drug and again at approximately 2 hours (range, 1 to 4 hours) after the on-site administration of study drug. A blood sample for PK analysis will be drawn only at an Early Termination Visit occurring before Week 8. The time of the subject’s last dose of study drug before the PK blood draw and the time of the blood draw for PK sampling should be recorded in the eCRF for all PK blood draws.

<sup>j</sup> Only female subjects of child-bearing potential must have pregnancy tests. (Additionally, a sample for FSH [follicle-stimulating hormone] should be drawn for female subjects who are ≥ 46 years old and who have been amenorrheic for >6 months and <1 year.) A serum pregnancy test (human chorionic gonadotropin [hCG]) should be done at Screening (within 5 weeks prior to Day 1) and at End of Treatment. A urine pregnancy test should be done on Day 1. Results must be negative before dispensing or administering (on-site at the Day 1 and Week 8 Visits) study drug. Thereafter, a urine pregnancy test...
<table>
<thead>
<tr>
<th>Study Week</th>
<th>Procedures</th>
<th>Visit Window (Days)</th>
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</thead>
<tbody>
<tr>
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<td>Lab Visit (LV) or Clinic Visit (CV)</td>
<td>1 CV</td>
</tr>
<tr>
<td>-2 to -1</td>
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<td>2 CV</td>
</tr>
<tr>
<td>(Day 1&lt;sup&gt;0&lt;/sup&gt;)</td>
<td></td>
<td>3 CV</td>
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<td></td>
<td>9 CV</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>CV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Drug Administration</th>
</tr>
</thead>
</table>

- Study drug will be administered at the clinical site.

- Study drug administered at the clinical site should be taken from the newly dispensed bottle, except at the End of Treatment or Early Termination Visit.

- Subjects and investigator (or trained designee) will review the training digital video disc (DVD) and agree upon/review what are considered the ON and OFF states. The subject will be instructed to complete the Daily Diary for 3 days starting upon waking 3 days before the next clinic visit.

- Subjects should be reminded to start collecting diary data upon waking 3 days before their next clinic visit.

- Give the subject a blank EQ-5D and PDQ-39 with instructions to fill it out the day before or the morning of the next scheduled clinic visit.

- Staff will review the Daily Diary with the subject, and the data listed below will be recorded for each half-hour time segment in the eCRF. If the subject does not know what category applied during a specific half-hour, enter 'not done' rather than leave a time point value blank.

  - OFF.
  - ON without dyskinesia.
  - ON with non-troublesome dyskinesia.
  - ON with troublesome dyskinesia.
<table>
<thead>
<tr>
<th>Lab Visit (LV)(^c) or Clinic Visit (CV)</th>
<th>Lab Visit (LV)(^c) or Clinic Visit (CV)</th>
<th>Lab Visit (LV)(^c) or Clinic Visit (CV)</th>
<th>Lab Visit (LV)(^c) or Clinic Visit (CV)</th>
<th>Lab Visit (LV)(^c) or Clinic Visit (CV)</th>
<th>Lab Visit (LV)(^c) or Clinic Visit (CV)</th>
</tr>
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<td>1 CV</td>
<td>2 CV</td>
<td>3 CV</td>
<td>4 CV</td>
<td>5 CV</td>
<td>6 CV</td>
</tr>
<tr>
<td>Diary Training(^b)</td>
<td>Diary Training(^b)</td>
<td>Diary Training(^b)</td>
<td>Diary Training(^b)</td>
<td>Diary Training(^b)</td>
<td>Diary Training(^b)</td>
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<tr>
<td>Baseline Randomization</td>
<td>Baseline Randomization</td>
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<tr>
<td>3 CV</td>
<td>4 CV</td>
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<td>6 CV</td>
<td>7 CV</td>
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</tr>
<tr>
<td>Follow-Up Period(^d)</td>
<td>Follow-Up Period(^d)</td>
<td>Follow-Up Period(^d)</td>
<td>Follow-Up Period(^d)</td>
<td>Follow-Up Period(^d)</td>
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<td>10 CV</td>
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<tr>
<td>-5 to -2</td>
<td>-2 to -1(^a)</td>
<td>(Day 1(^{0.5}))</td>
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<td>4</td>
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</tbody>
</table>

- Asleep.
- Register in IVRS by visit as follows:
  - At Visit 1, register the subject’s Screening Number.
  - At Visit 2, register Clinic Visit.
  - At Visit 3, register the subject’s Randomization Number and any Drug Dispensing Activity.
  - At Visit 4, register Clinic Visit.
  - At Visit 6, register Lab Visit.
  - At Visits 5 and 7, register Drug Dispensing Activity
  - At Visit 8, register the subject’s status as Treatment Complete or Going into Extension Trial.
  - Register Visit 9 as the End of Trial.
  - At an Early Termination Visit, register the subject’s status as Treatment Discontinued and enter Reason for Discontinuation.
### 2.2.1 UPDRS Evaluations (P07037)

<table>
<thead>
<tr>
<th>Lab Visit (LV) or Clinic Visit (CV)</th>
<th>Screening Period</th>
<th>Double-Blind Treatment Period</th>
<th>Follow-Up Period</th>
<th>Early Termination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-5 to -2</td>
<td>1 CV</td>
<td>2 CV</td>
<td>3 CV</td>
<td>4 CV</td>
</tr>
<tr>
<td>-2 to -1</td>
<td>5 CV</td>
<td>6 LV</td>
<td>7 CV</td>
<td>8 CV</td>
</tr>
<tr>
<td>Procedure</td>
<td>Visit Window (Days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre Study Drug UPDRS Parts 1, 2, 3, &amp; 4 (Optimal ON State)</td>
<td>±3</td>
<td>±7</td>
<td>±7</td>
<td>±14</td>
</tr>
<tr>
<td>≥1 Hour after the 1st Dose UPDRS Part 3 (Optimal ON State)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 Hour after the AM Dose UPDRS Parts 1, 2, 3, &amp; 4 (Optimal ON State)</td>
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UPDRS: Unified Parkinson's Disease Rating Scale

**Notes:**

- On the days of CVs, for **before** and **during** the visit, record in the eCRF the time(s) at which study drug was taken.
- Record the start time of each UPDRS evaluation in the eCRF.
- For any given subject, UPDRS evaluations should be performed by the same experienced qualified rater at each visit.
- The UPDRS should always be evaluated when the subject is in the optimal ON state.

a On **Day 1**, the UPDRS must be performed **twice**: Parts 1, 2, 3, and 4 must be evaluated once before study drug administration, and Part 3 only must be evaluated once, at least 1 hour after the first dose of study drug.

b The UPDRS evaluation should occur at approximately the same time of day at each visit. (The post study drug UPDRS evaluations for Week 2 through End of Treatment [or Early Termination] should occur at approximately the same time of day as the Day 1 predose UPDRS.)
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<td>Adenosine type 2a receptor</td>
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<td>Adverse Event</td>
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<td>ALK-P</td>
<td>Alkaline Phosphatase</td>
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<td>Alanine Aminotransferase (SGPT)</td>
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<td>ANCOVA</td>
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<td>Code of Federal Regulations</td>
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<td>Confidence Interval</td>
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<td>Constrained Longitudinal Data Analysis</td>
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<td>Cytomegalovirus</td>
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<td>Epstein-Barr Virus</td>
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<td>Electrocardiogram</td>
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SCHERING-POUGH RESEARCH INSTITUTE
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<td>eCRF</td>
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<td>EDC</td>
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<td>EU</td>
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<td>Food and Drug Administration, USA</td>
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<td>FSH</td>
<td>Follicle Stimulating Hormone</td>
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<td>GABAergic</td>
<td>( \gamma )-aminobutyric-acid-containing</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GLIMMIX</td>
<td>Generalized Linear Mixed Model</td>
</tr>
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<td>GPV</td>
<td>Global Pharmacovigilance, A sub-unit of SPRI that is responsible for worldwide safety surveillance of all Schering marketed and investigational drugs, biologics and devices.</td>
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<td>HbA1c</td>
<td>Hemoglobin A1c</td>
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<td>High Density Lipoprotein</td>
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<td>Human lymphocyte antigen</td>
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<td>ICF</td>
<td>Informed Consent Form</td>
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<td>ICH</td>
<td>International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use</td>
</tr>
<tr>
<td>ICMJE</td>
<td>International Committee of Medical Journal Editors</td>
</tr>
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<td>IgG</td>
<td>Immunoglobulin G</td>
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<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
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<tr>
<td>IND</td>
<td>Investigational New Drug Application; legal instrument in the USA that allows trial of unapproved, investigational new drugs in human subjects</td>
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<td>International Normalized Ratio</td>
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<td>Investigational Product</td>
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<td>Institutional Review Board</td>
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<td>IUD</td>
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<td>Interactive Voice Response System</td>
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<td>1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine</td>
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<td>Parkinson’s Disease</td>
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<td>PK/PD</td>
<td>Pharmacokinetic/Pharmacodynamic</td>
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<td>SOP</td>
<td>Standard Operating Procedure</td>
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<td>SPRI</td>
<td>Schering-Plough Research Institute, a division of Schering Corporation</td>
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<td>[Human bilirubin] uridine 5’-diphospho-glucuronosyltransferase [promoter]</td>
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<td>Upper Limit of Normal</td>
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<td>Term</td>
<td>Definition</td>
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<td>Unified Parkinson’s Disease Rating Scale</td>
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<td>United States of America</td>
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<td>White Blood Cell</td>
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5.0 INTRODUCTION

Redacted
Redacted
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6.0 TRIAL OBJECTIVES AND HYPOTHESES

6.1 Primary Objectives and Hypotheses

6.1.1 Primary Efficacy Objective

The Primary Efficacy Objective of this trial is to evaluate the efficacy of the preladenant doses 2 mg twice daily and 5 mg twice daily compared with placebo in subjects with moderate to severe PD experiencing motor fluctuations and receiving a stable dose of L-dopa, as measured by “off” time.

Primary Hypothesis

• Hypothesis 1: At least the 5 mg twice daily dose of preladenant is superior to placebo as measured by the change from Baseline to Week 12 in the mean “off” time.

6.1.2 Primary Safety Objective

The Primary Safety Objective of this trial is to assess the safety and tolerability of preladenant compared with placebo in subjects with moderate to severe PD experiencing motor fluctuations and receiving a stable dose of L-dopa.
6.2 Key Secondary Objectives and Hypotheses

The Key Secondary Efficacy Objectives for this trial are to evaluate the efficacy of the preladenant doses 2 mg twice daily and 5 mg twice daily compared with placebo in subjects with moderate to severe PD experiencing motor fluctuations and receiving a stable dose of L-dopa, as measured by the proportion of Responders and by "on" time without troublesome dyskinesia.

Key Secondary Hypotheses

- **Hypothesis 2**: At least the 5 mg twice daily dose of preladenant is superior to placebo as measured by the proportion of subjects with at least a 30% reduction in mean “off” time from Baseline to Week 12.
- **Hypothesis 3**: At least the 5 mg twice daily dose of preladenant is superior to placebo as measured by the change from Baseline to Week 12 in mean “on” time without troublesome dyskinesia.

6.3 Other Trial Objectives

Other objectives of this trial are to evaluate the effect of the preladenant doses 2 mg twice daily and 5 mg twice daily as measured by the UPDRS, BDI-II, MoCA, EQ-5D, and PDQ-39.

7.0 INVESTIGATIONAL AND ANALYSIS PLAN

7.1 Overall Trial Design

Throughout this section, please refer to the following visual aids:

- Flow Chart, Section 2.2
- UPDRS Evaluations, Section 2.2.1

This is a randomized, placebo-controlled, parallel-group, multiple-center, double-blind trial of preladenant in adult subjects with moderate to severe PD to be conducted in conformance with Good Clinical Practice. A neurologist experienced in movement disorders will evaluate and diagnose idiopathic PD. For the entire
duration of the trial, including during study visits, subjects will continue to take their usual, prescribed, stable regimen of L-dopa or L-dopa plus adjunct PD medications.

After a Screening Period of up to 5 weeks, subjects will be randomized into one of three treatment groups (preladenant 2 or 5 mg twice daily or placebo) in a 1:1:1 ratio and receive double-blind treatment for 12 weeks. At the end of the Double-Blind Treatment Period, subjects may choose to enter into an extension trial (up until the maximum number of subjects for that extension trial has been reached) or return for a Follow-Up Visit 2 weeks later.

Data will be collected using a Daily Diary (20-22) and the following assessment instruments, validated as indicated below (samples of which are provided in the Manual of Sample Questionnaires to Accompany Protocol P07037 Amendment 2): a modified version of Montreal Cognitive Assessment (MoCA), (23) Unified Parkinson’s Disease Rating Scale (UPDRS), (24-27) Beck Depression Inventory (BDI-II), (27) Columbia - Suicide Severity Rating Scale (C-SSRS), (28) Epworth Sleepiness Scale, (29) Questionnaire for Impulsive-Compulsive Disorders in PD – Rating Scale (QUIP-RS; the QUIP-RS is an abbreviated version of the QUIP which has been validated in subjects with PD), (30,31) Apathy Scale, (32) and other patient reported and economic outcomes (eg, EuroQoL Five Dimension Questionnaire [EQ-5D] (33,34) and Parkinson’s Disease Questionnaire [PDQ-39] (35,36). Additionally, a Sleep Attack Questionnaire, (37) will be used to gather information about the adverse event of sleep attacks. Safety data, such as vital signs, hematology, and blood chemistry will also be collected as indicated in Section 2.2, Study Flow Chart.

The assessments are listed below with comments regarding the timing of the UPDRS, the EQ-5D, and the PDQ-39 (see Note at the bottom of the list). On Day 1, evaluations specified in the Flow Charts (Section 2.2 and Section 2.2.1) will be performed before any study drug is dispensed (and Part 3 of the UPDRS will be performed at least 1 hour after the administration of study drug). After Day 1, the assessments marked with an asterisk (*) below (at the time points specified in the Flow Charts) may be performed at any time in relation to dose of study drug. Numbers 6 and 7 may be completed by the patient at home prior to the Clinic Visit. Number 8 will be performed by the investigator or qualified designee. Numbers 9 and 10 will be performed by an experienced qualified rater.

1. MoCA*
2. BDI-II*
3. Epworth Sleepiness Scale*
4. QUIP-RS*
5. Apathy Scale*
6. EQ-5D*
7. PDQ-39*
8. Sleep Attack Questionnaire*
9. C-SSRS*

10. UPDRS – On Day 1, the UPDRS must be performed twice: Parts 1, 2, 3, and 4 must be evaluated once before study drug administration, and Part 3 only must be evaluated once, at least 1 hour after the first dose of study drug when the subject is in the optimal “on” state. The Day 1 pre study drug UPDRS evaluation should occur at approximately the same time of day as the post study drug UPDRS evaluations for Week 2 through End of Treatment. At Week 2 through End of Treatment (and at Early Termination) the UPDRS (Parts 1, 2, 3, and 4) will be performed at least 1 hour after the morning dose of study drug when the subject is in the optimal “on” state.

Note: The EQ-5D and PDQ-39 may be filled out by the subject at home on the day before or the morning of a clinic visit. If these tests are done by the subject at home, they do not need to be repeated in the clinic. However, site staff must review them for completeness. All paper questionnaires are considered the source documents, and site staff will transcribe subject-reported information or experienced qualified rater information from each questionnaire into the electronic case report form (eCRF).

7.1.1 Screening Period

The Screening Period consists of two visits.

At the First Screening Visit:

• The subject will be evaluated for eligibility
• The subject will be trained by the investigator (or his/her trained designee) to recognize “on” and “off” states and dyskinesia using a training digital video disc (DVD) provided to all sites.
• The subject will be trained to maintain the Daily Diary.

The investigator (or his/her trained designee) will review the subject’s “on” and “off” symptoms with the subject, and the investigator (or his/her trained designee) and subject will agree to a consistent interpretation of when “on” and “off” symptoms begin and end. The subject will be given a Daily Diary to be filled out manually at home and instructed to maintain the diary for the 3 consecutive days immediately before the next clinic visit.
At the Second Screening Visit:

- The subject and the investigator (or his/her trained designee) will assess the subject’s competence to fill out the Daily Diary.
- The subject and the investigator (or his/her trained designee) will review the training DVD and reinforce recognition of “on” and “off” states and maintenance of the Daily Diary.
- The subject will receive a new Daily Diary and instructions to maintain the diary for the 3 consecutive days immediately before the next visit.

7.1.2 12-Week Double-Blind Treatment Period

At the Baseline Visit, the subject’s eligibility will be verified, including verification that the subject meets the requirement of the minimum of 2 hours/day of “off” time as indicated in the Daily Diary, and the subject will be randomized using the Interactive Voice Response System (IVRS) into one of three treatment groups (preladenant 2 or 5 mg twice daily or placebo). Subjects will receive assigned treatment for 12 weeks. Subjects will have clinic visits (CVs) at Day 1 and Weeks 2, 4, 8, and 12 and a lab-only visit (LV) at Week 6 (Section 2.2, Trial Flow Chart).

On Day 1, the UPDRS must be performed twice: Parts 1, 2, 3, and 4 must be evaluated once before study drug administration, and Part 3 only must be evaluated once, at least 1 hour after the first dose of study drug when the subject is in the optimal “on” state. Because PD symptoms often fluctuate depending on the time of day, the Day 1 pre study drug UPDRS evaluation should occur at approximately the same time of day as the post study drug UPDRS evaluations for Week 2 through End of Treatment. For Week 2 through End of Treatment (and at Early Termination), the UPDRS (Parts 1, 2, 3, and 4) should be performed at least 1 hour after the morning dose of study drug when the subject is in the optimal “on” state.

At each clinic visit during the Double-Blind Treatment period including the Baseline and End of Treatment Visits, the Daily Diary will be assessed and the subject and investigator (or his/her trained designee) will review recognition of “on” and “off” states using the training DVD (except for the DVD at the End of Treatment Visit). The subject will receive a new Daily Diary and instructions to maintain the diary for the 3 consecutive days immediately before the next clinic visit.

Study drug will be administered at the clinical site (“on-site”) on Day 1 and at Week 8. At Week 8, predose and postdose pharmacokinetics (PK) samples will be drawn for a population PK analysis. Blood pressure will be measured at every clinic visit (3 BP cycles predose and 3 BP cycles postdose on Day 1 and Week 8, and one BP cycle at steady-state for all other clinic visits; See Section 7.6., Trial Procedures for details). A 12-lead electrocardiogram will be recorded (3 sets) both
on Day 1 and at End of Treatment (or Early Termination). The timing of other assessments (eg, questionnaires, safety laboratory bloodwork, etc) is provided in Section 2.2, Trial Flow Chart.

At the end of the Double-Blind Treatment Period, a subject may choose to participate in an extension study (up until the maximum number of subjects for that extension study has been reached) or return for a Follow-Up Visit 2 weeks after the End of Treatment Visit.

7.1.3 Follow-Up Period

Subjects who do not choose to enroll in an extension study will be followed for adverse events by telephone contact at 48 hours and 7 days after the subject's last dose of study drug as detailed in Section 7.7.2.2.3 and will return for a Follow-Up Visit 2 weeks after the End of Treatment Visit. Blood for a chemistry panel should be obtained at the Safety Follow-Up Visit. Blood samples for hematology and/or serology must be drawn and/or urine collected at the Safety Follow-Up only if there were clinically relevant abnormal lab results at the subject’s previous visit. Subjects who discontinue from the trial early should be followed for adverse events by telephone contact at 48 hours and 7 days after the subject's last dose of study drug and should return for a 2-week Follow-Up Visit.

7.1.4 Early Termination

Subjects who discontinue participation in this trial before completing the End of Treatment Visit should complete an Early Termination Visit. All the procedures scheduled for the End of Treatment Visit should be conducted at the Early Termination Visit. Whenever a subject is discontinued from the trial because of elevated liver enzymes, the subject must be followed until there is evidence of recovery and resolution. Blood for a chemistry panel should be obtained at the Early Termination Visit. Blood samples for hematology and/or serology must be drawn and/or urine collected at the Early Termination Visit only if there were clinically relevant abnormal lab results at the subject’s previous visit. A blood sample for PK analysis will be drawn only at an Early Termination Visit occurring before Week 8. Subjects who terminate early cannot participate in the extension study. Subjects who discontinue from the trial early will be followed for adverse events by telephone contact at 48 hours and 7 days after the subject's last visit on study drug as detailed in Section 7.7.2.2.3 and early should also return for a 2-week Follow-Up Visit.
7.2 Beginning and End of the Trial

A subject is considered

• to be enrolled in the trial when the subject (or the subject’s legal representative) has provided written informed consent;
• to have fulfilled participation in the trial when he/she has completed the last protocol-specified contact (eg, visits or telephone contacts);
• to have completed Treatment if he/she has completed up through the End of Treatment Visit (Week 12);
• to have completed the trial after he/she has completed all of the protocol-specified visits and activities (including the Follow-Up Visit);
• to have discontinued the trial after he/she has withdrawn consent or has been discontinued under the conditions specified in Section 7.3.3;
• to have been lost to follow-up if he/she is unable to be contacted by the investigator.

The end of participation for a subject lost to follow-up is the last known contact (eg, visit or telephone contact).

The overall trial begins when the first subject is enrolled (ie, signs the Informed Consent Form [ICF]). No trial-related assessments can be performed until after the subject has signed the ICF. The overall trial ends when the last remaining subject has ended participation in the trial, by completing the trial, being discontinued from the trial, or being lost to follow-up.

Each subject will be monitored for the occurrence of serious adverse events (SAEs) immediately after the subject has signed the ICF. Each subject will be followed for SAEs for up to and including 30 days after the last dose of study drug. Follow-up procedures related to pregnancy or SAEs may continue beyond the end of the clinical trial.

At the end of the Double-Blind Treatment Period, a subject who has completed the trial may choose to participate in an extension trial (up until the maximum number of subjects for that extension trial has been reached). If the subject does not choose to participate in an extension trial, the investigational product from the trial will no longer be available to the subject and any future care will be provided according to the subject’s personal physician.

Each subject will participate in the trial for approximately 15 to 18 weeks from the time the subject signs the ICF through the final protocol-specified contact. After a screening phase of up to 5 weeks, each subject will receive assigned treatment...
(Section 7.4.1) for approximately 12 weeks. After the End of Treatment, the subject will be followed for adverse events by telephone contact at 48 hours and 7 days after the subject's last dose of study drug as detailed in Section 7.7.2.2.3. and may choose to enroll in an extension trial, or return for a Follow-Up Visit 2 weeks later. Subjects who terminate early from the trial also should return for a 2-week Follow-Up Visit.

7.3 Trial Population

Adult subjects with a diagnosis of moderate to severe idiopathic PD will be selected to participate in the trial.

7.3.1 Subject Inclusion Criteria

The subject must fulfill ALL the criteria listed below for entry.

Inclusion Criteria Related to PD

1. Each subject must have a diagnosis of idiopathic PD based on the United Kingdom Parkinson's Disease Society Brain Bank Criteria (see Appendix 1) and the inclusion/exclusion criteria for this protocol. Each subject should have bradykinesia and at least one of the following symptoms:
   i. Muscular rigidity
   ii. Resting tremor (4 to 6 Hz; Please note that for the purposes of this study, a diagnosis based solely on bradykinesia and postural instability is insufficient for diagnosis of idiopathic Parkinson's Disease, and subjects diagnosed in this manner cannot be enrolled in the study).
2. Each subject must have received prior therapy with L-dopa for approximately 1 or more years immediately before Screening and must continue to have a beneficial clinical response to L-dopa at Screening.
3. Each subject must have been on a stable, optimal dopaminergic treatment regimen, defined as maximum therapeutic effect achieved with available anti-parkinsonian treatment, for at least the 5 weeks immediately before Randomization.
4. Subjects receiving the adjunct PD medications listed in Table 1 are permitted to enroll in this trial. Each subject who is receiving one or more of the adjunct PD medications listed in Table 1 must have been on a stable regimen of treatment for at least the 5 weeks immediately before Randomization.

<table>
<thead>
<tr>
<th>Table 1 Adjunct PD Medications Permitted During the Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol No. P07037</td>
</tr>
<tr>
<td>Amantadine</td>
</tr>
<tr>
<td>Anticholinergics</td>
</tr>
<tr>
<td>Dopa decarboxylase inhibitors</td>
</tr>
<tr>
<td>Dopamine agonists</td>
</tr>
<tr>
<td>Entacapone</td>
</tr>
<tr>
<td>L-dopa</td>
</tr>
</tbody>
</table>

5. Each subject’s Hoehn and Yahr stage must be \( \geq 2.5 \) and \( \leq 4 \) in the optimum “on” state at Screening.

6. Each subject must be experiencing motor fluctuations with or without dyskinesias following optimum titration of treatment medications and within the 4 weeks immediately before Screening.

7. Each subject must be experiencing a minimum of 2 hours/day of “off” time as estimated by the investigator and supported by the 3-day symptom diary (Daily Diary) at Randomization.

8. Each subject, with or without the help of a caregiver, must be capable of maintaining an accurate and complete symptom diary (Daily Diary) as assessed at the Diary Training Visit.

**Other Inclusion Criteria**

9. For subjects who are interested in participating in the P06153 extension study, an adequate washout period must be followed as per the prohibited medication table (Table 6) prior to entry into P07037 to be eligible for P06153.

10. Each subject (or subject’s legal representative) must be willing and able to provide written informed consent for the trial. For a subject who is unable to provide independent consent, a legal representative may provide written informed consent. Subjects who are unwilling to provide written informed consent for exploratory pharmacogenetic testing may be included in the trial; however, exploratory pharmacogenetic samples must not be obtained.

11. Each subject must be \( \geq 30 \) to \( \leq 85 \) years of age. A subject may be of either sex, any race/ethnicity.
12. Each subject must have results of Screening clinical laboratory tests (hematology, blood chemistries, and urinalysis) drawn within 5 weeks prior to Randomization, clinically acceptable to the investigator, and not within the parameters specified for exclusion (below).

13. Each subject must have results of a physical examination within normal limits or clinically acceptable limits to the investigator.

14. Each subject must be able to adhere to dose and visit schedules.

15. All subjects that are sexually active or plan to be sexually active agree to use a highly effective method of birth control while the subject is in the study and for 2 weeks after the last dose of study drug. A male subject must also not donate sperm within 2 weeks after the last dose of study drug. Complete details regarding contraceptive requirements are specified in protocol Section 7.7.2.7.

7.3.2 Subject Exclusion Criteria

A subject must not violate any of the exclusion criteria listed below before entry.

Exclusion Criteria Related to PD (Neurologic and Psychiatric)

1. A subject must not have a form of drug-induced or atypical parkinsonism, cognitive impairment (ie, MoCA score <22), bipolar disorder, schizophrenia, or other psychotic disorder. (Subjects with non-troublesome hallucinations, stable on low dose quetiapine or clozapine are allowed to enroll.)

2. A subject must not have a history of any of the following:
   - repeated strokes with stepwise progression of Parkinsonian features
   - repeated head injury
   - definitive encephalitis
   - oculogyric crises
   - neuroleptic treatment at onset of symptoms
   - more than one first degree relative affected
   - sustained remission
   - strictly unilateral features after 3 years
   - supranuclear gaze palsy
   - cerebellar signs
   - early severe autonomic involvement
   - severe symptomatic autonomic involvement unrelated to medications
• early severe dementia with disturbances of memory, language, and praxis
• Babinski sign with clear, clinically significant pyramidal tract involvement
• presence of cerebral tumor or communicating hydrocephalus on neuroimaging (by history)
• negative response to large doses of L-dopa (if malabsorption excluded)
• MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) or known neurotoxin exposure
• hallucinations unrelated to medications
• stroke within 6 months of Screening or persistent neurological deficit that may interfere with study assessments
• surgery for PD

3. A subject must not have an untreated major depressive disorder meeting Diagnostic and Statistical Manual of Mental Disorders IV Text Revision (DSM-IV-TR) criteria or Beck Depression Inventory II (BDI II) score ≥19. A subject who is successfully treated [Beck Depression Inventory-II (BDI-II) score < 19] with stable doses of allowed antidepressant medications for at least the 5 weeks immediately before Screening is eligible to enroll in the trial.

4. A subject must not be at imminent risk of self-harm or harm to others, in the investigator’s opinion based on clinical interview and responses provided on the Columbia - Suicide Severity Rating Scale (C-SSRS). Subjects must be excluded if they report suicidal ideation of Type 4 or 5 in the past 2 months or suicidal behavior in the past 6 months as measured by the C-SSRS during Screening or Randomization Visits.

5. In the judgment of the investigator, a subject must not have sleep attacks or compulsive behavior that would interfere with the integrity of the trial or would pose a risk to the subject in participating in the trial.

Other Exclusion Criteria

6. **Blood Pressure:** A subject must not have a systolic blood pressure (BP) ≥150 mm Hg OR diastolic BP ≥ 95 mm Hg at Screening and at a BP recheck prior to Randomization. Should the BP remain elevated, the subject may not enter the trial until the BP has been adequately controlled with antihypertensive medication as demonstrated by 2 BP measurements meeting this criterion at consecutive separate visits (scheduled or unscheduled) within 5 weeks prior to Randomization. If antihypertensive medications are used to control a subject’s BP, the subject’s BP and doses of antihypertensive medications must be stable for at least 2 weeks prior to randomization. Note: during the course of the study,
antihypertensive medication may be initiated or increased to control a subject's BP at any time during treatment in P07037 as needed.

7. **Cardiovascular Disease:** A subject must not have had any clinically significant cardiovascular event or procedure for 6 months prior to Randomization, including, but not limited to, myocardial infarction, prolonged QTc interval [a subject must not have a QTcF result > 500 msec], angioplasty, unstable angina, or heart failure; and a subject must not have heart failure staged New York Heart Association Class III or IV.

8. **Liver Enzymes:** A subject must not have an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 x ULN or total bilirubin (T-BIL) ≥ 1.5 x ULN. Should an LFT be abnormal (ALT/AST > ULN but <3 x ULN, T-BIL > ULN but <1.5 x ULN) at Screening, the investigator should attempt to characterize at entry the reason(s) for elevation(s), eg, alcohol abuse (see next exclusion criterion), metabolic syndrome with fatty liver, etc. No repeat testing is allowed. Subjects with suspected Gilbert's Syndrome who have isolated T-BILI ≥ 1.5 x ULN may enter the study upon genetic confirmation (UGT1A1 assessment).

9. **Liver Disease:** A subject must not have active serologically confirmed hepatic dysfunction (defined as viral infection [Hepatitis B, C, or E; Epstein-Barr virus {EBV}; cytomegalovirus {CMV}]) or a history of diagnosis of drug- or alcohol-induced hepatic toxicity or frank hepatitis. If a subject has abnormal ALT or AST at Screening (>1.5 x ULN), the subject must have serology testing to rule out active viral hepatitis. A subject who has a history of serologically confirmed EBV or CMV may be enrolled in the trial as long as his/her viral infection was not associated with hepatitis in the past, and his/her ALT and AST are normal at Screening. Types of serology assays to be performed are specified in the table of Laboratory Tests (Table 7).

10. A subject must not have a history within the past 5 years of a primary or recurrent malignant disease with the exception of adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or in situ prostate cancer with a normal prostate-specific antigen (PSA) post resection.

11. **Prohibited Concomitant Medications:** A subject must not have received any treatment listed in Table 2 more recently than the indicated period before Randomization.

12. A subject must not need to continue to receive any treatment listed in Table 2 during the trial.

**Note:** Warnings and Contraindications detailed in the Prescribing Information for the allowed medications (listed in Table 1) should be followed.
Table 2  Prohibited Medications, Supplements, and Other Substances for Entry into the Trial

<table>
<thead>
<tr>
<th>Prohibited Medications, Supplements, and Other Substances for Entry into the Trial</th>
<th>Period Before Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolcapone</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Irreversible MAO inhibitors, eg, rasagiline, selegiline, Zydis selegiline</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Reversible MAOB or MAOA inhibitors</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Centrally acting dopamine antagonist (including metoclopramide, sulpiride, tiapride, etc.)</td>
<td>4 weeks</td>
</tr>
<tr>
<td>α-methyldopa</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Reserpine</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Flunarizine</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Cinnarizine</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Theophylline</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Diphenhydramine used to treat parkinsonism</td>
<td>4 weeks</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Other potentially hepatotoxic drugs (including amiodarone, azathioprine, felbamate, imatinib, isoniazid, isotretinoin, leflunomide, methotrexate, nevirapine, pioglitazone, rosiglitazone, pyrazinamide, valproic acid, and voriconazole)</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Potent CYP3A4 inhibitors (eg, ritonavir, nelfinavir, indinavir); macrolide antibiotics (eg, erythromycin, clarithromycin, troleandomycin, telithromycin, [azithromycin is allowed]); and systemically administered antifungal agents (eg, ketoconazole, itraconazole)</td>
<td>4 weeks</td>
</tr>
<tr>
<td>CYP3A4 inducers (eg, phenytoin, phenobarbital, barbiturates, systemic glucocorticoids)</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Atypical and typical neuroleptics (including depot formulations) except low dose quetiapine fumarate and clozapine</td>
<td>6 months</td>
</tr>
</tbody>
</table>

13. A subject must not have an average daily consumption of more than three 4-ounce glasses (118 mL) of wine or the equivalent.
14. A subject must not have poorly controlled diabetes (eg, HbA1c >8.5) or significantly abnormal renal function (eg, creatinine >2.0 mg/dL) in the opinion of the investigator.
15. A subject must not have a severe or ongoing unstable medical condition (eg, any form of clinically significant cardiac disease, symptomatic orthostatic hypotension, seizures, or alcohol/drug dependence).
16. A subject must not have participated in any studies using preladenant.
17. A subject must not have allergy/sensitivity to the investigational products or their excipients.
18. A female subject must not be breast-feeding or considering breast-feeding.
19. A female subject must not be pregnant or intending to become pregnant.
20. A subject must not have any clinically significant condition or situation, other than the condition being studied that, in the opinion of the investigator, would interfere with the trial evaluations or optimal participation in the trial.

21. A subject must not have used any investigational drugs within 90 days immediately before Screening.

22. A subject must not have been participating in any other clinical trial within 90 days, inclusive, of signing the informed consent form of this trial.

23. A subject must not be a member or a family member of the personnel of the investigational or sponsor staff directly involved with this trial.

### 7.3.3 Subject Discontinuation Criteria

A subject may discontinue from the clinical trial at any time for any reason.

It is the right and the duty of the investigator or subinvestigator to stop treatment in any case in which emerging effects are of unacceptable risk to the individual subject. In addition, the investigator or subinvestigator is to stop treatment of any subject with unmanageable factors that may interfere significantly with the trial procedures and/or the interpretation of results. A subject may be withdrawn by the investigator or the SPONSOR if he/she violates the study plan or for administrative and/or other safety reasons.

Discontinuation is “permanent”: once a subject is discontinued, he/she shall not be allowed to enroll again.

At a minimum collect the following information when a subject discontinues:

1. The reason the subject discontinued.
2. The date of the last dose of test products from the trial.
3. The date of the last assessment and/or contact. A follow-up contact (telephone or visit) will be arranged as appropriate.
4. (Serious) Adverse events.
5. Compliance with the test product administration as specified in this protocol.
6. Final Assessments:
7. Every effort should be made to ensure that all procedures and evaluations scheduled for the follow-up period and safety follow-up visit are performed (Section 2.2, Trial Flow Chart).
8. Retrieve all investigative product and test articles from the subject.
A subject must be discontinued from the trial for any of the following reasons:

1. The subject reports a score of 4 (active suicidal ideation with some intent to act) or 5 (active suicidal ideation with specific plan and intent) for suicidal ideation – such a score indicates serious suicidal ideation and must trigger further evaluation and immediate contact with a subject’s mental health practitioner. Note: those subjects with any level of suicidal ideation (ie, a score >0) but with a score <4 are not required to discontinue from the study but should seek psychiatric consultation as soon as possible.

2. The subject or legal representative (such as a parent or legal guardian) withdraws consent.

3. Failure to comply significantly, in the opinion of the investigator, with the dosing, evaluations, or other requirements of the trial.


5. Severe allergic reaction to the drug.

6. Following treatment for an occurrence of BP above the Closely Monitored Event Criteria in Section 7.7.2.2.3, elevated BP as follows:
   - Systolic BP ≥180 mm Hg or diastolic BP ≥105 mm Hg at two consecutive visits separated by 7 days.
   - Elevation (from Baseline) of systolic BP >40 mm Hg or diastolic BP >20 mm Hg at two consecutive visits separated by 7 days. Note: during the course of the study, antihypertensive medication may be initiated or increased to control a subject’s BP at any time during treatment in P07037, but the subject must be discontinued if discontinuation criteria are met.

7. Elevated ALT, AST or T-BIL meeting any one of the following criteria:
   - ALT or AST >8 x ULN.
   - ALT or AST >5 x ULN for more than 2 weeks.
   - ALT or AST >3 x ULN and T-BIL >2 x ULN or international normalized ratio [INR] >1.5 that is not due to anti-coagulation at the same visit.
   - ALT or AST >3 x ULN with the appearance of worsening fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

7.3.4 Replacement of Subjects

A subject that discontinues from the trial will not be replaced.
7.4 Treatments

7.4.1 Trial Treatments

Investigational Product

Preladenant (SCH420814) will be supplied as 2- and 5-mg tablets. Subjects will receive one 2-mg tablet or one 5-mg tablet of preladenant orally twice daily for 12 weeks (Table 3).

Reference Product

Subjects will receive one matching placebo tablet orally twice daily for 12 weeks (Table 3).

Table 3 12-Week, Daily Oral Study Treatment Dose Administration

<table>
<thead>
<tr>
<th></th>
<th>AM</th>
<th>PM (Approximately 8 hours after AM dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preladenant Groups</td>
<td>2 mg Preladenant Tablet</td>
<td>2 mg Preladenant Tablet</td>
</tr>
<tr>
<td></td>
<td>or 5 mg Preladenant Tablet</td>
<td>or 5 mg Preladenant Tablet</td>
</tr>
<tr>
<td>Placebo Group</td>
<td>Placebo Tablet</td>
<td>Placebo Tablet</td>
</tr>
</tbody>
</table>

7.4.1.1 Treatments Administered

The first dose of the investigational product will be administered at the study site after all the Day 1 evaluations have been completed (Section 2.2 and Section 2.2.1). Subsequent doses of the study drug will be self-administered (ie, unsupervised at home or by a caregiver) at approximately the same times each day (except at Week 8 when one dose of study drug will be administered on-site).

Subjects from each group will self-administer their respective blinded treatment shown in Table 3 for 12 weeks. The first dose and one Week 8 dose will be taken at the site under medical supervision. Morning visits are preferred, but if this is not possible, visits may be conducted in the afternoon. The time of the visits should be consistent throughout the study.

During the Double-Blind Treatment Period, subjects will continue to self-administer L-dopa and adjunct PD medications listed in Table 1 (if they are taking any adjunct PD medication) according to their usual prescribed schedule. Doses of the
concomitant adjunct PD medications must remain constant (with exceptions for increases only as noted in Section 7.4.2.1.2). Doses of L-dopa may be adjusted downward if clinically significant dopamine-related side effects develop (such as nausea, hallucinations, psychiatric disturbances, dyskinesia). All dose changes of L-dopa and adjunct PD medications must be captured in the electronic case report form (eCRF).

7.4.1.2 Method of Treatment Assignment, Randomization, and/or Stratification

Randomization of subjects will occur centrally using an interactive voice response system (IVRS). Subjects who have satisfied the inclusion (Section 7.3.1) and exclusion (Section 7.3.2) criteria will be randomized in a 1:1:1 ratio to one of three treatment arms (preladenant 2 or 5 mg twice daily or placebo) according to a computer-generated random code provided by the sponsor to the IVRS vendor. No stratification based on site, age, gender, or other characteristics will be performed.

7.4.1.3 Selection and Timing of Dose for Each Subject

7.4.1.3.1 Selecting the Dose for Each Subject

The rationale for the selection of doses to be used in this trial is presented in Section 5.3.

7.4.1.3.2 Determining the Timing of Dose Administration for Each Subject

The study drug will be administered by the subject (or by a caregiver trained in the trial conduct) twice each day: once in the morning and again 8 hours later. If a subject misses a dose, then the subject should not take two doses at the same time but should continue with the regular schedule by taking the next dose at the regular time. Treatments to be taken each day are shown in Table 3. Although morning visits are preferred, if this is not possible, visits may be conducted in the afternoon. The time of the afternoon visit (or the morning visit) should be consistent throughout the study.

With the exception of Day 1 and Week 8, on the days of lab visits and clinic visits and on the days in between them, subjects should take the first daily dose of study drug at home at their regular time. The second dose should be taken 8 hours later.
At the Day 1 and Week 8 Visits, study drug will be administered at the clinic site. On Day 1, study drug will be administered at the clinic site after all the Baseline measurements have been collected and all predose procedures have been performed. The day before the Week 8 Visit, each subject should be called and reminded not to take the dose of study drug before the visit. At Week 8, if the subject is scheduled for a morning visit, the subject should not take the morning dose of study drug. The morning dose of study drug will be administered at the clinical site after the pre study drug dose activities. If a subject is scheduled for an afternoon visit, the subject should take the morning dose of study drug but should not take the afternoon/evening dose of study drug. The afternoon/evening dose of study drug will be administered at the clinical site after the pre study drug dose activities.

On the days of CVs, for before and during the visit, record in the eCRF the time(s) at which study drug was taken.

The dose of the blinded study drug may not be reduced at any time during the study (subjects should always take all the pills they are assigned to take, ie, one tablet each morning and one tablet each evening).

At all times during the study, including on clinic visit and lab visit days, each subject should continue taking his/her regular dose(s) of L-dopa and adjunct PD medications, according to his/her individually prescribed, stable regimen. Doses of the permitted adjunct PD medications must remain constant (allowed exceptions with strict guidelines are set forth in Section 7.4.2.1.2).

### 7.4.1.4 Blinding Trial Treatments

A double-blind technique will be used as shown in Table 3. Preladenant (2 mg and 5 mg) and its matching placebo will be identical in appearance and will be packaged identically so that the treatment blind is maintained. The placebo tablet is similar to the investigational product as regards appearance, weight, smell and taste. Computer-generated randomization will be used as described in Section 7.4.1.2. Neither the subject nor the investigational staff (sponsor, investigator, and evaluators) will know which treatment the subject is receiving.

See Section 7.7.2.6.4 for a description of the method of unblinding a subject during the trial, should such action be warranted.
7.4.1.5 Investigational Medicinal Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, handling, storage, distribution, and usage of these materials in accordance with the protocol and any applicable laws and regulations.

7.4.1.5.1 Identity of Investigational Medicinal Product

Blinded study drug will be formulated and packaged by the sponsor. Please see the Investigator’s Brochure for a description of the investigational medicinal product. Placebo tablets will be identically matched in appearance to the active study drugs.

7.4.1.5.2 Source

The sponsor will provide study drug as follows:

- Preladenant 2 mg tablets
- Preladenant 5 mg tablets
- Matching placebo tablets

7.4.1.5.3 Labeling

Preladenant/placebo bottle labels should include the following information and comply with the regulatory requirements appropriate for the clinical site: Dosing directions will state, ‘Take one tablet in the morning and one tablet in the evening 8 hours apart as directed’. The label will also contain a space for the subject number, which will be written in at the study center.

7.4.1.5.4 Packaging

Preladenant 2 and 5 mg and matching placebo tablets will be packaged in bottles. A bottle will be treated as a single kit.
7.4.1.5.5 Storage

Trial treatment supplies must be stored in a secure, limited-access location under the storage conditions specified on the supply label. Site storage conditions should be monitored by the site personnel for adherence to label specifications and reviewed during site visits.

7.4.1.5.6 Dispensing

The investigator or qualified designee(s) will dispense trial treatments at the designated site(s) to subjects who have provided written informed consent and meet the entry criteria. Clinical supplies may not be used for any purpose other than that which is stated in this protocol.

See the Trial Flow Chart in Section 2.2 for a schedule of when clinical supplies are to be dispensed to the subjects.

On Day 1 each subject will receive 2 bottles: 1 bottle containing enough study drug for the first 4 weeks of the double-blind treatment period and 1 bottle to be used for extra treatment days because of visit scheduling difficulties. At the Week 4 and Week 8 Visits, each subject will receive 1 bottle containing enough study drug for the next 4 weeks.

7.4.1.5.7 Replacement of Investigational Product

There will be no replacement of subjects; therefore, replacement supplies for this purpose will not be provided. If a subject damages or loses a bottle of study drug, the site must contact the sponsor to request a replacement treatment and document the following information in the source document and in the electronic case report form (eCRF): the subject number, the original treatment kit number, and the reason a replacement treatment kit is required.

7.4.1.5.8 Investigational Medicinal Product Accountability

Accurate and current accounting of the dispensing and return of investigational product will be maintained on an ongoing basis by a member of the trial site staff.
• Investigational medicinal product dispensed to each site will be recorded in the trial-specific Site Investigational Medicinal Product (IMP) Accountability Log (or equivalent document approved by the sponsor);

• Investigational medicinal product dispensed to each subject will be recorded in the trial-specific Subject IMP Accountability Log (or equivalent document approved by the sponsor) and reported in the eCRF.

• Instances where a subject failed to take study medication as prescribed should be documented and reported in the eCRF. The subject will be counseled by the study staff regarding the importance of study drug compliance.

• Potential intentional medication misuse: Procedures for a subject who returns less study medication than prescribed but denies taking extra study medication are as follows. If no more than 1 pill per week is missing (e.g., no more than 4 pills over a month), then no action is needed. If the equivalent of more than 1 pill per week is missing (e.g., more than 4 pills over a month), then the event must be reported as a Closely Monitored Event with the AE term, "potential study medication misuse". Please see Section 7.7.2.2.3 for standard reporting procedure of Closely Monitored Events. In such cases, the investigator will contact the SPONSOR to discuss additional actions regarding the subject's participation in the study.

The Site IMP Accountability Log and Subject IMP Accountability Log will be verified by the sponsor’s trial monitor. The original Site IMP Accountability Log and Subject IMP Accountability Log will be approved by the investigator and retained at the trial site and a copy supplied to the sponsor when the trial is complete.

Each subject will be instructed by the investigator or designee to return all unused and partially used test articles to the site at all protocol-specified visits.

The sponsor’s trial monitor will instruct the site on the return of all investigational product supplies. A final inventory of the total amount of investigational product received at each trial site against the amount used and returned must be recorded in the Site IMP Accountability Log. Inventory records must be readily available for inspection by the trial monitor and/or auditor, and open to government inspection at any time.
7.4.2 Non-Trial Treatments

7.4.2.1 Prior and Concomitant Medications

Prior Medications

All prior medications used to treat the motor symptoms of the subject's Parkinson's disease within 2 years immediately prior to the Screening Visit must be recorded.

For non-PD prior medications, only the drugs listed in Table 2 (medications prohibited until the given washout period has been achieved) need to be recorded, if taken within 2 years immediately prior to the Screening Visit. Fill in the fields requested in the eCRF for drugs listed in Table 2. It is not necessary to record any other non-PD prior medications.

Concomitant Medications

All ongoing concomitant medications (including adjunct PD medications and non-PD medications) taken by the subject at the time of Screening and during the study are to be recorded on the concomitant medication page of the eCRF. The name of the therapy, dose, unit, route of administration, frequency, start/stop dates (or notation of “continuing” if that is the case), and the reason for use must be recorded whenever a concomitant medication is listed. PD medications including up to the 30 days prior to Screening must be recorded precisely (i.e., exact doses and times throughout the day) using the standardized abbreviations and allowed fields provided in the eCRF. When recording proprietary drug names, the L-dopa dose must be captured (e.g., Sinemet 10/100).

Any change in dose of a concomitant medication since Screening must be captured on the concomitant medication eCRF page. Refer also to Section 7.4.2.1.2.

7.4.2.1.1 Medications, Supplements, and Other Substances Prohibited Prior to Randomization and During the Trial

The subject must not take the treatments listed in Table 4 at any time during the trial after Randomization, except as specified in this protocol.

The medications, supplements, and foods prohibited prior to Randomization are the same as for during the trial and are listed in Table 2 in Section 7.3.2 with the subject exclusion criteria (and in the synopsis) with their respective washout periods.
Note About Prohibited Medications: Warnings and Contraindications detailed in the Prescribing Information for the allowed medications (listed in Table 1) must be followed.

Table 4 Concomitant Medications, Supplements, and Other Substances Prohibited During the Trial

<table>
<thead>
<tr>
<th>Concomitant Medications, Supplements, and Foods Prohibited During the Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolcapone</td>
</tr>
<tr>
<td>Rasagiline, selegiline, Zydis selegiline, or other MAOB or MAOA inhibitor</td>
</tr>
<tr>
<td>Centrally acting dopamine antagonist (including metoclopramide, sulpiride, tiapride, etc)</td>
</tr>
<tr>
<td>α-methyldopa</td>
</tr>
<tr>
<td>Methylphenidate</td>
</tr>
<tr>
<td>Reserpine</td>
</tr>
<tr>
<td>Amphetamines</td>
</tr>
<tr>
<td>Flunarizine</td>
</tr>
<tr>
<td>Cinnarizine</td>
</tr>
<tr>
<td>Diphenhydramine used to treat parkinsonism</td>
</tr>
<tr>
<td>Theophylline</td>
</tr>
<tr>
<td>St. John’s wort</td>
</tr>
<tr>
<td>Other potentially hepatotoxic drugs (including amiodarone, azathioprine, felbamate, imatinib, isoniazid, isotretinoin, leflunomide, methotrexate, nevirapine, pioglitazone, rosiglitazone, pyrazinamide, valproic acid, and voriconazole)</td>
</tr>
<tr>
<td>Potent CYP3A4 inhibitors (eg, ritonavir, nelfinavir, indinavir); macrolide antibiotics (eg, erythromycin, clarithromycin, troleandomycin, telithromycin, [azithromycin is allowed]); and systemically administered antifungal agents (eg, ketoconazole, itraconazole)</td>
</tr>
<tr>
<td>CYP3A4 inducers (eg, phenytoin, phenobarbital, barbiturates, systemic glucocorticoids)</td>
</tr>
<tr>
<td>Atypical and typical neuroleptics (including depot formulations) except low dose quetiapine fumarate and clozapine</td>
</tr>
</tbody>
</table>

7.4.2.1.2 Concomitant Medications, Supplements, and Other Substances Allowed During the Trial

PD medications allowed during the trial are listed in Table 5, and they should be recorded on the concomitant medication page of the eCRF. All dose changes whether reflective of an increase or a decrease must be captured in the eCRF.
If a subject’s physical functioning is significantly compromised, a temporary increase of immediate release L-dopa for the management of troublesome “off” time is acceptable if the following L-dopa dose increase conditions are met:

- No more than 6 individual increased L-dopa doses per subject in the entire P07037 study
- No more than 3 individual increased L-dopa doses in a 2-week period, and
- Temporary increases in L-dopa are not allowed:
  - Within 24 hours prior to a Clinic Visit,
  - Within 24 hours prior to completion of a Diary, or
  - During days on which the Diary is being completed.

No change in overall prescribed dosage of L-dopa is permitted. All transitory increases in L-dopa dose must be captured in the eCRF.

Additionally, coenzyme Q-10 is allowed.

### Table 5 Adjunct PD Medications Permitted During the Trial

<table>
<thead>
<tr>
<th>Protocol No. P07037</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine</td>
</tr>
<tr>
<td>Anticholinergics</td>
</tr>
<tr>
<td>Dopaminergic drugs</td>
</tr>
<tr>
<td>Entacapone</td>
</tr>
<tr>
<td>Dopa decarboxylase inhibitors</td>
</tr>
<tr>
<td>L-dopa</td>
</tr>
</tbody>
</table>

Note that the use of any concomitant medication must be recorded and relate to the documented medical history, prophylaxis, physical exam, or an adverse event of the subject.

#### 7.4.2.2 Other Treatments

Subjects are permitted to take concomitant medications to treat intermittent problems (eg, infections) or controlled diseases (eg diabetes and hypertension), as specified in the study entry criteria.

Stable, low dose quetiapine and clozapine are allowed.
Note that the use of any concomitant medication must be recorded and relate to the documented medical history, prophylaxis, physical exam, or an adverse event of the subject.

7.4.3 Procedures for Monitoring Subject Compliance With Administration of Trial Treatments

At all protocol-specified visits, the investigator or qualified designee is to record whether treatment had been taken per protocol in the preceding interval. If not, the date(s) and reason for each dosing noncompliance must be recorded.

7.5 Trial Schedule

The visit-by-visit schedule of trial activities is provided in the Trial Flow Chart in Section 2.2.

The timing of each visit is relative to Day 1, which is defined as the day of the administration of the first dose of trial medication at the Baseline/Randomization Visit, Visit 3 (Section 7.4.1.1).

All visits should be performed within the windows specified in Section 2.2, the Trial Flow Chart. Every attempt should be made to have each subject attend each visit as scheduled. However, if a subject is unable to attend a visit within the specified windows, the visit should be scheduled as closely as possible to these windows. A subject should not miss a protocol-specified visit due to scheduling difficulties.

7.6 Trial Procedures

Throughout this section, refer to the following visual aids which summarize the trial procedures to be performed at each visit.

- Section 2.2, Trial Flow Chart
- Section 2.2.1, UPDRS Evaluations
Individual trial procedures are described below.

In order to minimize variability of evaluations, site staff should make every effort to ensure that the same individuals perform the same types of evaluations for all subjects at each trial site throughout the study.

Since some subjects may experience diurnal fluctuations, site staff should make every effort to ensure that the UPDRS evaluations occur at approximately the same time of day for any given subject across visits throughout the trial. For all UPDRS evaluations, the subject should be in the optimal “on” state.

1. **Clinic Visit (CV)**
   A CV is one in which all assessments indicated in the Trial Flow Chart (Section 2.2) are performed. At every CV, each subject should be reminded to carry all his/her study drug AND any and all adjunct PD medications to the next CV.

2. **Lab Visit (LV)**
   A Lab Visit is one in which the following laboratory safety bloodwork is collected: total serum bilirubin [T-BIL], serum aspartate aminotransferase [AST], serum alanine aminotransferase [ALT], serum alkaline phosphatase [ALK-P]. Each lab visit should be registered in IVRS.

3. **Telephone Contact the Day Before the Week 8 Visit**
   The day before the Week 8 Clinic Visit, each subject should be called and reminded not to take the dose of study drug before the visit. At Week 8, if the subject is scheduled for a morning visit, the subject should not take their morning dose of study drug. The morning dose of study drug will be administered at the clinical site. If a subject is scheduled for an afternoon visit, the subject should take their morning dose of study drug but should not take their afternoon/evening dose of study drug. The afternoon/evening dose of study drug will be administered at the clinical site.

   **NOTE:** Please refer to item number 43 in the Trial Procedures section for post study drug telephone follow-up information (due to End of Treatment or Early Termination).

4. **Explain Trial and Obtain Written Informed Consent**
   The investigator or qualified designee will explain the P07037 trial to the subject, answer all of his/her questions, and obtain written informed consent before performing any trial-related procedure. A copy of the informed consent will be given to the subject (see Section 9.1.2 for further description of the Informed Consent Form [ICF]). The written informed consent for P07037 includes consent for pharmacokinetic testing and HLA and UGT1A1 potential pharmacogenetic...
testing. Subjects will be counseled at the P07037 Screening Visit regarding the required washout period for medications disallowed in the extension study, P06153, as outlined in Table 6. Subjects who wish to participate in the P06153 extension study but who are taking medication that is prohibited in P06153 must washout on the prohibited medication (according to Table 6) prior to entry into P07037 to be eligible to enter the P06153 extension study.

At Visit 7, the subject must be provided with the ICF for, and further counseled (as above) regarding specifics about, the extension study in order to provide sufficient time for an informed decision about whether or not to participate in the extension study. Any subject taking a concomitant medication at Visit 7 that is prohibited in the P06153 extension study (Table 6) will not be allowed to participate in P06153. The subject must NOT washout on any prohibited medication (ie, stop taking it) at any time during participation in P07037 for the sole purpose of enrolling in the P06153 extension study.

If a subject wishes to participate in the extension study (up until the maximum number of subjects for that extension study has been reached), he/she will be asked to sign the ICF for the extension study at the End of Treatment Visit (Visit 8) in P07037.

Table 6 Medications Not Allowed for Entry into P06153

<table>
<thead>
<tr>
<th>Prohibited Medications, Supplements, and Other Substances for P06153</th>
<th>Period Before P06153 Day 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meperidine, tramadol, methadone, propoxyphene, cocaine, or local anesthesia containing sympathomimetic vasoconstrictors</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Mirtazapine (a tetracyclic antidepressant), and cyclobenzaprine (a tricyclic muscle relaxant)</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Sympathomimetic amines including cold products, nasal and oral decongestants, and weight-reducing preparations that contain vasoconstrictors (eg, ephedrine, pseudoephedrine, phenylephrine, and phenylpropanolamine)</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and selective serotonin reuptake inhibitors with the following exceptions: citalopram ≤20 mg/day, escitalopram ≤20 mg/day, paroxetine ≤30 mg/day, amitriptyline or nortriptyline ≤50 mg/day, trazodone or sertraline ≤100 mg/day</td>
<td>5 weeks</td>
</tr>
<tr>
<td>High tyramine-containing aged cheeses (eg, Stilton)</td>
<td>2 weeks</td>
</tr>
</tbody>
</table>

5. **Assign Screening Number**

Assign screening number and register subject with the central IVRS.

6. **Explain Trial and Obtain Written Informed Consent for Exploratory Pharmacogenetic Testing**
The investigator or qualified designee will explain the exploratory pharmacogenetic testing to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to exploratory pharmacogenetic testing. A copy of the informed consent will be given to the subject. (See Lab Manual and Appendix 2 for further description of the pharmacogenetic testing procedures.) A subject does not have to provide an exploratory pharmacogenetic sample to be in the main trial.

7. **Issue or Collect Subject Identification Card**

The investigator or qualified designee will provide the subject with a Subject Identification Card after the subject provides written informed consent, at the Baseline/Randomization Visit before dispensing study drug on Day 1. At the End of Treatment Visit, Subject Identification Cards will be collected only from subjects continuing into the extension trial. For subjects not continuing into the extension trial, Subject Identification Cards will be collected at the Safety Follow-Up or Early Termination Visit. (See Section 9.1.3 for further description of the Subject Identification Card).

8. **Review Inclusion/Exclusion Criteria**

The inclusion and exclusion criteria will be reviewed by the investigator or qualified designee as indicated in Section 2.2, Study Flow Chart, to ensure that the subject qualifies for the trial.

9. **Assign Subject Number and Randomized Treatment**

Once all of the entry criteria have been met, subjects will be randomized in a 1:1:1 ratio to one of three treatment arms by means of a computer-generated randomization code (Section 7.4.1.2). Site staff will call the IVRS to receive the randomization.

10. **Obtain Medical History Including Date of Diagnosis of PD, Caffeine and Alcohol Use and Smoking, and Family History of Premature Coronary Heart Disease**

At Screening, a medical history will be obtained by the investigator or qualified designee. Subject history should include information on family history and personal history. Any non PD condition(s) should be noted. In appropriate fields of the eCRF, the date the subject was diagnosed with PD must be recorded as well as the subject’s daily caffeine intake (average number of cups of tea, coffee, or equivalent per day), alcohol consumption (average number of alcoholic drinks/day [as defined in the eCRF]), and current use of cigarettes (average number of cigarettes or equivalent per day). Additionally, family history of premature coronary heart disease (1st degree relative, age/gender dependent) should be recorded on the Family History of Premature Coronary Heart Disease eCRF.

Note: For subjects who entered P07037 under the initial protocol, the investigator or qualified designee should contact the subjects and obtain the subjects’ family history of premature coronary heart disease. This information must be recorded in the subjects’ source documentation and on the Family History of Premature Coronary Heart Disease eCRF.
11. Record Prior Medications
   At Screening, subjects should be questioned (and answers recorded) regarding
   the use of any prior medications (since the subject was first diagnosed with PD)
   used to treat the motor symptoms of the subject’s Parkinson’s disease up to
   2 years prior to the Screening visit. Also at Screening, review and record
   prohibited prior medications taken within 1 year immediately prior to the
   Screening Visit, including the necessary washout times (Table 2). Fill in the
   fields requested in the eCRF for prior medications (Section 7.4.1.2).

12. Record Concomitant Medications
   All ongoing concomitant medications (including adjunct PD medications and non-
   PD medications) taken by the subject at the time of Screening and during the
   study are to be recorded on the concomitant medication page of the eCRF. The
   name of the therapy, dose, unit, route of administration, frequency, start/stop
   dates (or notation of “continuing” if that is the case), and the reason for use must
   be recorded whenever a concomitant medication is listed. PD medications
   including up to the 30 days prior to Screening must be recorded precisely
   (ie, exact doses and times throughout the day) using the standardized
   abbreviations and allowed fields provided in the eCRF. When recording
   proprietary drug names, the L-dopa dose must be captured (eg, Sinemet 10/100).
   Any change in dose of a PD medication since Screening must be captured on the
   concomitant medication eCRF page.
   During this review, the subject will be instructed to take his/her
   L-dopa/dopaminergic therapy as prescribed, including on clinic visit days, and to
   bring L-dopa and adjunct PD medications to the clinic on clinic visit days. The
   L-dopa/dopaminergic therapy may be decreased if clinically warranted. If a
   subject’s physical functioning is significantly compromised, a temporary increase
   of immediate release L-dopa for the management of troublesome “off” time is
   acceptable if the following L-dopa dose increase conditions are met:
   • No more than 6 individual increased L-dopa doses per subject in the entire
     P07037 study
   • No more than 3 individual increased L-dopa doses in a 2-week period, and
   • Temporary increases in L-dopa are not allowed:
     • Within 24 hours prior to a Clinic Visit,
     • Within 24 hours prior to completion of a Diary, or
     • During days on which the Diary is being completed.
   No change in overall prescribed dosage of L-dopa is permitted. All transitory
   increases in L-dopa dose should be captured in the eCRF.
Review the drugs, foods, nutraceuticals and other substances prohibited for subjects to ingest during the trial. During this review, the subject should be instructed to take his/her PD medication as prescribed.

13. **Record (Serious) Adverse Events**

   See Section 7.7.2.4, for instructions on the assessment and reporting of (Serious) Adverse Events and Section 7.7.2.5 for instructions on the reporting of (Serious) Adverse Events to the sponsor. (Serious) Adverse Events can be reported at any time during the trial.

14. **Conduct Physical Examination Including Melanoma Examination** (by a Board Certified Dermatologist)

   A complete physical examination including an examination for melanoma conducted by a board certified dermatologist will be performed. All relevant findings should be recorded in the medical history page of the eCRF at Screening. Any significant changes in the subjects’ clinical condition during the trial should be captured in the AE page of the eCRF. If the subject is discontinued for any reason during the treatment phase, every attempt should be made to perform a final physical examination.

15. **Hoehn and Yahr Stage (in the Optimal “On” State)**

   The Hoehn and Yahr Stage will be determined for each subject while in the optimal “on” state, before the subject has taken any study drug, by an experienced qualified rater according to the Modified Hoehn and Yahr Scale (see Manual of Sample Questionnaires to Accompany Protocol P07037 Amendment 2) and entered into the eCRF.

16. **Montreal Cognitive Assessment (MoCA)**

   The MoCA (see Manual of Sample Questionnaires to Accompany Protocol P07037 Amendment 2) will be evaluated at the specified time points indicated in Section 2.2, Trial Flow Chart. Site staff should review the paper questionnaire for completeness with each subject, then transcribe the data to the eCRF.

17. **Beck Depression Inventory (BDI-II)**

   The BDI-II (see Manual of Sample Questionnaires to Accompany Protocol P07037 Amendment 2) will be evaluated at the specified time points indicated in Section 2.2, Trial Flow Chart. Site staff should review the paper questionnaire for completeness with each subject, then transcribe the data to the eCRF.

18. **Epworth Sleepiness Scale**

   The Epworth Sleepiness Scale (see Manual of Sample Questionnaires to Accompany Protocol P07037 Amendment 2) will be evaluated at the specified time points indicated in Section 2.2, Trial Flow Chart. Site staff should review the paper questionnaire for completeness with each subject, then transcribe the data to the eCRF.

The QUIP-RS (see Manual of Sample Questionnaires to Accompany Protocol P07037 Amendment 2) will be evaluated at the specified time points indicated in **Section 2.2**, Trial Flow Chart. Site staff should review the paper questionnaire for completeness with each subject, then transcribe the data to the eCRF.

20. **Apathy Scale**

The Apathy Scale (see Manual of Sample Questionnaires to Accompany Protocol P07037 Amendment 2) will be evaluated at the specified time points indicated in **Section 2.2**, Trial Flow Chart. Site staff should review the paper questionnaire for completeness with each subject, then transcribe the data to the eCRF.

21. **EuroQoL Five Dimension Questionnaire (EQ-5D)**

The EQ-5D (see Manual of Sample Questionnaires to Accompany Protocol P07037 Amendment 2) will be evaluated at the specified time points indicated in **Section 2.2**, Trial Flow Chart. It also may be completed at home and brought in with the subject’s diaries. In cases where it is completed at home, it must be completed the day before or morning of the visit to the clinic. Site staff should review the paper questionnaire for completeness with each subject, then transcribe the data to the eCRF.

22. **Parkinson’s Disease Questionnaire (PDQ-39)**

The PDQ-39 (see Manual of Sample Questionnaires to Accompany Protocol P07037 Amendment 2) will be evaluated at the specified time points indicated in **Section 2.2**, Trial Flow Chart. It also may be completed at home and brought in with the subject’s diaries. In cases where it is completed at home, it must be completed the day before or morning of the visit to the clinic. Site staff should review the paper questionnaire for completeness with each subject, then transcribe the data to the eCRF.

23. **Sleep Attack Questionnaire (SAQ)**

The Sleep Attack Questionnaire (see Manual of Sample Questionnaires to Accompany Protocol P07037 Amendment 2) will be evaluated at the specified time points indicated in **Section 2.2**. This assessment should be performed by the investigator or a qualified designee. Site staff should review the paper questionnaire for completeness with each subject, then transcribe the data to the eCRF.

24. **Columbia - Suicide Severity Rating Scale (C-SSRS)**

The C-SSRS (see Manual of Sample Questionnaires to Accompany Protocol P07037 Amendment 2) will be evaluated at the specified time points indicated in **Section 2.2**, Trial Flow Chart. The "Baseline" version of the C-SSRS will be used at Screening Visit 1, since it assesses suicidality over the course of a subject’s lifetime. The lifetime assessment is only needed once, so all remaining visits, including the Randomization visit, must use the "Since Last Visit" version of the C-SSRS.
An experienced qualified rater must administer the C-SSRS. Site staff should review the paper questionnaire for completeness, then transcribe the data to the eCRF.

25. Predose Unified Parkinson’s Disease Rating Scale (UPDRS)

The complete UPDRS (Parts 1, 2, 3, and 4) (see Manual of Sample Questionnaires to Accompany Protocol P07037 Amendment 2) will be performed before the administration of the first dose of study drug, by an experienced qualified rater, on Day 1 as indicated in Section 2.2.1, UPDRS Evaluations. The subject should be in the optimal “on” state. The start time of the UPDRS should be recorded in the eCRF. The Day 1 pre study drug UPDRS evaluation should occur at approximately the same time of day as the post study drug UPDRS evaluations for Week 2 through End of Treatment. Site staff should review the paper questionnaire for completeness, then transcribe the data to the eCRF.

26. Obtain and Record Blood Pressure, Pulse, and Other Vital Signs

Measures to control/adjust BP can be taken to meet the BP entry criterion up to Randomization (Day 1), but if the patient’s blood pressure is not within range on Day 1 the patient cannot enter the study. Subsequent, repeated blood pressure measurements intended to obtain acceptable BP entry criteria are not allowed. That is, if the subject’s BP is not within the range specified in the BP exclusion criterion on Day 1, then s/he cannot be randomized. If blood pressure is elevated at the Screening Visit, initiation or alteration of the dose of antihypertensive medicine can be done between the Screening Visit and the Randomization Visit.

Blood pressure (BP) and pulse should be measured on the same arm for the same subject at about the same time of day at every clinic visit with the standardized, pre-programmed automated BPTru device provided by the sponsor.

For BP measurements, each orthostatic BP cycle consists of the following: The subject will lie supine at rest for 5 minutes, then have a single BP measurement taken (ie, 1 reading). The subject will stand for 3 minutes at rest (which can be assisted), followed by a single BP measurement (1 reading) in the standing position (please see below).

<table>
<thead>
<tr>
<th>One Orthostatic BP Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
</tr>
<tr>
<td>Lie at rest 5 minutes</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
At the Baseline/Randomization (Day 1) Visit, 3 cycles of orthostatic BP measurements will be performed before the on-site administration of study drug, and 3 cycles again, 2 hours (±1 hour) after the on-site administration of study drug (pre- and postdose). The 3 predose cycles are to be taken at least 10 minutes apart. Other predose trial procedures may be collected between predose BP cycles. Following on-site administration of study medication, the 3 postdose cycles of orthostatic BP measurements can be taken in immediate succession (ie, no interval is needed between cycles; please see below).

<table>
<thead>
<tr>
<th>Baseline/Randomization Visit (Day 1 Visit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predose</td>
</tr>
<tr>
<td>Step 1a: 1 BP Cycle</td>
</tr>
<tr>
<td>Step 1b: At least 10 minute interval: may perform Visit procedures</td>
</tr>
<tr>
<td>Step 2a: 1 BP Cycle</td>
</tr>
<tr>
<td>Step 2b: At least 10 minute interval: may perform Visit procedures</td>
</tr>
<tr>
<td>Step 3: 1 BP Cycle</td>
</tr>
<tr>
<td>Complete all Predose procedures prior to study medication administration</td>
</tr>
</tbody>
</table>

At the Week 8 Visit (Clinic Visit 7), 3 cycles of orthostatic BP measurements will be performed before the on-site administration of study drug, and 3 cycles again, 2 hours (±1 hour) after the on-site administration of study drug (pre- and postdose). The 3 predose and 3 postdose cycles of orthostatic BP measurements can be taken in immediate succession at the Week 8 Visit (i.e., no interval is needed between cycles; please see below).

<table>
<thead>
<tr>
<th>Week 8 Visit (Clinic Visit 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predose</td>
</tr>
<tr>
<td>Step 1: 1 BP Cycle</td>
</tr>
<tr>
<td>Step 2: 1 BP Cycle</td>
</tr>
<tr>
<td>Step 3: 1 BP Cycle</td>
</tr>
<tr>
<td>Complete all Predose procedures prior to study medication administration</td>
</tr>
</tbody>
</table>
In Visits with three (3) cycles, the BPTru software will calculate an average systolic and average diastolic pressure separately for the supine and standing positions. Orthostatic averages will NOT be calculated. The systolic and diastolic AVERAGES should be considered for either supine or standing positions when determining subject eligibility at Screening or when assessing BP for meeting criteria related to closely monitored events or discontinuation.

For all other Clinic Visits, 1 cycle of orthostatic BP measurements will be collected once during each visit at steady state.

Site staff will download the data from the BP device to a computer at the site, and later send it electronically to a central database (for electronic transfer to the CRO).

Temperature and respiratory rate should be measured at every clinic visit. Body weight should be recorded at the time points indicated in the Flow Chart. Height should be recorded on Day 1.

27. Obtain 12-Lead Electrocardiogram (ECG)
At the Baseline Visit and the End of Treatment or Early Termination Visit, record three sets of 12-lead ECGs, taken 5 to 10 minutes apart. Only a single set of 12-lead ECGs is required at Screening. The ECG will be sent to a central ECG vendor, where standard ECG parameters will be evaluated and analyzed. The QTc interval will be calculated using both Bazett and Fridericia formulae. Results of the ECG analysis will be faxed to the site by the central ECG vendor. The results of the ECG recording do not need to be entered into the eCRF. The ECG data will be electronically transferred to the CRO.

28. Obtain Blood Sample for Exploratory Pharmacogenetic Testing
Informed consent specific for exploratory pharmacogenetic sampling, must be obtained prior to collection. To obtain sufficient DNA for pharmacogenetic studies, a single 8.5-mL blood sample will be drawn prior to the first dose of study drug, into the appropriate tubes provided by the sponsor. (See Lab Manual and Appendix 2 for further description of the exploratory pharmacogenetic testing procedures.)

29. Obtain Blood Sample for HLA and UGT1A1
The sample for HLA and UGT1A1 is mandatory. A single 6-mL sample (for both HLA and UGT1A1) must be drawn before the first dose of study drug and will be stored for potential analysis if liver safety findings need further clarification.
30. **Obtain Predose Blood Sample for Pharmacokinetic Testing**

Blood samples for population pharmacokinetic analysis will be drawn before the on-site administration of study drug at Week 8. The time of the subject’s last dose before the PK blood draw and the time of the blood draw for PK sampling should be recorded in the eCRF. (See Appendix 3 for sample acquisition, shipping and labeling instructions and additional information on pharmacokinetic sample management.)

31. **Obtain Blood Samples for Hematology, Blood Chemistry, and Serology**

Laboratory tests for hematology, blood chemistry, and serology are specified in Table 7. Serology is to be performed only at Screening (according to the entry criterion), unless viral infection must be ruled out for any reason.

32. **Obtain Sample for Urinalysis**

Laboratory tests for urinalysis are specified in Table 7.

33. **Obtain Blood and/or Urine Sample for Pregnancy Test**

Only female subjects of child-bearing potential must have pregnancy tests. A serum pregnancy test (hCG) should be done at Screening (within 5 weeks prior to Day 1) and at End of Treatment. (Additionally, a sample for FSH [follicle stimulating hormone] should be drawn for female subjects who are ≥ 46 years old and who have been amenorrheic for >6 months and <1 year.) A urine pregnancy test should be done on Day 1. Results must be negative before dispensing or administering (on-site at the Day 1 and Week 8 Visits) study drug. Thereafter, a urine pregnancy test should be done every 4 weeks, visit schedule permitting. Subjects continuing on into the extension study must have both a serum and a urine pregnancy test at the End of Treatment Visit. Upon learning that a subject has become pregnant during the trial, immediately collect all her study drug and do not dispense any more. Pregnancy outcome should be followed.
### Table 7: Laboratory Tests

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Blood Chemistry</th>
<th>Serology&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Urinalysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basophils</td>
<td>Albumin</td>
<td>CMV (IgG)</td>
<td>Blood</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>Alkaline phosphatase (ALK-P)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>EBV (IgG)</td>
<td>Glucose</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>ALT (SGPT)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Hepatitis A (Total Ab, IgM)</td>
<td>Ketones</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>AST (SGOT)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Hepatitis B (surface antigen, and core antibody [Total, IgM])</td>
<td>Microscopic Exam</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>Bicarbonate</td>
<td>Hepatitis C (Total Ab)</td>
<td>pH</td>
</tr>
<tr>
<td>Monocytes</td>
<td>Blood Urea Nitrogen (BUN)</td>
<td>Hepatitis E (IgG, IgM)</td>
<td>Protein</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Calcium</td>
<td></td>
<td>Specific Gravity</td>
</tr>
<tr>
<td>Platelets</td>
<td>Chloride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC</td>
<td>Non-fasting Total Cholesterol, HDL, &amp; LDL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td>Conjugated Bilirubin&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Creatine Phosphokinase</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Creatinine</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GGT&lt;sup&gt;a&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inorganic Phosphorus</td>
<td></td>
<td>Follicle Stimulating Hormone (FSH)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Lactate Dehydrogenase (LDH)</td>
<td></td>
<td>Urine Pregnancy Test&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td></td>
<td>International Normalized Ratio (INR)</td>
<td></td>
</tr>
<tr>
<td>Serum Pregnancy Test (beta hCG)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>Hemoglobin A1c (HBA1c)&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Bilirubin&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Protein</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unconjugated Bilirubin&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> If a subject has abnormal liver function test results (AST, ALT, T-BIL) at Screening, the subject must have serology testing to rule out active viral hepatitis.

<sup>b</sup> FSH is only for female subjects who are ≥ 46 years old and who have been amenorrheic for >6 months and <1 year; a subject is considered postmenopausal if FSH >40 IU/mL.

<sup>c</sup> Serum and urine pregnancy tests are only for female subjects of reproductive potential.

<sup>d</sup> HbA1c should be collected only for diabetics and only at Screening.
34. Medication Compliance/Drug Accountability

Study drug will be inventoried and recorded in the Subject Investigation Medicinal Product (IMP) Accountability Log (or equivalent document approved by the sponsor) and eCRF at each clinic visit (refer to Section 7.4.1.5.8).

35. Dispense Study Drug

The investigator or qualified designee(s) will dispense trial treatments at the designated site(s) to subjects who have provided written informed consent and meet the entry criteria. Clinical supplies may not be used for any purpose other than that which is stated in this protocol. See the Trial Flow Chart in Section 2.2 for a schedule of when clinical supplies are to be dispensed to the subjects.

On Day 1 each subject will receive 2 bottles: 1 bottle containing enough study drug for the first 4 weeks of the double-blind treatment period and 1 bottle to be used for extra treatment days because of visit scheduling difficulties. At the Week 4 and Week 8 Visits, each subject will receive 1 bottle containing enough study drug for the next 4 weeks.

All drug dispensing activity should be registered in IVRS.

36. On-Site Administration of Study Drug (Day 1 and Week 8)

At the Day 1 and Week 8 Visits, study drug will be administered at the clinic site. On Day 1, study drug will be administered at the clinic site after all the Baseline measurements have been collected and all predose procedures have been performed (Section 2.2).

(The day before the Week 8 Visit, each subject should be called and reminded not to take the dose of study drug before the visit.) At Week 8, if the subject is scheduled for a morning visit, the subject should not take their morning dose of study drug at home. The morning dose of study drug will be administered at the clinical site, after the pre-study-drug activities specified in the Section 2.2, Flow Chart, have occurred. Although morning visits are preferred, if this is not possible, visits may be conducted in the afternoon. If the subject is scheduled for an afternoon visit, the subject should take the morning dose of study drug as usual but should not take their afternoon/evening dose of study drug at home. The afternoon/evening dose of study drug will be administered at the clinical site after the pre-study-drug activities specified in the Section 2.2, Flow Chart, have occurred. The time of the afternoon visit (or the morning visit) should be consistent throughout the study.

Before administering study drug at Day 1 and Week 8, make sure the subject has had BP measured. Before administering study drug at Week 8, also make sure the subject has had a blood draw for PK.

On the days of CVs, for before and during the visit, record in the eCRF the time(s) at which study drug was taken.

37. Postdose Unified Parkinson’s Disease Rating Scale (UPDRS)

The UPDRS (see Manual of Sample Questionnaires to Accompany Protocol P07037 Amendment 2) will be performed at each visit (except the Safety Follow-Up Visit) by an experienced, qualified rater (and twice on Day 1, ie, predose and postdose). On Day 1, only Part 3 of the UPDRS will be
performed at least 1 hour after the first dose of study drug when the subject is in the optimal “on” state. For Week 2 through End of Treatment, the complete UPDRS (Parts 1, 2, 3, and 4) will be performed at least 1 hour after the morning dose of study drug when the subject is in the optimal “on” state. The start time of the UPDRS should be recorded in the eCRF. Site staff should review the paper questionnaire for completeness, then transcribe the data to the eCRF. Refer to the UPDRS Evaluations flow chart in Section 2.2.1.

38. **Obtain Postdose Blood Sample for Pharmacokinetics**

Blood samples for population pharmacokinetic analysis will be drawn at approximately 2 hours (range, 1 to 4 hours) following the on-site administration of the AM or PM dose at Week 8. A blood sample for PK analysis will be drawn at an Early Termination only when the Early Termination Visit occurs before Week 8. The time of the subject’s last dose of study drug before the PK blood draw and the time of the blood draw for PK sampling should be recorded in the eCRF. (See Appendix 3 for sample acquisition, shipping and labeling instructions and additional information on pharmacokinetic sample management.)

39. **“On”/“Off” and Diary Training**

**First Screening Visit:** The investigator (or his/her trained designee) and subject will review the training DVD and the subject’s “on,” “off,” and dyskinesia symptoms. The subject and investigator (or his/her trained designee) will then agree to a consistent interpretation of when “on” and “off” symptoms begin and end, and when dyskinesias occur. The subject will also be instructed on how to complete the Daily Diary (Manual of Sample Questionnaires to Accompany Protocol P07037 Amendment 2). The subject will then be given a Daily Diary to be filled out at home, and instructed to maintain the diary for the 3 consecutive days immediately before the next visit.

**Second Screening Visit:** The subject and the investigator (or his/her trained designee) will review and assess the subject’s Daily Diary. The subject must be assessed as competent to use the Daily Diary to be included in the study. The subject and the investigator (or his/her trained designee) will also review the training DVD and reinforce recognition of “on” and “off” states and maintenance of the Daily Diary. The subject will receive a new Daily Diary and instructions to maintain the diary for the 3 consecutive days immediately before the next visit.

**Visits During the Double-Blind Treatment Period:** On Day 1, the subject and the investigator (or his/her trained designee) will review and assess the subject’s Daily Diary to determine eligibility for randomization. (No repeats are allowed once Randomization day [Day 1] arrives.) Also, at each subsequent Visit, the subject and the investigator (or his/her trained designee) will review and assess the subject’s Daily Diary. They also will review the training DVD and reinforce recognition of “on” and “off” states and maintenance of the Daily Diary. The subject will receive a new Daily Diary and instructions to maintain the diary for the 3 consecutive days immediately before the next visit.

40. **Diary Dispensing**

Give the subject a new Daily Diary and instructions to maintain the diary for the 3 consecutive days immediately before the next clinic visit.
41. **Give Blank EQ-5D/PDQ-39**
   Give the subject a blank EQ-5D and PDQ-39 with instructions to fill them out the day before or the morning of the next scheduled clinic visit. Tell the subject to carry the completed questionnaires to the next clinic visit.

42. **Diary Assessment**
   On the Daily Diary Card (see Manual of Sample Questionnaires to Accompany Protocol P07037 Amendment 2), subjects will be instructed to select one of the five options listed below for each half-hour period in the Daily Diary Card.
   - “off,”
   - “on” without dyskinesia,
   - “on” with non-troublesome dyskinesia,
   - “on” with troublesome dyskinesia, or
   - asleep.
   Staff will review the Daily Diary Card with the subject, and the data listed above will be recorded for each half-hour time segment in the eCRF. If the subject does not know what category applied during a specific half-hour, enter ‘not done’ rather than leave a time point value blank.

43. **Post study drug telephone contact.**
   Staff should contact the subject at 48 hours and 7 days following the last dose of study medication to evaluate how the subject is feeling.

44. **Register Visit in IVRS**
   At each visit register the visit information as directed in the Table 8 in IVRS:

<table>
<thead>
<tr>
<th>Table 8</th>
<th>IVRS Registration Information Per Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1</td>
<td>Subject’s Screening Number</td>
</tr>
<tr>
<td>Visit 2</td>
<td>Clinic Visit</td>
</tr>
<tr>
<td>Visit 3</td>
<td>Subject’s Randomization Number and Any Drug Dispensing Activity</td>
</tr>
<tr>
<td>Visits 4</td>
<td>Clinic Visit</td>
</tr>
<tr>
<td>Visit 6</td>
<td>Lab Visit</td>
</tr>
<tr>
<td>Visits 5 and 7</td>
<td>Drug Dispensing Activity</td>
</tr>
<tr>
<td>Visit 8</td>
<td>Treatment Complete or Going Into Extension Trial</td>
</tr>
<tr>
<td>Visit 9</td>
<td>End of Trial</td>
</tr>
<tr>
<td>Early Termination Visit</td>
<td>Treatment Discontinued and enter Reason for Discontinuation</td>
</tr>
</tbody>
</table>
7.7 Assessments

7.7.1 Efficacy Assessments

7.7.1.1 Primary Efficacy Endpoint

The Primary Efficacy Endpoint is related to the Primary Trial Objective.

The Primary Efficacy Endpoint for the trial is:

- The change from Baseline to End of Treatment (Week 12) in mean “off” time in hours per day.

The endpoint is derived from the available diary data collected for the 3 days immediately before a subject’s clinic visit during the Double-Blind Treatment Period.

7.7.1.2 Secondary Efficacy Endpoints

The Key Secondary Efficacy Endpoints are:

- The proportion of Responders, where Responder is defined as a subject with at least a 30% reduction in mean “off” time from Baseline to End of Treatment (Week 12).
- The change from Baseline to End of Treatment (Week 12) in mean “on” time without troublesome dyskinesias in hours per day.

7.7.1.3 Other Efficacy Endpoints

Other Efficacy Endpoints for this trial are listed below.

Change from Baseline in the following items:

- Diary data which include:
- Mean hours per day spent in the “off” state at Weeks 2, 4 and 8.
- Mean hours per day spent in the “on” state at Weeks 2, 4, 8, and 12.
- Mean hours per day spent in the “on” state without troublesome dyskinesia at Weeks 2, 4 and 8.
• Mean hours per day spent in the “on” state with troublesome dyskinesia at Weeks 2, 4, 8, and 12.
• Proportion of “on” time with no dyskinesias at Weeks 2, 4, 8, and 12.
• Proportion of “on” time without troublesome dyskinesias at Weeks 2, 4, 8, and 12.
• Proportion of “on” time with troublesome dyskinesias at Weeks 2, 4, 8, and 12.
• Mean total sleep time at Weeks 2, 4, 8, and 12.
• Total UPDRS score in the “on” state.
• UPDRS score for Parts 1, 2, and 3 combined.
• UPDRS score for Parts 2 and 3 combined.
• UPDRS subscale scores for Parts 1, 2, 3, and 4.
• Tremor domain of the UPDRS Part 3.
• MoCA score.
• EQ-5D score.
• PDQ-39 score.
• BDI-II score.
• Apathy score.

7.7.2 Safety Monitoring and Assessments

7.7.2.1 Safety Endpoints

7.7.2.1.1 Prespecified Safety Endpoints

Prespecified Safety Endpoints (Tier 1 events) are defined as the incidences of:

• Systolic BP \( \geq 180 \text{ mm Hg} \)
• Diastolic BP \( \geq 105 \text{ mm Hg} \)
• ALT \( \geq 3 \times \text{ULN} \) and \( \geq 10\% \) increase from Baseline
• AST \( \geq 3 \times \text{ULN} \) and \( \geq 10\% \) increase from Baseline
• C-SSRS (Appendix 4)
  - Suicidality
  
  and
• Epworth Sleepiness Scale score
7.7.2.1.2 Commonly Occurring Safety Endpoints

The Commonly Occurring Safety Endpoints include the AE preferred terms not included in the Prespecified Safety Endpoints, but observed to be “common.” For this trial, an AE is considered “common” if it occurs in ≥4 subjects in any treatment group.

7.7.2.1.3 Descriptive Endpoints

Descriptive Endpoints include all other AE preferred terms plus laboratory assessments, ECGs, vital signs, QUIP-RS score, Suicidal Behavior, Suicidal Ideation, Sleep Attack Questionnaire results, etc, not analyzed in the Prespecified Safety Endpoints or identified among the Commonly Occurring Safety Endpoints.

7.7.2.2 Definition of Terms

7.7.2.2.1 Adverse Event

Per the International Conference on Harmonization (ICH), an adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

7.7.2.2.2 Serious Adverse Event

Serious Adverse Event (SAE) is any untoward medical occurrence or effect that at any dose:

1. Results in death;
2. Is life-threatening;
3. Requires hospitalization or prolongation of existing inpatients’ hospitalization;
4. Results in persistent or significant disability or incapacity; and/or
5. Is a congenital anomaly or birth defect.
Life-threatening in the definition of a serious adverse event refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Medical judgment should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

7.7.2.2.3 Closely Monitored Event

A “closely monitored event” is a non-serious adverse event or occurrence that is designated to be of special interest and must be reported to the sponsor as though it were a serious adverse event – as described in Section 7.7.2.5.1. The following events are considered closely monitored for this trial:

1. Liver-related findings:
   Note: Detailed guidance for assessment, follow-up, and documentation of liver-related findings will be provided by the sponsor in a separate A2a Neuro hepatic Guidance document.

   • ALT or AST >8 x ULN
   • ALT or AST >5 x ULN for more than 2 weeks.
   • ALT or AST >3 x ULN and T-BIL >2 x ULN or International Normalized Ratio [INR] >1.5 that is not due to anti-coagulation.
   • ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).
   • ALT or AST ≥3 x ULN and a ≥10% increase from the Baseline value (obtained predose at the Randomization visit, CV3).

   Note: For ALT or AST ≥3 x ULN and a ≥10% increase from the Baseline value, subjects should return to the clinic for repeat testing within 48-72 hours per the A2a Neuro hepatic Guidance document.

   • Diagnosis of hepatitis.
2. Increase in systolic BP to ≥155 mm Hg OR diastolic BP to ≥100 mm Hg at two consecutive visits separated by 7 days. If BP is ≥155 mm Hg systolic OR ≥100 mm Hg diastolic, the subject must come back to the clinic in 7 days for a follow-up visit (unscheduled, per protocol). If, at this 7-day follow-up visit, the subject’s blood pressure continues to be at or above 155 mm Hg systolic OR 100 mm Hg diastolic, the Sponsor should be contacted and a discussion initiated regarding the adjustment or addition of blood pressure medication to the subject’s regimen. Note: during the course of the study, antihypertensive medication may be initiated or increased to control a subject's BP at any time during treatment in P07037 as needed.

3. Elevation (from Baseline) of systolic BP >40 mm Hg or diastolic BP >20 mm Hg at two consecutive visits separated by 7 days.

4. Overdose not associated with an AE.

5. Potential intentional study medication misuse whereby the subject returns less study medication than prescribed but denies taking extra study medication. This is defined as the equivalent of more than 1 missing pill per week (e.g., more than 4 pills over a month). Please see Section 7.4.1.5.8 for details.

6. Adverse events occurring while the subject is on study drug:
   - Depersonalization
   - Derealization
   - Dissociation
   - Dissociative disorder
   - Euphoria/euphoric mood
   - Mania
   - Perceptual and other cognitive disorders
   - Anxiety
   - Delusion
   - Restlessness
   - Aggression
   - Agitation
   - Irritability
   - Nervousness
   - Disturbance in attention

For adverse events that fit into these categories, detailed information should be obtained from the patient. The sponsor will provide a separate guidance document for assessment, follow-up and characterization of these adverse experiences leading to a written narrative summarizing the event.

7. Adverse events occurring following discontinuation of study drug:
   - Depression
   - Somnolence
   - Fatigue
   - Lethargy
   - Irritability
Subjects will be followed closely by telephone contact at 48 hours and 7 days following the subject’s last dose of study drug, as well as at the safety follow-up visit, and assessed for spontaneous reports of depression, somnolence, fatigue, lethargy, and irritability after discontinuation of treatment. The sponsor will provide a separate guidance document for assessment, follow-up and characterization of these adverse experiences leading to a written narrative summarizing the event.

7.7.2.2.4 Overdose

7.7.2.2.4.1 Definition

For this protocol an overdose is defined as ingestion of a dose of study medication exceeding the specified dose to be administered daily. Therefore, in this trial an overdose of the investigational product is a total of more than 2 tablets per day (ie, \( \geq 3 \) tablets per day).

7.7.2.2.4.2 Reporting of Overdose to SPONSOR

Overdose will be collected and defined as either Accidental Overdose or Intentional Overdose based on the subject's response. If an adverse experience(s) is associated with an overdose of the test drug, the adverse experience(s) is reported as a serious adverse experience, even if no other criteria for serious are met. If a dose of test drug meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a "closely monitored event", using the terminology "Accidental Overdose without AE" or "Intentional Overdose without AE". All reports of overdose with and without an adverse experience must be reported within 1 working day to one of the individuals listed on the sponsor contact information page found in the Administrative Binder. The overdose will be captured on the appropriate eCRF in the clinical database and the Safety Data Reporting Form 1727.

7.7.2.2.5 Product Quality Complaint

A product quality complaint (PQC) is any written, electronic or oral communication that alleges a product defect. A Product Quality Complaint includes suspected product counterfeit, diversion or tampering. A Product Quality Complaint does not include Product Complaints alleging an Adverse Event.
7.7.2.2.6 Planned Hospitalization

A hospitalization planned by the subject prior to signing the ICF is considered a therapeutic intervention and not the result of a new SAE and should be recorded as medical history. If the planned hospitalization or procedure is executed as planned, the record in the subject’s medical history is considered complete. However, if the event/condition worsens during the trial, it must be reported as an AE.

7.7.2.2.7 Medication Error

A medication error is any preventable event that may cause or lead to inappropriate medication use, including unintended accidental exposure or subject or patient harm while the medication is in the control of a health care professional, subject or patient, or consumer. Such events may be related to professional practice, clinical trials, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, and nomenclature; compounding, dispensing, distribution, administration, education, monitoring, and use.

7.7.2.2.8 Potential Medication Error

A potential medication error is an individual case safety report of information or complaint about product name, labeling, or packaging similarities that does not involve a subject or patient (eg, if a subject reports that one of the investigational products looks like a different product, the report would be considered a potential medication error).

7.7.2.2.9 Trial Procedure Related Events

A clinical trial procedure related event is an adverse event which could be associated with the trial procedures, rather than the investigational product or its administration. Trial procedures include all treatment procedures and medical procedures for physical examinations, medical investigations, and laboratory assessments or other activities specified in the protocol for the purpose of the clinical trial.

See the Trial Flow Chart in Section 2.2 and Section 7.6 for the list of trial activities.
7.7.2.3 Monitoring

7.7.2.3.1 Monitoring Adverse Events

Subjects will be monitored for the occurrence of SAEs immediately after the subject has signed the ICF. Each subject will be followed for SAEs for up to and including 30 days after the last dose of study drug.

Subjects will be questioned and/or examined by the investigator or a qualified designee for evidence of AEs. The questioning of subjects with regard to the possible occurrence of adverse events will be generalized such as, “How have you been feeling since your last visit?” The presence or absence of specific AEs should not be elicited from subjects.

Subjects having AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the investigator.

AEs, actions taken as a result of AEs, and follow-up results must be recorded in the Case Report Forms (CRF; Section 9.2), as well as in the subject’s source documentation. Follow-up laboratory results should be filed with the subject’s source documentation.

For all AEs that require the subject to be discontinued from the trial and SAEs, relevant clinical assessments and laboratory tests will be repeated as clinically appropriate, until final resolution or stabilization of the event(s).

7.7.2.3.2 Monitoring Laboratory Assessments

All laboratory assessments will be performed centrally at a certified laboratory selected by the sponsor. The clinical laboratory values will be reported to the investigator by the laboratory and he/she will review them for significance and consideration as an AE.

7.7.2.3.2.1 Adjudication

7.7.2.3.2.1.1 Adjudication of ALT/AST ≥3 x ULN and ≥ 10% Increase from Baseline

Any post-Screening cases of ALT and/or AST ≥3 x ULN and ≥10% increase from baseline will be captured. These findings, if confirmed upon repeat testing, will be adjudicated by a blinded independent expert committee external to the sponsor in
order to assess whether or not any confounding factors accompanied the elevation. This blinded ‘Hepatic Adjudication Committee’ will report to the DMC.

When an eligible event is reported to the sponsor, sponsor personnel or delegates may request copies of the CRFs and/or source documents, including any specialist records and/or supplemental laboratory testing relevant to the event. It may be necessary for the investigator to request permission of the patient to complete these requirements. Adjudication of ALT and/or AST \( \geq 3 \times ULN \) and \( \geq 10\% \) increase from baseline findings will be conducted according to a standard operating procedure (SOP) maintained by the sponsor.

7.7.2.3.2.1.2 Adjudication of Vascular Adverse Events

In order to ensure a uniform approach to the classification of serious vascular events, certain serious adverse experiences will be adjudicated by a blinded independent expert committee external to the sponsor. This blinded ‘Vascular Events Committee’ will report to the DMC. The events to be adjudicated include ‘hard’ (categorical as opposed to continuous) endpoints such as myocardial infarctions, thromboembolic events, and stroke.

When an eligible event is reported to the sponsor, sponsor personnel or delegates may request copies of the CRFs and/or source documents, including hospital records relevant to the event. It may be necessary for the investigator to request permission of the patient to complete these requirements. Adjudication of vascular events will be conducted according to an SOP maintained by the sponsor.

7.7.2.4 Assessment of Adverse Events

7.7.2.4.1 Assessment of Severity

Where the determination of adverse event severity rests on medical judgment, the determination of severity must be made with the appropriate involvement of a medically-qualified investigator.

The National Cancer Institute’s Common Terminology Criteria for Adverse Events v4 (CTCAE) will be used for grading severity of AEs. (CTCAE is available at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

For AEs not covered by this grading system, the following definitions will be used:
Mild: awareness of sign, symptom, or event, but easily tolerated;

Moderate: discomfort enough to cause interference with usual activity and may warrant intervention;

Severe: incapacitating with inability to do normal daily living activities or significantly affects clinical status, and warrants intervention;

Life-threatening: immediate risk of death.

### 7.7.2.4.2 Assessment of Causality

A medically-qualified investigator must assess the relationship of any AE (including SAEs) to the use of the investigational product, as unlikely related, possibly related, or probably related, based on available information, using the guidelines listed below:

**Unlikely related:** no temporal association, or the cause of the event has been identified, or the drug, biological, or device cannot be implicated based on available information;

**Possibly related:** temporal association, but other etiologies are likely to be the cause; however, involvement of the drug, biological, or device cannot be excluded based on available information;

**Probably related:** temporal association, other etiologies are possible, but unlikely based on available information.

### 7.7.2.4.3 Reference Safety Information (RSI) for the Assessment of Expectedness of Adverse Events

The Reference Safety Information (RSI) for assessing the expectedness of an adverse event for the investigational product preladenant in this trial is to be the most recent Investigator’s Brochure for preladenant.
7.7.2.4.4 Known Potential Toxicities of Investigational Products

The following observations are known potential toxicities of the investigational product preladenant:

1. Elevation of liver enzymes.
2. Elevated systolic BP.
3. Cardiac malformations in animal embryos.

Refer to the Investigator’s Brochure for additional information on AEs related to toxicities observed to date.

7.7.2.4.5 Known Adverse Events Relating to the Underlying Clinical Condition

Some common AEs associated with PD include:

1. Muscular rigidity
2. Resting tremor
3. Postural instability
4. Bradykinesia/hypokinesia
5. Parkinsonism
6. Dementia
7. Depression
8. Psychosis
9. Sleep disturbance
10. Weight loss
11. Dysphagia
12. Constipation
13. Orthostatic hypotension

It should be noted that impulsive-compulsive disorder is a known adverse effect associated with D2 agonist therapy, but not of treatment with preladenant or with PD itself.
It should be noted that dyskinesias are a known adverse effect of treatment with L-dopa.

The judgment of relatedness of any AE to study treatment lies with the investigator as described in Section 7.7.2.4.2.

7.7.2.5 Reporting Safety Observations by the Investigator to the Sponsor

7.7.2.5.1 Expedited Reporting of Safety Observations by the Investigator to the Sponsor

Any occurrence of the following events in a subject in the trial must be reported expeditiously by the investigator or qualified designee to the sponsor’s Global Pharmacovigilance (GPV) department within 1 working day of becoming aware of the event using the Data Safety Reporting Form 1727. (Guidance for using the Data Safety Reporting Form 1727 is provided by the sponsor to the investigator in the “Data Safety Reporting Form 1727 Completion Guidance & Instructions”.)

1. SAE (including SAEs associated with overdose, medication errors, pregnancy, exposure during pregnancy or lactation – including the pregnancy of a male subject’s female partner who has provided written informed consent to provide information regarding pregnancy)
2. Death
3. Planned hospitalizations (not previously reported in the medical history)
4. Closely Monitored Event
5. Cancer

Any occurrence of a product quality complaint by a subject must be reported expeditiously by the investigator or qualified designee to the sponsor or designee using the Investigational Medicinal Product Quality Complaint Form provided by the sponsor/designee within 1 working day of becoming aware of the event.

Any occurrence of the following events or outcomes in a subject in the trial must be reported expeditiously by the investigator or qualified designee to the sponsor or designee using the Data Safety Reporting Form 1727 within 5 working days of becoming aware of the event.
1. Pregnancy, exposure during pregnancy or lactation NOT associated with an SAE – including the pregnancy of a male subject’s female partner who has provided written informed consent to provide information regarding pregnancy
2. Medication error
3. Potential medication error
4. Overdose

If the investigator is unsure about when to report an observation from the lists above, the event or outcome should be reported within 1 working day.

If an autopsy is performed on a deceased subject, the de-identified autopsy report must be provided to the sponsor within 1 working day of the results being available.

The Data Safety Reporting Form 1727 requires that the investigator assess causality of the event relative to the investigational product administered in the trial. Causality is described in Section 7.7.2.4.2.

7.7.2.5.2 Expedited Reporting by the Sponsor to a Regulatory Health Authority

Global Pharmacovigilance (GPV) will monitor data for safety. The Sponsor will manage the expedited reporting of relevant safety information to concerned health authorities, competent authorities, and Institutional review Boards (IRBs)/independent Ethics Committees (IECs) in accordance with local laws and regulations.

7.7.2.6 Discontinuation, Treatment Interruption, and Unblinding of Blinded Treatment Due to Safety Observations

7.7.2.6.1 Discontinuation

See Section 7.3.3 for the criteria by which a subject must be discontinued. Should a subject be discontinued from the trial, complete the visit activities as specified for discontinuation in the Trial Flow Chart in Section 2.2.
7.7.2.6.2 Temporary Interruption of Treatment for a Subject

Temporary interruption of treatment may occur for reasons other than adverse events related to study drug (e.g., previously scheduled medical interventions). The investigator is to discontinue a subject as necessary according to the criteria provided in Section 7.3.3. Interruptions of 5 or more consecutive daily doses of study drug will require that the investigator notify the SPONSOR.

7.7.2.6.3 Modification of Dose and/or Administration of Investigational Product for a Subject

The dose and administration to any subject may not be modified. If necessary a subject must be discontinued for the reasons described in Section 7.3.3.

7.7.2.6.4 Unblinding Treatment for a Subject During the Trial

To assess an occurrence of a safety observation, GPV may unblind the treatment of any subject for whom a Reporting Form 1727 was returned by the investigator to the sponsor.

Unblinding by the request of the investigator should occur only in the event of adverse event for which it is necessary to know the trial treatment to determine an appropriate course of therapy for the subject. If the investigator must identify the treatment assignment of an individual subject, the investigator or qualified designee is to call the IVRS. Unblinding performed by the IVRS at the request of the investigator is to be reported in writing by the investigator to the sponsor, including a written explanation of the reason why the blind was broken.

The random code will be sent to the Head of Bioanalytics (or regional head) to be used in the analysis of samples. Data will not be unblinded outside of Bioanalytics until the database has been locked.

7.7.2.7 Contraception and Pregnancy

Women of reproductive potential can be enrolled. However, appropriate contraception must be used throughout the study, including up to 2 weeks following
the last dose of study drug. Appropriate contraception in this trial is defined as the practice of true abstinence or the use of a highly effective method of birth control.

True abstinence, when this is in line with the preferred and usual lifestyle of the subject and is a locally acceptable method of contraception is an acceptable method of contraception. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

If a subject is not practicing true abstinence, the subject and his/her partners should use one of the highly effective methods of birth control listed below, where it is permitted by local regulation. These methods should be used while the subject is in the study and for 2 weeks following the last dose of study drug:

- intrauterine device (IUD)
- condoms + spermicide
- diaphragm + spermicide
- vasectomy
- bilateral tubal ligation

The use of barrier contraceptive (condom, diaphragm) should always be supplemented with the use of a spermicide. Patients taking hormonal contraceptives may continue their use during the trial, but must use one of the highly effective forms of non-hormonal contraception throughout the study period until data regarding potential interaction of preladenant with oral contraceptives are available. A formal drug-interaction study of oral contraceptives is planned. If results from the drug-interaction study show lack of clinically meaningful effects of preladenant on hormonal levels, then the sponsor may allow use of hormonal contraceptives as one of the highly effective methods of contraception during the study period. In this event, hormonal contraceptives must have been used for at least 2 months prior to signing the informed consent for patients to be eligible for enrollment into the study. The sponsor will formally notify the investigator sites of any change in the contraceptive requirements.

7.7.3 Pharmacogenetics Analysis

7.7.3.1 Mandatory Genotyping

There are known genetic associations with drug-induced liver injury, (specifically human lymphocyte antigen [HLA] alleles)\(^{(38,39)}\). A sample will be drawn to investigate presence of HLA genetic association with liver toxicity if it occurs during the course of the clinical trial.
A specific genetic test to assess for the presence of Gilbert’s syndrome may be performed. Gilbert’s syndrome is an inherited autosomal recessive condition characterized by mild unconjugated nonhemolytic hyperbilirubinemia, and is due to a polymorphism in the human bilirubin uridine 5’-diphospho-glucuronosyltransferase (UGT1A1) promoter. Subjects should provide one sample (for both HLA and UGT1A1) on Day 1; all samples will be stored at the central laboratory and analyzed only if liver safety findings need further clarification.

7.7.3.2 Exploratory Pharmacogenetics

Exploratory pharmacogenetic studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Exploratory pharmacogenetic studies will be conducted with Biostatistics design and analysis and compared to PK/PD results or clinical outcomes. Any significant exploratory pharmacogenetic relationships to outcome will require validation in future clinical trials. The Laboratory Manual for this study and Appendix 2 of this protocol provide details about pharmacogenetic sample handling.

Exploratory pharmacogenetic interrelationships (eg, pharmacodynamic/pharmacogenetic, pharmacokinetic/pharmacogenetic, and safety pharmacogenetics) may be explored.

7.7.4 Pharmacokinetics Analysis

Blood samples for population pharmacokinetic analysis will be drawn at Week 8 before the on-site administration of study drug and again at approximately 2 hours (range, 1 to 4 hours) after the on site administration of study drug. In addition, one sample will be drawn at any Early Termination visit only when the Early Termination Visit occurs before Week 8.

Individual subject preladenant plasma concentrations and concentrations of two preladenant metabolites (SCH 434748 and SCH 446637) will be listed together with the time of the blood sample relative to the last dose preceding the sample. A population pharmacokinetic-pharmacodynamic analysis may be undertaken as appropriate, to evaluate possible relationships between preladenant PK parameters (and its two metabolites, if deemed necessary) and various efficacy and/or safety variables. The results of this analysis will be reported separately, independent of the study report. Appendix 3 provides details about pharmacokinetic sample handling.
7.8 Criteria for Early Termination of the Trial

The clinical trial may be stopped if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable.

In addition, further recruitment in the trial or at (a) particular site(s) may be stopped due to insufficient compliance with the protocol, Good Clinical Practice (GCP) and/or other applicable regulatory requirements, procedure-related problems, or the number of discontinuations for administrative reasons is too high.

8.0 STATISTICAL AND ANALYTICAL PLANS

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post-hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) will be issued for this study.

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the sponsor.

This study will be conducted as a double-blind study under in-house blinding procedures and is projected to randomize approximately 450 subjects in a 1:1:1 ratio to one of three treatment arms (preladenant 2 or 5 mg twice daily or placebo).

The official, final database will not be unblinded until medical/scientific review has been performed, protocol violators have been identified, and data have been declared final and complete.

8.1 Data Sets

Analysis data sets are defined below:
• Full Analysis Set (FAS): All randomized subjects with subjects excluded for the following reasons:
  - Failure to receive at least one dose of study treatment.
  - Lack of any post-Randomization endpoint data subsequent to at least one dose of study treatment.
  - Lack of Baseline data for those analyses requiring Baseline data.
• All Subjects as Treated Set (ASaT): All subjects who receive at least one dose of study drug.

The FAS will serve as the primary population for the analyses of efficacy data in this study. Randomization will be preserved in the efficacy analyses. Safety analyses will be conducted using the ASaT. In the safety analyses, subjects will be analyzed according to the treatment actually received.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from Baseline, a Baseline measurement is also required.

Baseline values for diary endpoints will be derived from the available diary data collected for 3 days prior to Randomization. Baseline values for other efficacy and safety endpoints will be taken from the last observed value prior to administration of study treatment.

8.2 Demographic and Other Baseline Characteristics

Demographic variables (sex, race, age, weight, etc) and Baseline characteristics (Hoehn & Yahr stage, duration of PD, alcohol consumption, caffeine use, and current cigarette [or equivalent] use, as well as family history of premature coronary heart disease) will be summarized by treatment group to assess treatment group comparability. For categorical variables, numbers in each treatment group for all categories will be presented along with the percentages. For continuous variables, mean, median, minimum, maximum, and standard deviation for each treatment group will be presented. The number and percentage of patients screened, number and percentage of patients randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed.
8.3 Efficacy Analyses

Efficacy results for the Primary and Key Secondary Endpoints that will be considered to be statistically significant after consideration of the strategy for controlling the type I error are described below. Nominal p-values will be computed for other efficacy analyses as a measure of strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses. All statistical tests will be conducted at the alpha = 0.05 (2-sided) level except for tests of the Primary and Key Secondary Endpoints which will be conducted at the alpha = 0.049 level.

Table 9 summarizes the Primary and Key Secondary Efficacy Endpoint Analyses described in the following sections.
### Table 9  Analysis Strategy for Primary and Key Secondary Efficacy Endpoints

<table>
<thead>
<tr>
<th>Endpoint/Variable (Description, Time Point)</th>
<th>Primary vs Secondary Approach</th>
<th>Statistical Method(^{a})</th>
<th>Analysis Population</th>
<th>Missing Data Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from Baseline in Mean OFF time at Week 12</td>
<td>Primary</td>
<td>cLDA(^{b})</td>
<td>FAS</td>
<td>Model-based</td>
</tr>
<tr>
<td>Change from Baseline in Mean OFF time at Week 12</td>
<td>Secondary</td>
<td>ANCOVA(^{c})</td>
<td>FAS</td>
<td>LOCF(^{d})</td>
</tr>
</tbody>
</table>

**Key Secondary Endpoints / Hypotheses**

<table>
<thead>
<tr>
<th>Endpoint/Variable (Description, Time Point)</th>
<th>Primary vs Secondary Approach</th>
<th>Statistical Method(^{e})</th>
<th>Analysis Population</th>
<th>Missing Data Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of Responders at Week 12</td>
<td>Primary</td>
<td>GLIMMIX(^{e})/M&amp;N(^{f})</td>
<td>FAS</td>
<td>Model-based</td>
</tr>
<tr>
<td>Proportion of Responders at Week 12</td>
<td>Secondary</td>
<td>GLIMMIX(^{e})/M&amp;N(^{f})</td>
<td>FAS</td>
<td>Missings counted as failures</td>
</tr>
<tr>
<td>Change from Baseline in Mean ON time without Troublesome Dyskinesia at Week 12</td>
<td>Primary</td>
<td>cLDA(^{b})</td>
<td>FAS</td>
<td>Model-based</td>
</tr>
</tbody>
</table>

cLDA=constrained longitudinal data analysis; ANCOVA=analysis of covariance; FAS=Full Analysis Set; LOCF=last observation carried forward; GLIMMIX=generalized linear mixed model; M&N= Miettinen and Nurminen method

\(^{a}\) Statistical methods are described in further detail below.

\(^{b}\) Constrained longitudinal data analysis with terms for treatment, time, and treatment-by-time interaction.

\(^{c}\) Analysis of covariance accounting for the effects of Baseline and treatment.

\(^{d}\) Last observation carried forward method.

\(^{e}\) Generalized linear mixed model accounting for the effects of Baseline, treatment, time, and treatment-by-time interaction.

\(^{f}\) Miettinen and Nurminen method with estimates of response rates derived from GLIMMIX for comparisons of treatment group differences in response rates.

#### 8.3.1 Primary Efficacy Analysis

The Primary Objective of this trial is to evaluate the efficacy of the preladenant doses 2 mg twice daily and 5 mg twice daily compared with placebo in subjects with moderate to severe PD experiencing motor fluctuations and receiving a stable dose of L-dopa, as measured by “off” time. The Primary Hypothesis is stated below.

- **Hypothesis 1:** At least the 5 mg twice daily dose of preladenant is superior to placebo as measured by the change from Baseline to Week 12 in the mean “off” time.
The primary analysis will be conducted on the FAS. The Primary Efficacy Endpoint is the change from Baseline to End of Treatment (Week 12) in mean “off” time in hours per day, where mean “off” time is derived from the available diary data collected for 3 days immediately prior to a clinic visit. For the analysis of this endpoint, a constrained longitudinal data analysis (cLDA) method proposed by Liang and Zeger\(^{(41)}\) will be used. This model assumes a common mean across treatment groups at Baseline and a different mean for each treatment at each of the post-Baseline time points. In this model, the response vector consists of Baseline and the values observed at each post-Baseline time point. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The analysis model will also adjust for treatment and the interaction of time by treatment. The treatment difference in terms of mean change from Baseline to a given time point (the treatment difference in terms of the mean average change from Baseline over 12 weeks) will be estimated and tested from this model. An unstructured covariance matrix will be used to model the correlation among repeated measurements.

Although the Baseline measurement is included in the response vector, it is independent of treatment, and hence, the Baseline means are constrained to be the same for different treatment groups. Of note, in the event that there are no missing data, the estimated treatment difference from the above cLDA model will be identical to that from a traditional longitudinal analysis of covariance (ANCOVA) model which uses the Baseline value as a covariate. However, unlike longitudinal ANCOVA, the cLDA model accounts for variability in the Baseline values, thus providing more accurate standard errors and confidence intervals for individual treatment effects. Moreover, this model allows the inclusion of subjects who are missing either the Baseline or post-Baseline measurement, thereby increasing efficiency. Details of the model specification, assumptions, and SAS implementation codes are given in Appendix 5.

The LDA method assumes that data are missing at random (MAR). In this study, it is expected that Missing at Random and Missing Completely at Random (MAR/MCAR) mechanisms will underlie most of the ‘missingness,’ and the proportion of data missing not at random (MNAR), driven solely by unobserved values of the study endpoints, will be small. Reasons for discontinuation from the study may include lack of efficacy, clinical or laboratory adverse experiences, relocation, withdrawal of consent, protocol violations, and/or data processing issues. Missing data caused by relocation and data processing issues are likely to be MCAR. On the other hand, missing data caused by discontinuation due to lack of efficacy may belong to MAR because the discontinuation may depend on the observed efficacy outcomes. The MAR or MNAR mechanisms might each underlie the other reasons to some extent. If treatment in large part determines the loss of data for these other reasons (such as clinical or laboratory adverse experiences), the mechanism may be close to MAR because treatment assignment is an observed variable and included in the analysis model. Based on prior study results, missing data due to other reasons is relatively infrequent.
The least squares mean (LSM) response and pairwise differences between preladenant doses and placebo along with 95% confidence intervals will be provided. The p-values from these comparisons constitute tests of the primary hypotheses.

Multiplicity will be controlled using a sequential testing procedure (see Section 8.3.2 for details).

8.3.2 Key Secondary Efficacy Analysis

The Key Secondary Efficacy Objectives for this trial are to evaluate the preladenant doses 2 mg twice daily and 5 mg twice daily compared with placebo in subjects with moderate to severe Parkinson’s disease experiencing motor fluctuations and receiving a stable dose of levodopa (L dopa) as measured by the proportion of Responders and by “on” time without troublesome dyskinesia. The two Key Secondary Hypotheses are stated below:

- **Hypothesis 2**: At least the 5 mg twice daily dose of preladenant is superior to placebo as measured by the proportion of subjects with at least a 30% reduction in mean “off” time from Baseline to Week 12.
- **Hypothesis 3**: At least the 5 mg twice daily dose of preladenant is superior to placebo as measured by the change from Baseline to Week 12 in mean “on” time without troublesome dyskinesia.

The Key Secondary Endpoint analyses will be conducted on the FAS. The Key Secondary Efficacy Endpoints are:

- The proportion of Responders, where Responder is defined as a subject with at least a 30% reduction in “off” time from Baseline to End of Treatment (Week 12).
- The change from Baseline to Week 12 in mean “on” time without troublesome dyskinesias in hours per day.

“Responder” will be analyzed using a generalized linear mixed model (GLIMMIX). This model assumes a binary distribution for the response and uses a logit link. In this model, time is treated as a categorical variable and the response rate for each treatment at each of the repeated time points is allowed to be different. The analysis model will also adjust for Baseline “off” time. The treatment difference in terms of log odds ratio at a given time point will be estimated and tested from this model using the SAS PROC GLIMMIX procedure. An unstructured covariance matrix will be used to model the residual correlation among repeated measurements, and the
Satterthwaite approximation will be used for the denominator degrees of freedom for the tests of fixed effects. Of note, in the event that there are no missing data, the estimated treatment difference from the above GLIMMIX will be identical to that from a corresponding logistic regression model at the given time point. However, the GLIMMIX allows the inclusion of patients who have missing data at certain time points, thereby increasing efficiency. Additionally, the estimated proportion of responders in each treatment group at Week 12 will be provided along with 95% confidence intervals. Differences between treatment groups in the proportion of Responders will be estimated using Miettinen and Nurminen’s method. \(^{(42)}\) Details of the model specification, assumptions, and SAS implementation codes are given in Appendix 6. A cumulative distribution plot of percent change from Baseline in mean “off” time within each treatment arm will be presented.

Mean “on” time without troublesome dyskinesias is derived from the available diary data collected for 3 days immediately prior to a clinic visit. "On" time without troublesome dyskinesia is the sum of "on" time without dyskinesia plus "on" time with non-troublesome dyskinesia as recorded in the diary. The change in mean “on” time without troublesome dyskinesias will be evaluated using the same cLDA model used for the Primary Endpoint. The LSM response and pairwise differences between preladenant doses and placebo along with 95% confidence intervals will be provided.

Multiplicity for the Primary and Key Secondary Endpoints will be controlled using the sequential testing procedure shown in the figure below. Testing will begin with comparisons of the 5 mg twice daily dose versus placebo for the Primary Endpoint and Key Secondary Endpoints. If these comparisons are statistically significant \((p \leq 0.049)\), testing will continue with the 2 mg twice daily dose versus placebo for the Primary and Key Secondary Endpoints. Specifically, beginning with Step 1, the 5 mg twice daily dose versus placebo test will be conducted for the Primary Endpoint. If this comparison is statistically significant \((p \leq 0.049)\), testing will continue in the order specified in Figure 1, until a non-significant test is obtained or all tests have been conducted.
Figure 1  Sequential Testing Procedure (P07037)

BID = twice daily; w/o = without; TD = troublesome dyskinesia

If all tests in Step 1 are statistically significant (p ≤0.049), testing will continue with the endpoints in Step 2.

P-values for all other efficacy analyses and treatment comparisons will be considered nominal and as a measure of strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses.

8.3.3 Other Efficacy Analyses

The Secondary Efficacy Endpoints listed below will be analyzed using the same cLDA model as the Primary Efficacy Analysis.

Change from Baseline in the following endpoints:

• Diary data which include:
• Mean hours per day spent in the “off” state at Weeks 2, 4 and 8.
Mean hours per day spent in the “on” state at Weeks 2, 4, 8, and 12.
Mean hours per day spent in the “on” state without troublesome dyskinesia at Weeks 2, 4 and 8.
Mean hours per day spent in the “on” state with troublesome dyskinesia at Weeks 2, 4, 8, and 12.
Proportion of “on” time with no dyskinesias at Weeks 2, 4, 8, and 12.
Proportion of “on” time without troublesome dyskinesias at Weeks 2, 4, 8, and 12.
Proportion of “on” time with troublesome dyskinesias at Weeks 2, 4, 8, and 12.
Mean total sleep time at Weeks 2, 4, 8, and 12.
Total UPDRS score in the “on” state.
UPDRS score for Parts 1, 2, and 3 combined.
UPDRS score for Parts 2 and 3 combined.
UPDRS subscale scores for Parts 1, 2, 3, and 4.
Tremor domain of the UPDRS Part 3.

Mean hours per day spent in the “off”, “on” (with or without any/troublesome dyskinesia) or asleep state will be derived from the available diary data collected for 3 days immediately prior to a clinic visit. The following Secondary Endpoints will be summarized by treatment and time point using descriptive statistics.

Changes from Baseline in:

- MoCA score.
- EQ-5D score.
- PDQ-39 score.
- BDI-II score.
- Apathy score.

8.3.4 Additional Efficacy Analyses

An ANCOVA model with treatment effect and Baseline covariate will be conducted as a sensitivity analysis for the last-observation-carried-forward (LOCF) data for the Primary Endpoint. A sensitivity analysis will be conducted for the Responder endpoint in which all subjects who discontinue treatment prior to the 12-week time
point will be counted as non-responders (ie, percent change from Baseline in mean “off” time will be set to zero at all time points).

To assess whether the treatment effect is consistent across various subgroups, the between-group treatment effect (with a nominal 95% confidence interval) for the Primary Endpoint will be estimated within each category of the following classification variables:

- Age category (<65 vs ≥65 years)
- Sex (female, male)
- Region (US, Ex-US)

Additional exploratory analyses and subgroup analyses may be performed.

8.4 Justification of Sample Size

The difference between preladenant and placebo in decrease in mean “off” time is expected to be approximately 1 hour with a pooled standard deviation of 2.6 hours based on the Phase 2 study P04501.

The total target sample size in this study will be 450 subjects or 150 subjects per treatment group. A reduction in “off” time of 1 hour per day represents a clinically relevant functional gain for a subject with moderate or severe PD. With 150 subjects per arm this study has at least 90% power to detect a difference of 1 hour in change from Baseline to Week 12 in mean “off” time given a standard deviation of 2.6 hours and a two-sided alpha = 0.05. The table below summarizes the power for under various assumptions when the sample size is 150 subjects per treatment group, using a 2-sided alpha = 0.05.

<table>
<thead>
<tr>
<th>Underlying Standard Deviation of Change From Baseline</th>
<th>Underlying Difference of OFF Time Change from Baseline (Preladenant vs Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>.7</td>
</tr>
<tr>
<td>2.2</td>
<td>78</td>
</tr>
<tr>
<td>2.6</td>
<td>64</td>
</tr>
<tr>
<td>3.0</td>
<td>52</td>
</tr>
</tbody>
</table>
Considered marginally, power for the Key Secondary Endpoints is summarized under various assumptions in Table 10 and Table 11. The difference in mean “on” time without troublesome dyskinesia from Baseline to Week 12 is expected to be approximately 1 hour longer in the preladenant 2 and 5 mg twice daily treatment groups compared to placebo with a standard deviation of 2.6 hours based on results of the Phase 2 study, P04501. Table 10 above provides power calculations for this endpoint. With 150 subjects per arm this study has at least 90% power to detect a difference of 1 hour in change from Baseline to Week 12 in mean “on” time without troublesome dyskinesias given a standard deviation of 2.6 hours and a two-sided alpha = 0.05.

Based on the results from the same study, P04501, the Responder rate in the preladenant arms is expected to be approximately 55% in the 5 mg twice daily group, 41% in the 2 mg twice daily group, and 33% in the placebo group. With 150 subjects per arm and at least 40% Responders in a preladenant group, the study will have at least 93% power to detect a difference of 20% between preladenant and placebo.

An estimate of the overall power of jointly obtaining significance for the testing scheme consisting of the 5 mg twice daily comparison versus placebo for the Primary and Key Secondary Endpoints would be approximately 89%, considering the correlations observed in the Phase 2 study between endpoints within a dose (ie, 0.8 to 0.9).

<table>
<thead>
<tr>
<th>Percent of Placebo Responders</th>
<th>30</th>
<th>35</th>
<th>40</th>
<th>45</th>
<th>50</th>
<th>55</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>51</td>
<td>83</td>
<td>96</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>&gt;99</td>
</tr>
<tr>
<td>25</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>95</td>
<td>&gt;99</td>
<td>&gt;99</td>
</tr>
<tr>
<td>30</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>76</td>
<td>94</td>
<td>&gt;99</td>
</tr>
<tr>
<td>35</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>75</td>
<td>93</td>
</tr>
<tr>
<td>40</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>74%</td>
</tr>
</tbody>
</table>
8.5 Interim Analysis

No formal efficacy interim analysis is planned. A Data Monitoring Committee (DMC) will review the safety in this study on an ongoing basis (Section 8.9). The DMC may also ask to review efficacy results if deemed necessary; therefore, an alpha adjustment of 0.001 (Haybittle Peto method) will be made to account for this, and the final analysis will use a 0.049 alpha-level.

8.6 Accounting for Missing Data

No imputation of missing data will be done for the cLDA analyses. For the sensitivity analysis of the End-of-Treatment time point analyses, missing data will be imputed using the last-observation-carried-forward (LOCF) method. In the Responder sensitivity analysis, subjects who discontinue will be counted as non-responders as detailed in Section 8.3.4. There will be no imputation of missing data for MoCA, EQ-5D, PDQ-39, BDI-II, or Apathy Scale scores.

If L-dopa use above Baseline levels occurs within 24 hours of Diary data collection or the UPDRS assessment, then that Diary day(s) or UPDRS evaluation will be considered missing for statistical analysis purposes. Complete data will be reported in subject data listings with the affected day or test flagged to indicate that measurements were obtained within 24 hours of an increased L-dopa dose. The 3-day Diary average will be presented both with and without the affected day(s).

Calculation of the average daily diary endpoints will consider the following: if there are fewer than 3 consecutive days of diary data available prior to a visit, then the available number of days will be used to calculate the average value for that visit, and if more than 4 hours are missing for any given daily diary, that diary day will be considered missing and will not be included in the calculations of diary endpoints. A sensitivity analysis may be performed to evaluate the impact of incomplete diary data.

8.7 Safety

The Primary Safety Objective of this trial is to assess the safety and tolerability of preladenant compared with placebo in subjects with moderate to severe Parkinson’s disease experiencing motor fluctuations and receiving a stable dose of L-dopa.

Safety analyses will be based on All Subjects as Treated Set (ASaT) according to the treatment actually received. Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, vital signs, and ECG measurements.

The analysis of safety results will follow a tiered approach as shown in Table 12.
Table 12  Analysis Strategy for Safety Parameters

<table>
<thead>
<tr>
<th>Safety Tier</th>
<th>Safety Endpointa</th>
<th>p-Value</th>
<th>95% CI for Treatment Comparison</th>
<th>Descriptive Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tier 1</td>
<td>Incidence of Systolic BP ≥180 mm Hg</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Incidence of Diastolic BP ≥105 mm Hg</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Incidence of AST ≥3 X ULN with ≥10% increase from Baseline</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Incidence of ALT ≥3 X ULN with ≥10% increase from Baseline</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Incidence of C-SSRS Suicidality</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Epworth Sleepiness Scale</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tier 2</td>
<td>Any AE</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any Serious AE</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any Drug-Related AE</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any Serious and Drug-Related AE</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discontinuation due to AE</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Incidence of C-SSRS Suicidal Behavior</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Incidence of C-SSRS Suicidal Ideation</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Specific AEsb (incidence ≥4 subjects in one of the treatment groups)</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Tier 3</td>
<td>Specific AEs (incidence &lt;4 subjects in all of the treatment groups)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Labs, ECGs, Vital Signs, QUIP-RS Sleep Attack Questionnaire</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note:  X = results will be provided.

a  Adverse event references refer to both Clinical and Laboratory AEs.
b  Includes only those endpoints not prespecified as Tier 1 or not already prespecified as Tier 2 endpoints.

The tiers differ with respect to the analyses that will be performed. Safety parameters or AEs of special interest that are identified a priori constitute “Tier 1” safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Adverse events (specific terms as well as system organ class terms) and predefined limits of change in laboratory, vital signs, and ECG parameters that are not prespecified as Tier 1 endpoints will be classified as belonging to “Tier 2” or “Tier 3”, based on the number of events observed. Membership in Tier 2 requires that at
least 4 subjects in any treatment group exhibit the event; all other adverse
experiences and predefined limits of change will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in AEs and predefined limits of change.

Continuous measures such as changes from Baseline in laboratory, vital signs, ECG parameters and the QUIP-RS score and discrete measures such as the Sleep Attack Questionnaire that are not prespecified as Tier 1 endpoints will be considered Tier 3 safety parameters. Summary statistics for Baseline, on-treatment, and change from Baseline values will be provided by treatment group in table format. Additional details on presentations for laboratory and blood pressure data are summarized below in Section 8.7.3.

For this protocol, the prespecified safety endpoints identified in Section 8.7.1 are considered Tier 1 events. In addition, the broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, and subjects who discontinued due to an AE will be considered Tier 2 endpoints. Adjudicated hepatic and vascular events will be tabulated and listed separately from investigator-reported AEs. The potential abuse liability will be assessed by pooling AE data from similar protocols in the program in the integrated safety analysis. Potential abuse AE terms will be compared during the treatment period, and 14-day post treatment period. The list of abuse AE terms will be pre-specified in the integrated safety analysis plan for the preladenant program after receiving inputs from regulatory authorities. P-values (Tier 1 only) and 95% confidence intervals (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of subjects with Tier 1 LFT or BP events and Tier 2 events; these analyses will be performed using the Miettinen and Nurminen method,\textsuperscript{(42)} an unconditional, asymptotic method. Significant Tier 2 events will be flagged according to the modified Mehrotra-Heyes-Tukey Double False Discovery Rate (DFDR) approach (REF: In press). This modification simplifies the two-step application of the Benjamini and Hochberg FDR method by eliminating the need for resampling, while maintaining its ability to lower the false discovery rate and power to detect true signals.

The Epworth Sleepiness Scale score change from Baseline will be analyzed using the same cLDA model as for the Primary Endpoint. The LSM response and pairwise difference between preladenant doses and placebo along with 95% confidence intervals will be presented. The C-SSRS will be used to compute the total number of subjects with any Suicidal Behavior, Suicidal Ideation, and Suicidality,\textsuperscript{(28)} in
accordance with the Center for Suicidality Risk Assessment (Appendix 4 and correspondence on file with the sponsor). Between treatment group differences for preladenant versus placebo will be evaluated using the Miettinen and Nurminen approach. P-values for Suicidality will be reported if there are at least 4 events in any one treatment group; Suicidal Behavior and Suicidal Ideation will be considered Tier 2 events.

8.7.1 Analysis of Prespecified Safety Endpoints

Tier 1 events are defined as incidences of:

- Systolic BP ≥180 mm Hg
- Diastolic BP ≥105 mm Hg
- ALT ≥3 X ULN and ≥10% increase from Baseline
- AST ≥3 X ULN and ≥10% increase from Baseline
- C-SSRS (refer to Appendix 4)
  - Suicidality

as well as the change from Baseline in:

- Epworth Sleepiness Scale score

Analysis of Tier 1 events is presented in Section 8.7.

8.7.2 Analysis of Commonly Occurring Safety Events

For this study, an AE, is considered “common” (ie, a Tier 2 event) if it occurs in 4 or more subjects in a dose group.

Analysis of Tier 2 events is presented in Section 8.7.
8.7.3 Analysis of Descriptive Safety Endpoints

Descriptive Safety Endpoints include AEs that occur at a frequency of less than 4 subjects in each treatment group as well as vital signs (including BP measurements), laboratory parameters (including liver function test [LFT] results [ie, ALT, AST, alkaline phosphatase {ALK-P} and T-BIL]); ECG parameters, QUIP-RS scores, and Sleep Attack Questionnaire results (ie, Tier 3 events).

Laboratory data will be listed and values outside the normal range will be flagged. Summary statistics (mean, standard deviation, median, minimum, maximum) by treatment group and time point will be provided for the raw data and change from Baseline values. Frequency counts for ALT, AST, T-BIL, and ALK-P values will be summarized by treatment group and time point by category (eg, <1.5 x ULN, ≥1.5 to <3 x ULN, ≥3 to <5 x ULN, ≥5 x ULN). Frequency counts for laboratory tests with predefined limits of change specified in Appendix 7 will be summarized by treatment group and time point. Shift tables will count the number of subjects with changes from Baseline to their worst on-treatment value relative to the normal range (low, normal, high) by treatment group.

The highest on-treatment values for ALT, AST, and T-BIL will be used to evaluate Hy’s Law (Table 13) graphically. Hy’s Law cases are not considered Tier 1 due to the expected low incidence.

Table 13  Hy's Law

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control agent or placebo.</td>
</tr>
<tr>
<td>2.</td>
<td>Among trial subjects showing such aminotransferase (AT) elevations, often with ATs much greater than 3 x ULN, one or more also show elevation of serum T-BIL to &gt;2 x ULN, without initial findings of cholestasis (elevated serum ALK-P).</td>
</tr>
<tr>
<td>3.</td>
<td>No other reason can be found to explain the combination of increased AT and T-BIL, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury.</td>
</tr>
</tbody>
</table>


Vital signs will be listed for each subject. Replicate supine and standing measurements for pulse, systolic BP, and diastolic BP within a visit will be averaged for analysis. Summary statistics (mean, standard deviation, median, minimum, maximum) by treatment group and time point will be provided for the raw data and change from Baseline values.
Frequency counts and incidence rates will be used to summarize changes from Baseline for the following items by treatment group and time point:

- orthostatic systolic BP decrements ≥20 mm Hg and ≥40 mm Hg;
- orthostatic diastolic BP decrements ≥10 mm Hg and ≥20 mm Hg;
- supine and standing systolic BP ≥20 mm Hg and ≥40 mm Hg, as increments or decrements;
- supine and standing diastolic BP ≥10 mm Hg and ≥20 mm Hg, as increments or decrements; and
- supine and standing pulse ≥15 beats per minute (bpm) and ≥30 bpm, as increments or decrements,

where orthostatic BP decrement is the decrease in BP that may occur when a subject changes from the supine to the standing position. Within-day changes in BP will be summarized using descriptive statistics. The within-day change will be calculated using the predose and postdose BP measurements collected at the Day 1 and Week 8 Visits. Frequency counts for vital signs with predefined limits of change specified in Appendix 8 will be summarized by treatment group and time point.

Concomitant Medications will be summarized and listed. The frequency of subjects who took increased L-dopa doses above Baseline levels will be summarized by treatment group. Observed values and changes from Baseline in ECG data and QUIP-RS score will be summarized and listed. Results of the Sleep Attack Questionnaire will be listed and descriptive statistics will be used to summarize the data.

8.8 Treatment Compliance

Treatment compliance will be listed as well as summarized using descriptive statistics.

8.9 Data Monitoring Committee

The safety of subjects in this trial will be monitored by an external Data Monitoring Committee (DMC) on an ongoing basis. The composition, activities, and responsibilities of the DMC are described in the DMC Charter. The DMC convened for this study will also monitor the other active studies in the preladenant program. The DMC will serve an advisory role and make recommendations about the study conduct. Initial plans call for meetings every 6 months; however, meetings may be
held more frequently at the discretion of the DMC. The DMC will review data regarding enrollment and safety, and may include efficacy at the discretion of the DMC. They will also assess safety data coming from the blinded Transaminase and Vascular Events Committees (Section 7.7.2.3.2). Details will be provided in the DMC Charter and the blinded Transaminase and Vascular Events Committees’ standard operating procedures.

9.0 ADHERENCE TO ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

The trial must be conducted in accordance with Good Clinical Practice (GCP) as outlined in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, E6 Good Clinical Practice: Consolidated Guidance and other applicable laws and regulations. In addition, the trial must be conducted in accordance with: (i) the United States of America (USA) Code of Federal Regulations (CFR) if the trial is conducted under a USA Investigational New Drug Application (IND), regardless of the country involved; (ii) the European Union (EU) Clinical Trial Directive (CTD) and local regulations if the trial is conducted in the EU; and (iii) any specific local regulations if the trial is conducted elsewhere.

9.1 Ethical Conduct of the Trial

9.1.1 Independent Ethics Committee or Institutional Review Board

Prior to initiation of the trial at any site, the trial, including the protocol, informed consent, and other trial documents must be approved by an appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC). The IRB/IEC must be constituted according to applicable regulatory requirements. As appropriate, amendments to the protocol must also be approved by the IRBs/IECs before implementation at the sites, unless warranted to eliminate an immediate hazard. The IRB/IEC approval should be obtained in writing, clearly identifying the trial, the documents reviewed (including informed consent), and the date of the review. The trial as described in the protocol (or amendment), informed consent, and other trial documentation may be implemented only after all the necessary approvals have been obtained and the sponsor has confirmed that it is acceptable for the investigator to do so.

In the event that the IRB/IEC requires changes in the protocol, the sponsor shall be advised and must approve the changes prior to implementation. The investigator shall not modify the trial described in the protocol once finalized and after approval by the IRB/IEC without the prior written approval of sponsor.
In countries where the investigator submits the trial protocol and statement of informed consent to the IRB/IEC, the investigator or qualified designee will forward the approvals to the sponsor.

**9.1.2 Subject Information and Consent**

The details of the protocol must be provided in written format and discussed with each potential subject, and written informed consent must be obtained for all subjects before any trial-related procedure is performed. In obtaining informed consent, the information must be provided in language and terms understandable to the subject. The subject, or the subject’s legal representative, must give their written consent to participate in the trial. The signed and dated consent form itself must be retained by the investigator as part of the trial records. A copy of the signed and dated consent form must be given to the subject. The consent form must include all of the required elements of informed consent in accordance with ICH Guidelines E6 and local laws. In addition, the sponsor specifically requests that the consent form identify it as the sponsor and state that use of the investigational product(s) is experimental and the side effects of the investigational product(s) are not completely known. The consent form must be approved by the appropriate IRB/IEC and sponsor before trial initiation at a trial site. Any subsequent changes to the approved informed consent form must be reviewed and approved by the appropriate IRB/IEC and sponsor before implementation.

**9.1.3 Subject Identification Card**

A Subject Identification Card is provided to each subject to carry on his or her person (e.g., in a wallet) at all times while the subject is participating in the trial. The card is to be shown to caregivers in the event of an emergency.

At a minimum, the card must contain the following information:

1. Protocol number;
2. The subject’s protocol identification number;
3. A statement identifying the card-carrier as a participant in a clinical trial (e.g., “This person is participating in a clinical research trial.”);
4. A statement indicating the person might be taking an investigational drug (e.g., “This person is taking an experimental drug which could have interactions with other medications, or placebo”); and
5. Contact information in the event of an emergency or hospitalization. The contact information on the card is to be the investigator or a designated site contact, rather than a contact from within the sponsor;

The cards may also include other trial-specific information to assist with treatment decisions in the event of an emergency, such as types of concomitant therapies that may, or may not be, permitted as part of emergency treatment. As with any other information provided to subjects, the Subject Identification Card must be approved by the IRB/IEC. Monitors will request that Investigators provide Subject Identification Cards to each subject. Investigators will be asked to request that subjects carry the cards with them while they are participating in the trial.

The Investigator/site should collect the cards at the end of the trial and retain them with other clinical trial documents.

9.1.4 Registration of the Trial

The trial will be registered by the sponsor on an appropriate free public web site such as clinicaltrials.gov, which is a service of the United States National Institutes of Health.

9.2 Reporting Trial Data to the Sponsor

9.2.1 Data Collection Forms

The Sponsor will provide the site with data collection forms, be they Case Report Forms (CRF), either in paper format or electronic Case Report Forms (eCRF); diaries; Electronic Data Capture (EDC) screens; or other appropriate data collection forms as the trial requires. The investigator is to provide subject data according to the Sponsor’s instructions, in the designated data collection form, compliant with GCP practices. The Sponsor will also provide the site with instructions for assisting other parties – such as a central laboratory – to collect data. As instructed by the Sponsor, a designated central laboratory may collect data in a database and provide the completed database to sponsor. All data collection forms and the databases from the trial are the exclusive property of sponsor.

The investigator must maintain records and data during the trial in compliance with all applicable legal and regulatory requirements. Each data point must be supported by a source document at the trial site. Any records or documents used as the source of information (called the “subject source data”) are to be retained for review.
by authorized representatives of the sponsor or a regulatory agency. For example, if CRF pages or EDC screens will be used as source documents for specific information, then a copy of the completed CRF pages or EDC screen should be retained by the site.

The investigator will ensure that there are sufficient time, staff, and facilities available for the duration of the trial to conduct and record the trial as described in the protocol and according to all applicable guidances, laws, and regulations.

All data collection forms such as CRFs, diaries; EDC screens; electronic database entries, should be completed as soon as possible after the evaluation has occurred. All dates appearing on the sponsor’s subject data collection forms for laboratory tests, cultures, and other data collected, must be the dates on which the specimens were obtained, or the procedures performed.

### 9.2.2 Preparing Case Report Forms for All Subjects

A CRF must be completed for all subjects who have given informed consent. The Sponsor must not collect subject names, initials, or other personal information that is beyond the scope of the trial from any subject. Subjects are not to be identified by name or initials on the CRF or any trial documents. The only acceptable identification for a subject that may appear on a CRF or trial document is the unique subject identification number. The investigator must maintain contact information for each participant so that all can be quickly contacted by the investigator, if necessary.

All entries into CRFs are the responsibility of the investigator and must be completed by the investigator or a qualified designee. The investigator will attest, in writing, at the beginning of the trial that his/her electronic signature is the legally binding equivalent of a written signature and will acknowledge by entering his/her electronic signature that he/she has verified the accuracy of the recorded data.

### 9.2.3 Preparing Case Report Forms for Subjects Who Fail Screening

Data are to be collected from the time the informed consent form is signed until the subject is determined to have failed screening. A CRF with a minimum of the following information must be completed for subjects who fail screening: (1) demographics, (2) subject status, (3) reason for screen failure, and (4) serious adverse events.
9.3 Publications and Other Rights

9.3.1 Rights to Publish by the Investigator

The investigator has the right to publish or publicly present the results of the trial in accordance with this Section 9.3 of the protocol. In the event that the protocol is a part of a multi-site trial, it is understood that it is the intent of the sponsor and the investigator to initially only publish or present the trial results together with the other sites, unless specific written permission is obtained in advance from the sponsor to publish separate results. The sponsor shall advise as to the implications of timing of any publication in the event clinical trials are still in progress at sites other than the investigator’s site.

The investigator agrees not to publish or publicly present any interim results of the trial without the prior written consent of the sponsor. The investigator further agrees to provide to the sponsor 45 days prior to submission for publication or presentation, review copies of abstracts or manuscripts for publication (including, without limitation, slides and texts of oral or other public presentations and texts of any transmission through any electronic media, eg, any computer access system such as the Internet, World Wide Web, etc) that report any results of the trial. The sponsor shall have the right to review and comment with respect to publications, abstracts, slides, and manuscripts and the right to review and comment on the data analysis and presentation with regard to the following concerns:

1. proprietary information that is protected by the provisions contained in Section 9.3.2;
2. the accuracy of the information contained in the publication; and
3. to ensure that the presentation is fairly balanced and in compliance with FDA regulations.

If the parties disagree concerning the appropriateness of the data analysis and presentation, and/or confidentiality of the sponsor’s confidential information, investigator agrees to meet with the sponsor’s representatives at the clinical trial site or as otherwise agreed, prior to submission for publication, for the purpose of making good faith efforts to discuss and resolve any such issues or disagreement.

9.3.2 Use of Proprietary or Confidential Information in a Publication

No publication or manuscript shall contain any trade secret information of the sponsor or any proprietary or confidential information of the sponsor and shall be
confined to new discoveries and interpretations of scientific fact. If the sponsor believes there is patentable subject matter contained in any publication or manuscript submitted for review, the sponsor shall promptly identify such subject matter to investigator. If sponsor requests and at sponsor’s expense, investigator shall use its best efforts to assist sponsor to file a patent application covering such subject matter with the USA Patent and Trademark Office or through the Patent Cooperation Treaty prior to any publication.

9.3.3 Use of Trial Information in a Publication

Investigator is granted the right subject to the provisions of this protocol to use the results of all work provided by investigator under this protocol, including but not limited to, the results of tests and any raw data and statistical data generated for investigator’s own teaching, research, and publication purposes only. Investigator/Institution agrees, on behalf of itself and its employees, officers, trustees, and agents, not to cause said results to be knowingly used for any commercial purpose whatsoever except as authorized by the sponsor in writing.

9.3.4 Authorship of Publications

Authors of publications must meet the International Committee of Medical Journal Editors (ICMJE) guidelines for authorship and must satisfy the 3 criteria that follow:

1. Authors must make substantial contributions to the conception and design of the trial, acquisition of data, or analysis of data and interpretation of results;
2. Authors must draft the publication or, during draft review, provide contributions (data analysis, interpretation, or other important intellectual content) leading to significant revision of the manuscript with agreement by the other authors;
3. Authors must provide written approval of the final draft version of the publication prior to submission.

All contributors who do not meet the 3 criteria for authorship should be listed in an acknowledgments section within the publication, if allowed by the journal, per the ICMJE guidelines for acknowledgment.
9.4 Trial Documents and Records Retention

During the trial and after termination of the trial – including after early termination of the trial – the investigator must maintain copies of all documents and records relating to the conduct of the trial. This documentation includes, but is not limited to, protocols, CRFs and other data collection forms, advertising for subject participation, adverse event reports, subject source data, correspondence with health authorities and IRBs/IECs, consent forms, investigator’s curricula vitae/biosketch, monitor visit logs, laboratory reference ranges, and laboratory certification or quality control procedures and laboratory director curriculum vitae. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, or as specified below. The sponsor must be consulted if the investigator wishes to assign the files to someone else, remove them to another location, or is unable to retain them for the specified period.

The investigator must retain trial records for the amount of time specified by applicable laws and regulations. At a minimum, trial records must be retained for the amount of time specified by ICH Guidelines, the EU Good Clinical Practices Directive, or applicable laws whichever is longer:

1. The ICH Guidelines specify that records must be retained for a minimum of 2 years after a marketing application for the indication is approved (or not approved) or 2 years after notifying the appropriate regulatory agency that an investigation is discontinued.

2. The European Union (EU) Commission Directive 2003/63/EC which requires that Essential Documents (including Case Report Forms) other than subjects’ medical files, are retained for at least fifteen (15) years after completion or discontinuation of the trial, as defined in the protocol.

All trial documents shall be made available if required by relevant health authorities. The investigator should consult with the sponsor prior to discarding trial and/or subject files.

Sponsor will retain all sponsor-required documentation pertaining to the trial for the lifetime of the investigational product. Archived data may be held on microfiche or electronic record, provided that a back-up exists and that a paper copy can be obtained from it, if required.
10.0 INVESTIGATORS AND TRIAL ADMINISTRATIVE STRUCTURE

10.1 Sponsor

The sponsor of this trial is indicated in Section 1.0, Title Page.

10.2 Investigators

10.2.1 Selecting Investigators

Only investigators qualified by training and experience to perform a clinical investigation with preladenant are selected. The sponsor will contact and select all investigators (ie, the legally responsible party[ies] at each trial site), who, in turn, will select their staff.

10.2.2 Financial Disclosure Requirement

In connection with the clinical trial described in the protocol, the investigator certifies that, if asked, the investigator will read and answer the Certification/Disclosure Form or equivalent document truthfully and to the best of investigator’s ability. Investigator also certifies that, if asked, the investigator will have any other applicable party(ies) (eg, subinvestigators) read and answer the Certification/Disclosure Form as a condition of their participation in the trial.

If the financial interests reported on the Certification/Disclosure Form change during the course of the trial or within 1 year after the last subject has completed the trial as specified in the protocol, the investigator and the other applicable party(ies) are obligated to inform the sponsor of such financial change.

10.2.3 Clinical Study Report Coordinator Investigator

A Clinical Study Report (CSR) will be prepared by the sponsor or its qualified designee to describe the results of the trial. One of the investigators shall be selected by the sponsor to review the CSR and provide approval of the final CSR in writing. The investigator chosen to review and approve the CSR is to be called the CSR Coordinating Investigator. A second investigator shall be selected as the Alternate CSR Coordinating Investigator. The Alternate CSR Coordinating Investigator is to review and approve the CSR should the first CSR Coordinating Investigator be unable to do so. The sponsor is to select the CSR Coordinating
Investigator and Alternate CSR Coordinating Investigator from the investigators using the following criteria:

1. Must be the Principal Investigator at a trial site actively enrolling subjects and participating in the trial;
2. Must be willing and capable of completing the necessary reviews and providing approval of the CSR in writing;

10.3 Central Organizations

Central organizations to be used in this study will be provided on a List of Contacts provided by the sponsor.

11.0 REFERENCES


