CLINICAL TRIAL PROTOCOL

Protocol title:

Multi-centre, randomized, double-blind, placebo-controlled, parallel-group, 9 month, equivalence trial comparing the efficacy and safety and tolerability of GTR (Synthon BV) to Copaxone® (Teva) in subjects with relapsing remitting multiple sclerosis followed by an open-label 15 month GTR treatment part evaluating the long-term GTR treatment effects

Abbreviated title:	GATE
Protocol code:	GTR001
Drug product code:	GTR
Drug substance:	GTR.ace
EudraCT Number:	2011-000888-27
IND number:	110826
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Protocol Date:	May 2013
Authors:	<Information redacted>

1 Protocol synopsis

Title of trial:
Multi-centre, randomized, double-blind, placebo-controlled, parallel-group, 9 month, equivalence trial comparing the efficacy and safety and tolerability of GTR (Synthon BV) to Copaxone® (Teva) in subjects with relapsing remitting multiple sclerosis followed by an open-label 15 month GTR treatment part evaluating the long-term GTR treatment effects.

Number of trial sites:
The trial is planned to be conducted in approximately 175 sites worldwide.

Objectives:
The primary objective of this trial is:

- to demonstrate that the efficacy of Synthon's glatiramer acetate (GTR) is equivalent to Copaxone® (TEVA) in subjects with relapsing remitting multiple sclerosis (RRMS) as measured by the number of gadolinium-enhancing lesions on T1-weighted MRIs during the months 7-9.

The safety objective of the trial is to evaluate safety and tolerability of GTR in comparison to Copaxone® as based on the occurrence of adverse events, including local tolerability.

The other objectives for the double-blind part of this trial are:

- to compare the efficacy of GTR to Copaxone® based on the following MRI parameters:
  - Cumulative combined unique active lesions during months 7-9;
  - Change in T2 lesion number and volume from baseline to month 7;
  - Change in T2 lesion number and volume from baseline to month 9;
  - Change in T1 hypo-intense lesions volume from baseline to month 9;
  - Change in brain volume from baseline to month 9;
- to compare the efficacy of GTR to Copaxone® based on the annualized relapse rate;
- to compare the efficacy of GTR to Copaxone® based on the changes in EDSS;
- to compare the efficacy of GTR to Copaxone® based on the percentage subjects free from disease activity at month 9;
- to compare the percentage of subjects with anti-glatiramer antibodies after GTR and Copaxone® treatment.

The objectives for the open-label part of this trial are:

- to evaluate efficacy, safety and tolerability of long-term (2-years) GTR treatment;
- to evaluate efficacy, safety and tolerability of switching to GTR treatment after previous Copaxone® use.

Trial Design:
This trial consists of two parts:
Part 1 is a multi-country, multi-centre, randomized, double-blind, active and placebo-controlled, equivalence trial comparing the efficacy and safety and tolerability of GTR versus Copaxone® in subjects with RRMS. Eligible subjects will be randomly assigned to receive daily 20 mg GTR (Synthon BV), 20 mg Copaxone® (TEVA) or placebo for a period of 9 months.

In Part 2, the trial continues as an open-label uncontrolled trial to evaluate efficacy and safety of long-term treatment with GTR. Subjects completing the 9-month double-blind period will be treated with open-label 20 mg daily GTR for another 15 months.

Duration of subject treatment and participation and overall trial duration:

For each subject, the double-blind treatment duration is 9 months, followed by an open-label treatment duration of 15 months, leading to an overall treatment period of almost 2 years. For trial purposes, a month will be defined as 4 weeks.

With an anticipated recruitment duration of one year, the overall trial period is planned to last 3 years.

Trial Population:

The trial population in this trial will be subjects with RRMS complying with the following in- and exclusion criteria:

Inclusion criteria

1. Willing and able to sign written Informed Consent;
2. Female and male subjects aged 18-55 years inclusive at the time of Informed Consent signing;
3. Diagnosis of RRMS according to the revised McDonald criteria (2010 Revisions) [1];
4. Screening Expanded Disability Status Scale (EDSS) score of 0.0 up to and including 5.5;
5. Neurologically stable with no evidence of relapse within 30 days prior to baseline assessments;
6. Experienced at least 1 relapse in the year before first screening assessment;
7. At least 1 T1-weighted Gadolinium enhancing (T1-GdE) lesion on routine brain MRI taken within 3 months of starting screening or on screening brain MRI (as confirmed by central imaging laboratory)*;

   * If an eligible subject has no T1-GdE lesion at the first screening MRI, two repeat MRI scans are allowed which are to be taken at least 30 days after the previous MRI. If there is again no T1-GdE lesion on any of these scans, the subject cannot be randomized.
8. Having a routine brain MRI showing maximally 15 T1-GdE lesions if scan is taken without subject receiving immuno-modulatory treatment, or a routine brain MRI showing maximally 5 T1-GdE lesions when taken while on immune-modulatory treatment, or a screening MRI showing maximally 15 T1-GdE lesions;
9. Must decline initiation or continuation of treatment with other available disease-modifying drugs for MS, for whatever reason, after having been informed about their respective benefits and possible adverse events by the investigator

   [*for US only this should read as*: Is not currently on treatment or declines initiation or continuation of treatment with other available disease-modifying drugs for MS, for whatever reason, after having been informed about their respective benefits and possible adverse events by the investigator, since the patient: a) must have refused current established effective treatment, or b) must have not responded to current established effective treatment, or c) must not have access to current established effective treatment for whatever other reason.];
10. Female subjects of childbearing potential must agree to practice appropriate contraceptive methods (according to section 5: list of definitions) as assessed by the investigator.

Exclusion criteria

1. Any life-threatening, medically unstable or otherwise clinically significant condition or findings other than MS, in particular neoplastic disease, seizure disorders, or psychiatric disease (in case of doubt, the responsible Medical Officer will be consulted and a joint documented decision will be made between the investigator and the Medical Officer);
2. Any clinically significant deviation from reference ranges in laboratory tests (in case of doubt, responsible Medical Officer will be consulted and a joint documented decision will be made between investigator and the Medical Officer);
3. Positive laboratory test results for human immunodeficiency virus (HIV), HBsAg or HCV at screening;
4. Any significant deviation from reference ranges for hepatic function as defined by either AST

(SGOT), ALT (SGPT), GGT, or AP elevated 3-fold or higher beyond the upper limit of the reference range or total bilirubin elevated 2-fold or higher beyond the upper limit of the reference range (in case subjects are diagnosed with Gilbert's Syndrome, the Medical Officer needs to be contacted and a joint documented decision will be made between the investigator and the Medical Officer);

5. Positive urine drug screen or history of substance abuse within the year before screening (any use of illicit or prescription drugs or alcohol constituting an abuse pattern in the opinion of the investigator);
6. Having been treated with or having received
   a. at any time:
   - glatiramer acetate, cladribine, rituximab, cyclophosphamide, alemtuzumab, or other immunosuppressive treatments with effects potentially lasting for more than 6 months;
   - total lymphoid irradiation or bone marrow transplantation;

   b. within one year before screening:
   - mitoxantrone, but subject cannot be enrolled when mitoxantrone was taken at a cumulative lifetime dosing above 100 mg/m^2;

   c. within 6 months before screening:
   - fingolimod, immunoglobulins and/or monoclonal antibodies (including natalizumab), leflunomide, or putative MS treatments;
   - chronic oral or injected corticosteroids or injected ACTH (more than 30 consecutive days);

   d. within 3 months before screening:
   - azathioprine, methotrexate;
   - plasma exchange;
   - any other experimental intervention, in particular experimental drugs;

   e. within 1 month before screening:
   - Interferon-β 1a or 1b;
   - short-term oral or injectable corticosteroids for treatment of a relapse;
   - short-term ACTH;
7. Having, in the opinion of the investigator, consecutively failed on efficacy grounds two full and adequate courses of accepted treatment modalities (normally at least one year of treatment for each);
8. Pregnancy or breastfeeding;
9. Known hypersensitivity to gadolinium-containing products, glatiramer acetate or mannitol;
10. Having an estimated glomerular filtration rate (eGFR) < 50 mL/min/1.73m^2;
11. Inability to undergo (repeat) MRI investigations as judged by the investigator, e.g., due to claustrophobia, metal implants or fragments, tattoos or permanent make-up;
12. Any reason why, in the investigator's opinion, the subject should not participate.

Investigational Product(s), Dose, Mode of administration:

Part 1: 9 month, randomized, double-blind treatment part

GTR (Synthon BV, The Netherlands)

GTR is a solution for injection in single-use, 1 mL, pre-filled syringes containing 20 mg/mL glatiramer acetate. GTR is to be administered subcutaneously (SC) at a daily dose of 20 mg for a treatment duration of 9 months.

Copaxone® (TEVA Pharmaceuticals; Country of origin: EU)

Copaxone® is a solution for injection in single-use, 1 mL, pre-filled syringes containing 20 mg/mL glatiramer acetate.

Copaxone® is to be administered SC at a daily dose of 20 mg for a treatment duration of 9 months.

Placebo (Synthon BV, The Netherlands)
Placebo is a solution for injection in single-use, 1 mL, pre-filled syringe. Placebo is to be administered SC and daily for a treatment duration of 9 months.

Part 2: 15 month, open-label treatment part
Upon completion of the 9 month double-blind part, treatment will continue with daily SC administration of 20 mg open-label GTR, supplied in pre-filled syringes for daily SC injection for a duration of 15 months.

After an initial training, subjects can daily self administer the SC injections for the entire trial period.

Trial Assessments and Procedures:
During screening the subjects will undergo physical and neurological examinations, clinical chemistry and haematology testing and brain MRI. The subject should return for the baseline visit (i.e. Day 1) within 30 days of signing of ICF (in the event a routine MRI is used for inclusion), or within 30 days of the screening MRI on which eligibility was based. During the double-blind part, subjects will return to the clinic for assessment visits in months 1, 3, 6, 7, 8 and 9. MRI assessments will be repeated at baseline and months 7, 8, and 9. EDSS, vital signs, adverse events, concomitant medications, clinical chemistry and haematology testing will be assessed as indicated in the detailed assessment scheme for Part 1 (see Table 1).

Upon completion of all scheduled assessments for the 9 months visit, the trial and data collection will continue during the open-label treatment part of the trial. A detailed assessment scheme for Part 2 is provided in Table 2.

Statistical methods
Data sets
The primary analysis set will include all subjects who were randomized and have received at least 1 dose of trial treatment (i.e. the Full Analysis Set (FAS)). For efficacy, subjects will be analyzed according to the treatment groups to which they were randomized. For safety, subjects will be analyzed according to the actual treatment they received, regardless the randomization.

Efficacy analysis
Primary outcome:
The number of enhancing lesions during the months 7-9 will be analyzed using a random effects generalized linear model with negative binomial distribution and logarithmic link function. The independent variables will be treatment group, month, baseline lesion count, screening lesion count and geographical region. GTR will be considered equivalent to Copaxone® when the 95% confidence interval for the ratio of GTR versus Copaxone® on the primary endpoint remains within the interval 0.73 - 1.375.

Assay sensitivity
Assay sensitivity will be evaluated by showing superiority of the active treatments versus placebo, using the linear model described above.

Other outcomes
1. MRI parameters:
   a. Cumulative combined unique active lesions during months 7-9 (new gadolinium-enhanced lesions on T1-weighted, or new lesions on T2-weighted MRI scans, without

double counting);
   b. Change in T2 lesion number and volume from baseline to month 7;
   c. Change in T2 lesion number and volume at month 9 from baseline;
   d. Change in T1-hypointense lesions volume at month 9 from baseline;
   e. Change in brain volume from baseline to month 9.
2. Annualized relapse rate.
3. Changes in EDSS score at month 9 from baseline.
4. Percentage "Free from disease activity" at month 9.
5. Percentage of subjects with anti-glatiramer antibodies formation.

Safety analysis

The outcomes related to safety and tolerability are:

1. Incidence of adverse events, including local tolerability;

An evaluation of adverse events and local tolerability will be performed by descriptive statistics.

Sample Size

GTR (Test) will be considered equivalent to Copaxone® (Reference) when the two-sided 95% confidence interval for the Test/Reference ratio for the primary endpoint is between 73% and 137.5%. For 92% power, approximately 600 subjects should complete the trial: 300 subjects treated with GTR and 300 subjects treated with Copaxone®. In addition, for 98% power of the evaluation of the assay sensitivity, approximately 70 evaluable subjects on placebo are required. The probability (power) to show both assay sensitivity and equivalence is approximately 90%. To compensate for dropouts, approximately 12% extra subjects will need to be randomized. To assure the target number of 70 evaluable subjects in the placebo group is met, the drop-out rate in the placebo group will be monitored through an unblinded, trial-independent statistician. Assuming equal distribution of drop-outs, approximately 750 subjects in total will be randomized.

Interim analysis/DSMB evaluation

No interim analysis will be done. As soon as all subjects have completed the double-blind intervention part of the trial, i.e. as soon as the last subjects has conducted all assessments planned for month 9, the database of this part will be locked, the data will be unblinded and an analysis on the primary endpoint and other efficacy and safety analysis will be performed and described in a report for regulatory submission. A full clinical trial report, including Part 2 (the 15 month open-label GTR treatment part) will be written when all data have been collected and cleaned.

Safety will be monitored on an ongoing basis during the entire trial by an external Data Safety and Monitoring Board (DSMB), of which the composition, roles and responsibilities will be described in a separate charter.

1.1 Trial flow chart (assessments and procedures)

Notes to the assessment scheme (Table 1):

- The reference point for scheduling in-treatment visits both for the double-blind and for the open-label part is the date of the first IMP injection
- A month is defined as 4 weeks (i.e. 28 calendar days).
- Every attempt should be made to keep subjects on visit schedules with an allowed visit window of ±7 days for the assessments in the double-blind 9 month treatment period.
- The screening MRI has to be taken within 30 days of the screening visit (i.e. the date of or after ICF signature on which the first protocol assessment was carried out).
- Every attempt should be made to have all assessments of a certain visit performed on the same day.
- The Day 1 MRI assessment can be done up to two days before the other Day 1 assessments, the other MRI assessments of the double blind part can be done two days before or after the other assessments of that visit, as long as this remains within the overall ±7 day window.
- Month 9 assessments should be considered as the baseline assessment for the open-label part and need to be done within the visit window AND before the subject receives the first open-label IMP injection.

Table 1: Assessment scheme for Part 1 (randomized double-blind treatment with GTR, Copaxone® or placebo)

	Screening Visit 1	(Screening Visit 2-3[1])	Day 1[2]	Month 1	Month 3	Month 6	Month 7	Month 8	Month 9	Discon-tinuation[12]
Visit number	**1**	**2-3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**unscheduled**
Obtain Informed Consent	✓[3]									
Medical history	✓									
In/Exclusion criteria[4]	✓	✓	✓							
Randomization			✓							
Physical examination	✓	Targeted exam only whenever indicated by AE review								✓
Vital signs										
Blood pressure/heart rate/ body temperature	✓		✓	✓	✓	✓			✓	✓
Weight	✓		✓						✓	✓
Height	✓									
Central laboratory										
Drug screen	✓									
Serology: HIV, HBsAg, HCV	✓									
Pregnancy test (urine)[5]	✓		✓	✓	✓	✓	✓	✓	✓	✓
Blood chemistry	✓	✓	✓	✓	✓	✓			✓	✓
Haematology	✓	✓	✓	✓	✓	✓			✓	✓
Urinalysis	✓	✓	✓						✓	✓
Anti-glatiramer antibodies			✓	✓	✓	✓			✓	✓
Biomarker sample			✓						✓	
Neurological examination & EDSS[6]	✓		✓			✓			✓	✓
MRI	✓[7]	✓	✓				✓	✓	✓[16]	✓
Relapse assessment	Whenever subject reports suspicion of relapse									
Previous and concomitant medication	✓	Whenever concomitant medication is used[13]								✓
(S)AEs	✓	Whenever a (serious) adverse event occurs[13]								✓
IMP Dispensing			✓	✓[10]	✓[10]	✓	✓	✓	✓[11]	
First IMP administration[14]			✓						✓	
Subject Dosing Diary			✓[8]	✓	✓	✓	✓	✓	✓[15]	✓[15]
Local Tolerance Diary			✓[9]		✓[9]				✓[9]	
Final status									✓	✓

1 Screening visit 2 and/or 3 are only to be performed if the previous MRI scan does not reveal at least 1 T1-GdE lesion.
2 Day 1 (baseline) assessments are to be done prior to the first injection of trial medication (except for Local Tolerance); subject should return for this visit within 30 days of the (repeat) screening MRI or signing of ICF (in the event a routine MRI is used for inclusion).
3 Before any screening assessment is conducted.
4 After all screening results are available and prior to randomization.
5 Additional pregnancy test whenever pregnancy is suspected in-between the planned visits.
6 Targeted neurological examination and EDSS to be conducted in any case of suspicion of a relapse.
7 Screening MRI is only to be taken when there is no routine brain MRI available showing 1-15 T1-GdE lesions (without concomitant immuno-modulating treatment) or 1-5 lesions while on concomitant immuno-modulating treatment (as confirmed by the central imaging laboratory) within 3 months of signing ICF.
8 Prior to the first IMP dosing in DB part, subjects need to receive appropriate training.
9 First assessment to be performed after the injection under supervision of clinical trial site personnel, following 13 days reporting will be done by subject at home; assessment at month 9 is start of the OL part and to be done after GTR injection
10 Depending on medication kit size (and subject preference), additional monthly dispensing visits are to be scheduled at months 2, 4 and 5. Subjects not using this optional visit will be called by a delegate from the trial site at these time points to remind them on the alternative injection sites and to check on compliance.
11 Handing out of open-label IMP.
12 Assessments performed if a subject discontinues the trial before month 9.
13 During each visit subjects will be queried for use of concomitant medication and occurrence of (S)AEs; additionally subjects are instructed to report any use of concomitant medication or occurrence of (S)AEs in-between visits to the site
14 First IMP injection on day 1 of DB part and OL part is to be supervised by a medically trained person and the subject is to be kept under supervision in the clinic for at least 30 minutes.
15 Final check and return of the dosing diary.
16 Month 9 MRI has to be done prior to first Open-label IMP injection.

Table 2: Assessment scheme for Part 2 (open-label treatment with GTR)

	Month					Discontinuation[6]
	12	15	18	21	24	
Visit number	**11**	**12**	**13**	**14**	**15**	**unscheduled**
Physical Examination	Targeted exam only whenever indicated by AE review				✓	✓
Pregnancy test[1]	✓	✓	✓	✓	✓	✓
Vital signs						
Blood pressure/heart rate/ body temperature	✓		✓		✓	✓
Weight					✓	✓
Central laboratory						
Blood chemistry	✓		✓		✓	✓
Haematology	✓		✓		✓	✓
Urinalysis					✓	✓
Anti-glatiramer antibodies	✓		✓		✓	✓
Biomarker sample					✓	
Neurological Examination & EDSS[2]	✓		✓		✓	✓
MRI	✓		✓		✓	✓
Relapse assessment	Whenever subject reports suspicion of relapse					
IMP Dispensing[3]	✓	✓	✓	✓	✓	
Local Tolerance Diary	✓[4]					
Concomitant medication	Whenever concomitant medication is used[5]					✓
(S)AEs	Whenever a (serious) adverse event occurs[5]					✓
Final status					✓	✓

Note: Every attempt should be made to keep subjects on visit schedules with an allowed visit window of ±14 days for the assessments in the open-label 15 month treatment period. The MRI scan can be taken up to three days before or after the planned visit (which is to be performed within the window of ± 14 days), to allow the results of the eGFR as assessed by the central laboratory to be available (if applicable). A month is defined as 4 weeks.

1 Additional pregnancy test whenever pregnancy is suspected in-between the planned visits.
2 Targeted neurological examination and EDSS to be conducted in any case of suspicion of a relapse.
3 Depending on medication kit size (and subject preference), additional monthly dispensing visits can be scheduled in-between.
4 First assessment to be performed after the injection under supervision of clinical trial site personnel, following 13 days reporting will be done by subject at home.
5 During each visit subjects will be queried for use of concomitant medication and occurrence of (sS)AEs; additionally subjects are instructed to report any use of concomitant medication or occurrence of (S)AEs in-between visits to the site.
6 Assessments performed if a subject discontinues the trial before month 24.

2 Sponsor information and responsibilities

A current version of all contact information for functions involved in the clinical trial conduct and emergency contacts will be maintained in the Trial Master File and Investigator Site File. The protocol will therefore not be amended solely for changes in e.g. responsibilities, contact information details etc. as presented below.

Sponsor: **Synthon BV**
<Personal and confidential information redacted>

Chair Steering Committee:
<Personal and confidential information redacted>

CRO:
<Personal and confidential information of all supporting CROs redacted>

Chair Data Safety and Monitoring Board (DSMB):
<Personal and confidential information redacted>

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List of abbreviations

AE	Adverse Event
ALT	Alanine AminoTransferase
AP	Alkaline phosphatase
AST	Aspartate-Amino-Transferase
BMI	Body Mass Index
CCUAL	Cumulative Combined Unique Active Lesions
CIS	Clinically Isolated Syndrome
eCRF	electronic Case Report Form
CRA	Clinical Research Associate
CRO	Contract Research Organization
DSMB	Data Safety and Monitoring Board
ECG	Electro Cardio Gram
EDSS	Expanded Disability Status Scale
eGFR	Estimated Glomerular Filtration rate
FAS	Full Analysis Set
FS	Functional System
GCP	Good Clinical Practice
Gd	Gadolinium
GdE	Gadolinium Enhancing
GGT	Gamma Glutamyl Transpeptidase
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IRB	Institutional review Board
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal product Dossier
IPIR	Immediate Post-Injection Reaction
IXRS	Interactive voice/web Response System
LDL	Low Density Lipoprotein
LISR	Local Injection Site Reaction(s)
IFN	Interferon
MAA	Marketing Authorisation Application
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NSF	Nephrogenic Systemic Fibrosis
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per-Protocol
PPMS	Primary Progressive Multiple Sclerosis
PRMS	Progressive Relapsing Multiple Sclerosis
RBC	Red Blood cell Count

RRMS	Relapsing Remitting Multiple Sclerosis
SAE	Serious Adverse Event
SAF	Safety (population)
SC	Subcutaneous(ly)
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SPMS	Secondary Progressive Multiple Sclerosis
TMF	Trial Master File
WBC	White Blood cell Count

4 List of definitions

Adverse Event (AE)	Any untoward medical occurrence in a subject 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 unfavourable 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 the medicinal product
Adverse drug reaction (ADR)	An AE that is considered to be probably or possibly related to the IMP
Appropriate contraception	The following methods will be considered as appropriate contraception for this study protocol unless decided differently by investigator discretion: a. double-barrier contraception, or b. any oral contraceptives containing estrogens or progestins, or (MRI compatible) intrauterine devices, or c. monogamous relationship with vasectomised partner, or sexual abstinence
Baseline	Results or values obtained from the most recent assessment prior to the first drug administration (i.e. generally day 1 values, but in case of missing data, values obtained at the most recent screening visit will be used)
Baseline visit	Day 1 visit
Cumulative combined unique active lesions (CCUAL)	The CCUAL is calculated by adding the following lesions from the MRI scans taken at months 7, 8 and 9 (without double-counting): 1. all new T1-GdE lesions when compared to the previous scan, 2. all new T2 lesions (which are not T1-GdE) when compared to the previous scan
Enrolled subject	a subject who has signed IC and received a subject number
Full Analysis Set	Includes all subjects who were randomized and have received at least 1 dose of trial treatment
Free from disease activity	Subjects having no clinical relapse, no new or enlarged T2 lesions at month 9 compared to baseline, no T1-GdE lesions at months 7, 8, 9 on MRI and no 3-month sustained change in EDSS score (defined as ≥ 1.0-point increase from a baseline score of ≥1.0, or a ≥1.5-point increase from a baseline score of 0.0)
Investigational Medicinal Product (IMP)	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorised indication, or when used to gain further information about the authorized form. Under the current protocol, GTR, Copaxone® and placebo are considered IMP
Not of childbearing potential	Lack of childbearing potential will be considered under these circumstances: • post-menopausal for at least two years, or • bilateral oophorectomy, ovariectomy, salpingectomy, or tubal ligation, or • hysterectomy, or • congenital sterility
PP population	Includes all subjects for which at least one of the month 7, 8 or 9 primary outcome assessments is available and who did not have any major protocol violations
Positive drug screen	A drug screen will be assessed as positive when positive for cocaine, amphetamines, methadone, opiates, phencyclidine, barbiturates or benzodiazepines. A positive test result for barbiturates or benzodiazepines, can be overruled by the investigator, when it is clear (and documented in the source and Concomitant medication CRFs) that the barbiturate and benzodiazepine use is not representing drug abuse
Unexpected Adverse Drug Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational medicinal product)
Relapse	The appearance of one or more new neurological symptoms or the reappearance of one or more previously experienced ones. The neurological deterioration has to last at least 24 hours, occur in the absence of fever, and should be starting at least 30 days after the onset of any previous confirmed relapse. Fever is defined as a body temperature measured either axillary, orally, or intrauricular of > 37.5°C or 99.5°F. An event will be counted as a relapse only when the subject's symptoms will be accompanied by

	objective changes in the neurological examination corresponding to an increase of at least 0.5 points on the EDSS, or one grade in the score of two or more Functional Systems (FS), or two grades in one FS. A change in bowel/bladder or cognitive function cannot be solely responsible for the changes in the EDSS or the FS
SAF population	Subjects participating in this trial who received at least one dose of the trial medication
Screening period	Period from the first screening assessment (i.e. signing IC at screening visit 1) up to the randomization
Serious Adverse Event (SAE)	The E2A ICH guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting: E2A, 1994) has specified the following definition for SAEs. This guideline will be adhered to when determining and reporting all SAEs. An SAE is defined as an AE that is/ results in: – Fatal. – Life threatening. – Persistent or significant disability/incapacity. – Admission to hospital as an in-patient or prolongation of hospital stay. – A congenital anomaly – Important Medical Event Note when assigning one of the above 'serious' outcomes the following should be referred to: Life-threatening: Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death. Hospitalization: Admission overnight to an acute care hospital. Procedures done in or visits to a clinic or outpatient facility are not considered serious adverse events. Admission to a rehabilitation facility, transitional care unit, or nursing home is not considered a hospitalization. Prolonged hospitalization: Any adverse event that extends a subject's hospital stay beyond the normal expected time. Disability: A substantial disruption of a person's ability to conduct normal life functions. Congenital anomaly: Intrauterine development of an organ or structure that is abnormal in form, structure, or position. Important medical event: Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

5 Introduction

5.1 Therapeutic background and trial rationale

MS is a chronic, inflammatory autoimmune disease affecting the white matter of the central nervous system which consecutively leads to axonal damage. The protective myelin sheet surrounding the nerves is degraded, leading to improper signal transduction by the nerves. This consecutive neurodegeneration eventually results in accumulating disability. The degree of neurological impairment in MS is scored in trials with the expanded disability status scale (EDSS) [2].

A diagnosis of MS is based upon the occurrence of distinct attacks (relapse, exacerbation) and objective evidence of lesions in separate locations within the myelinated regions of the CNS [1]. The objective evidence can be obtained with MRI, evoked potentials, and cerebrospinal fluid analysis. With MRI scans, both parameters for disease severity such as lesion load (e.g. accumulated number and area or volume of all MS attributed lesions) and also for disease activity (e.g. contrast-enhancing lesions and occurrence of new lesions in serial MRI) can be determined.

Traditionally MS is subdivided into 4 subtypes:
- Relapsing-remitting MS (RRMS): characterized by clearly defined relapses with full recovery or with sequelae and residual deficit upon recovery. There is no disease progression during the periods between disease relapses.
- Secondary progressive MS (SPMS), characterized by a steady progression of clinical neurological damage with or without superimposed relapses and minor remissions and plateaus. People who develop SPMS will have previously experienced a period of RRMS which may have lasted anything from two to forty years or more. Superimposed relapses and remissions tend to tail off over time. The majority of people with the RRMS, but not all, will eventually develop SPMS, but the time taken varies enormously.
- Primary progressive MS (PPMS), characterized by a gradual progression of the disease from its onset with no superimposed relapses and remissions at all. There may be periods of a levelling off of disease activity and there may be good and bad days or weeks.
- Progressive relapsing MS (PRMS), characterized by a steady progression of clinical neurological damage with superimposed relapses and remissions. There is significant recovery immediately following a relapse but between relapses there is a gradual worsening of symptoms.

More recent, clinically isolated syndrome (CIS) was introduced as a fifth subtype. CIS is diagnosed upon the first clinical relapse when the diagnostic procedure indicates that MS is highly suspect but there are still some features missing to enable an official diagnosis of MS.

Treatment of MS distinguishes symptomatic and disease-modifying approaches. Currently, beta-interferons and glatiramer acetate (Copaxone®) are widely available as first-line disease-modifying treatments. In some regions, additional drugs like azathioprine,

cladribine, or fingolimod are also registered as first-line agents. The medicinal product under study here is GTR (glatiramer acetate), a similar version of Copaxone®.

Glatiramer acetate is the acetate salt of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine, and L-lysine. In the EU and the USA it is approved under the trade name Copaxone®. Copaxone® is one of the first-line treatment options for RRMS and CIS which has proven to be safe and efficacious in reducing the number of relapses and number of lesions seen on MRI. Copaxone® is available in 20 mg/mL solution for injection in prefilled syringes by TEVA Pharmaceutical Industries Ltd and requires daily subcutaneous (SC) injection.

The mechanism of action of glatiramer acetate is not fully understood, but is thought to act by modifying immune processes that are considered to be responsible for the pathogenesis of MS by:

- contributing to a shift from pro-inflammatory Th1 cells to regulatory Th2 cells that mitigate the inflammatory response, and by
- diverting the autoimmune response against myelin due to its resemblance of myelin basic protein (MBP).

<Background information redacted>

6 Objective(s)

6.1 Primary objective

The primary objective of this pivotal phase III trial is to demonstrate that the efficacy of Synthon's glatiramer acetate (GTR) is equivalent to Copaxone® in subjects with relapsing remitting multiple sclerosis (RRMS), as measured by the number of gadolinium-enhancing lesions on T1-weighted MRIs during the months 7-9.

The safety objective of the trial is to evaluate safety and tolerability of GTR in comparison to Copaxone® as based on the occurrence of adverse events including local tolerability.

6.2 Other objectives

The other objectives for the double-blind part of this trial are:

- to compare the efficacy of GTR to Copaxone® based on the following MRI parameters:
  - Cumulative combined unique active lesions during months 7-9;
  - Change in T2 lesion number and volume from baseline to month 7;
  - Change in T2 lesion number and volume from baseline to month 9;
  - Change in T1 hypointense lesions volume from baseline to month 9;

- Change in brain volume from baseline to month 9;
- to compare the efficacy of GTR to Copaxone® based on the annualized relapse rate;
- to compare the efficacy of GTR to Copaxone® based on the changes in EDSS score;
- to compare the efficacy of GTR to Copaxone® based on the percentage free from disease activity at month 9;
- to compare the percentage of subjects with anti-glatiramer antibodies after GTR and Copaxone® treatment.

The objectives for the open-label part of this trial are:
- to evaluate efficacy, safety and tolerability of long-term (2-years) GTR treatment;
- to evaluate efficacy, safety and tolerability of switching to GTR treatment after previous Copaxone® use.

7 Trial design

This phase III trial will be designed as a multi-centre, randomized, double-blind, active and placebo-controlled, parallel-group, equivalence trial comparing the efficacy and safety and tolerability of GTR versus Copaxone® in subjects with RRMS. Eligible subjects will be randomly assigned with IXRS to receive daily 20 mg GTR (Synthon BV) (n=336), 20 mg Copaxone® (n=336) or placebo (n=78) for a period of 9 months.
After completing the 9-month double-blind part, all subjects will be treated with open-label 20 mg daily GTR for another 15 months.

8 Trial population

Male and female subjects aged between 18 and 55 years and diagnosed with RRMS will be recruited for this trial. Subjects will be recruited from the investigator's general practice or via referral networks.

8.1 Eligibility criteria

8.1.1 Inclusion criteria

Any subject is eligible for inclusion in this trial if all of the following criteria apply:

1. Willing and able to sign written Informed Consent;
2. Female and male subjects aged 18-55 years inclusive at the time of Informed Consent signing;
3. Diagnosis of RRMS according to the revised McDonald criteria (2010) [1];
4. Screening Expanded Disability Status Scale (EDSS) score of 0.0 up to and including 5.5;

5. Neurologically stable with no evidence of relapse within 30 days prior to baseline assessments;
6. Experienced at least 1 relapse in the year before first screening assessment;
7. At least 1 T1-weighted Gadolinium enhancing (T1-GdE) lesion on routine brain MRI taken within 3 months of starting screening or on screening brain MRI (as confirmed by central imaging laboratory)*;
   * If an eligible subject has no T1-GdE lesion at the first screening MRI, up to two repeat MRI scans are allowed which are to be taken at least 30 days after the previous MRI. If there is again no T1-GdE lesion on any of these scans, the subject cannot be randomized.
8. Having a routine brain MRI showing maximally 15 T1-GdE lesions if scan is taken without subject receiving immuno-modulatory treatment, or a routine brain MRI showing maximally 5 T1-GdE lesions when taken while on immuno-modulatory treatment, or a screening MRI showing maximally 15 T1-GdE lesions;
9. Must decline initiation or continuation of treatment with other available disease-modifying drugs for MS, for whatever reason, after having been informed about their respective benefits and possible adverse events by the investigator [*for US only this should read as*: Is not currently on treatment or declines initiation or continuation of treatment with other available disease-modifying drugs for MS, for whatever reason, after having been informed about their respective benefits and possible adverse events by the investigator, since the patient: a) must have refused current established effective treatment, or b) must have not responded to current established effective treatment, or c) must not have access to current established effective treatment for whatever other reason.];
10. Female subjects of childbearing potential must agree to practice appropriate contraceptive methods (according to section 5: list of definitions) as assessed by the investigator.

8.1.2 Exclusion criteria

Any subject who meets any of the exclusion criteria below must be excluded from participation in the trial:

1. Any life-threatening, medically unstable or otherwise clinically significant condition or findings other than MS, in particular neoplastic disease, seizure disorders, or psychiatric disease (in case of doubt, the responsible Medical Officer will be consulted and a joint documented decision will be made between the investigator and the Medical Officer);
2. Any clinically significant deviation from reference ranges in laboratory tests (in case of doubt, responsible Medical Officer will be consulted and a joint documented decision will be made between investigator and the Medical Officer);
3. Positive laboratory test results for human immunodeficiency virus (HIV), HBsAg or HCV at screening;
4. Any significant deviation from reference ranges for hepatic function as defined by either AST (SGOT), ALT (SGPT), GGT, or AP elevated 3-fold or higher beyond the upper limit of the reference range or total bilirubin elevated 2-fold or higher beyond the upper limit of the reference range (in case subjects are diagnosed with Gilbert's Syndrome, the

Medical Officer needs to be contacted and a joint documented decision will be made between the investigator and the Medical Officer);

5. Positive urine drug screen or history of substance abuse within the year before screening (any use of illicit or prescription drugs or alcohol constituting an abuse pattern in the opinion of the investigator);
6. Having been treated with or having received
   a. at any time:
      - glatiramer acetate, cladribine, rituximab, cyclophosphamide, alemtuzumab, or other immunosuppressive treatments with effects potentially lasting for more than 6 months;
      - total lymphoid irradiation or bone marrow transplantation;
   b. within one year before screening:
      - mitoxantrone, but subject cannot be enrolled when mitoxantrone was taken at a cumulative lifetime dosing above 100 mg/m^2;
   c. within 6 months before screening:
      - fingolimod, immunoglobulins and/or monoclonal antibodies (including natalizumab), leflunomide, or putative MS treatments;
      - chronic oral or injected corticosteroids or injected ACTH (more than 30 consecutive days);
   d. within 3 months before screening:
      - azathioprine, methotrexate;
      - plasma exchange;
      - any other experimental intervention, in particular experimental drugs;
   e. within 1 month before screening:
      - Interferon-β 1a or 1b;
      - short-term oral or injectable corticosteroids for treatment of a relapse;
      - short-term ACTH;
7. Having, in the opinion of the investigator, consecutively failed on efficacy grounds two full and adequate courses of accepted treatment modalities (normally at least one year of treatment for each);
8. Pregnancy or breastfeeding;
9. Known hypersensitivity to gadolinium-containing products, glatiramer acetate or mannitol;
10. Having an estimated glomerular filtration rate (eGFR) < 50 mL/min/1.73m^2;
11. Inability to undergo (repeat) MRI investigations as judged by the investigator, e.g. due to claustrophobia, metal implants or fragments, tattoos or permanent make-up;
12. Any reason why, in the investigator's opinion, the subject should not participate.

9 Treatments

9.1 Treatment regimen and individual administration procedure

After screening and inclusion into the trial, subjects will be randomized to GTR, Copaxone® or Placebo in a 4.3 : 4.3 : 1 ratio. All three treatments are considered IMP for this trial.
Treatment will comprise of daily SC injections of 20 mg glatiramer acetate or placebo (i.e. one pre-filled syringe) for a treatment duration of 9 months. Upon completion of the 9 month double-blind part, treatment will continue with daily SC administration of 20 mg open-label GTR, supplied in pre-filled syringes for daily SC injection for a duration of 15 months. After an initial training in self-injection techniques, the first injection of the double-blind part and of the open-label treatment part is to be given in the trial site. <Injection details redacted>. On treatment Day 1 of the double-blind part and on treatment day 1 of the open-label part, the subjects are to be supervised by a health-care professional during the self-injection and for at least 30 minutes afterwards. Subjects are advised to select different injection sites each day, in order to reduce the chances of any irritation or pain at the site of the injection. Areas for self-injection include the abdomen, arms, hips and thighs. The subjects will be instructed to adhere strictly to the once-daily dosing scheme and not to take any extra injections to catch up for missed injections.

In the event subjects are not returning for the optional IMP dispensing visits at 2, 4 and 5 months of treatment, subjects will be called by a delegate from the trial site in-between subsequent visits to remind subjects on the alternative injection sites and to check on compliance. From the subject's Dosing and Local tolerance diary the compliance will be calculated. Subjects having taken less than 80% or more than 120% of the required number of injections over the full 9-month study period as well as subjects having missed more than 7 subsequent injections will be considered as non-compliant and excluded from the PP analysis. The dosing diaries will only be used during the double-blind treatment part.

9.2 Treatment assignment, randomisation and stratification

After signing Informed Consent, the investigator (or authorized delegate) will enter the eCRF to obtain a subject number. This will be done for all subjects who sign Informed Consent. The eCRF will be provided by an external vendor and detailed instructions will be made available through training sessions and/or in a separate manual, which is to be filed in the TMF and Investigator Site File.

When all screening data are available, including the confirmation by the central MRI laboratory on the number of T1-GdE lesions and the confirmation on the occurrence of a relapse in the previous year (as documented in the subject's chart), the subject can be randomized if the subject matches all inclusion criteria and violates none of the exclusion criteria.

A subject should return for randomization and the baseline visit within 30 days of signing of ICF (in the event a routine MRI is used for inclusion), or within 30 days of the screening MRI on which eligibility was based. The screening MRI has to be taken within 30 days of the screening visit (i.e. the date of or after ICF signature on which the first protocol assessment was carried out).

An extended screening window of maximally 90 days after the screening MRI must be approved in writing by the sponsor, and will only be granted when this is caused by logistical factors beyond the PI's or subject's control or when the subject has a relapse in-between the moment that all in- and exclusion criteria were fulfilled and the baseline assessments. For subjects with an extended screening window, a repeat screening laboratory assessment (blood chemistry, haematology and urinalysis) will be performed and the subject can only be randomized if he/she still complies with all in- and exclusion criteria.
To randomize a subject, the investigator (or authorized delegate) should contact the IXRS (Interactive Voice/Web Response System). The IXRS will be provided by an external vendor and detailed instructions will be made available through training sessions and/or in a separate manual, which is to be filed in the TMF and Investigator Site File. The system will generate one or more medication numbers for the double-blind medication. Randomization should be done on the day of treatment initiation (or the day before if this turns out to improve logistics).

Using a computer-generated randomization list as prepared by the IXRS provider, eligible subjects will be randomly assigned with IXRS in a 4.3 : 4.3 : 1 ratio to receive daily SC injections of 20 mg GTR, 20 mg Copaxone® or matching placebo for a period of 9 months.

The allocation will be stratified for geographical region (<regions redacted>) and number of T1-GdE lesions at screening: 1 T1-GdE lesion versus 2 to 15 T1-GdE lesions.

After completing the 9-month double-blind part, all subjects will be treated with open-label 20 mg daily GTR for another 15 months. At month 9, subjects must return all double-blind medication to the trial site, in order to ensure appropriate drug accountability, and prevent accidental use of double-blind medication in Part 2 of the trial.

The IXRS system will also be used to manage IMP supplies and to unblind a subject in case of an emergency. An IXRS manual provided under separate cover will be available to support to the proper use of the system.

9.2.1 Re-screening

In principle, re-screening is not allowed: a subject who failed one of the in- or exclusion criteria cannot be screened again at a later time point. If a subject has clinically significant deviations in laboratory values as mentioned in exclusion criterion 2 and/or significant

deviations as detailed in exclusion criterion 4, it is not allowed to repeat the laboratory assessment and the subject cannot be randomized.

For subjects without T1-GdE lesions at the screening MRI, but otherwise meeting all other in- and exclusion criteria, a repeat scan can be made at the second screening visit. This repeat scan can only be taken at least 30 days after the previous MRI scan. At this second screening visit, another blood and urine sample are to be taken to confirm that haematology, blood chemistry, and urine parameters are still clinically acceptable. The subject undergoing a repeat screening MRI scan will keep the same subject number as originally assigned to. If this second MRI does not reveal any gadolinium enhancing lesion either, the procedure can be repeated once more. If then again the MRI does not reveal a T1-GdE lesion, the subject cannot be randomized and is considered a screen failure.

9.3 Masking/Blinding

The initial 9 month treatment period of this trial is designed to be double-blind, meaning that neither the participating subjects, nor the trial site personnel or the central MRI laboratory personnel are aware of the treatment any subject is receiving. Accordingly, GTR, Copaxone® and placebo will be identical in appearance and will be packaged identically and will only be identified by means of a medication number. The randomization list that relates medication number to type of treatment is located at a central location and not available to trial personnel (sponsor, investigator, evaluators).

Upon completion of all assessments to be performed at the 9 month visit, subjects will receive open-label GTR for another 15 months.

9.4 Description of Investigational Products

Table 3: Overview of IMP

Test Product: Formulation:	GTR (glatiramer acetate) <IMP information redacted>
Reference Product: Formulation:	Copaxone® (glatiramer acetate) <IMP information redacted>
Reference Product: Formulation:	Placebo GTR <IMP information redacted>

For Part 1, the randomized, double-blind 9 month period, the above medication will be prepared. For Part 2, the 15 month open-label treatment period, all subjects will be treated with GTR, which will be identical to the formulation described above and supplied by Synthon BV.

9.4.1 Packaging

For each subject, trial medication will be packed in cartons containing four trays with 7 pre-filled syringes and in cartons with one tray of 7 pre-filled syringes of GTR, Copaxone® or placebo.
Alcohol prepared swabs to disinfect the injection site and sharps bins to dispose syringes after use are not included and will need to be supplied by the trial site.

9.4.2 Labeling

Individual IMP syringes will have a tear-off booklet attached to an acetate wrap label. The booklet labels will meet (local) regulatory requirements, will be translated to the local language and will generally include the following information:
- Sponsor identification
- Dose and route of administration
- Protocol number
- Packaging number
- Medication number

The medication kits will also contain a booklet label with all required information in the local languages. The subject number and investigator name should be entered on each medication kit whenever this is dispensed to the subject.

For Part 2, the open-label treatment period, the label will include the same information as for the double-blind part, with the exception that it is stated that the active substance is GTR.

9.4.3 Storage

Trial IMP supplies should be stored in a secure, limited access location and kept out of the reach and sight of children. The pre-filled syringes should be kept in the original package in order to protect from light and stored in a refrigerator (2 - 8 °C or 36-46 °F). The supplies should not be frozen and not be used beyond the expiration date.

9.4.4 Dispensing

Dispensing of the trial medication will occur at the time points as indicated in the flow chart. Upon dispensing, the subject number will be recorded on all medication boxes that are dispensed at that visit.

Depending on the location of the site and the expected weather conditions, subjects will be supplied with coolbags and instructions for use, to assure the trial medication remains between 2 - 8 ° C (or 36-46 °F) while the subject is travelling.

In the event a subject prefers to return to the clinic for the optional dispensing visits and will not take home all medication as allocated by the IXRS at that point in time, this needs to be recorded on the drug accountability forms. These dispensed medication kits on which the subject numbers have already been recorded need to be stored according to the provided storage conditions in the clinic. To prevent these medication kits are accidentally dispensed to another trial subject, their storage needs to be clearly distinguishable from the medication that has not yet been allocated.

On the first treatment day of the double-blind and of the open-label treatment part, the self-injection will be supervised by a medically qualified healthcare professional and the subject will remain under supervision for at least 30 minutes after the injection. In addition, during the double-blind phase, subjects will be handed out paper diaries, to record the daily injections on. Details on local tolerance reporting are given in section 12.1.15.

9.4.5 Treatment compliance

Administration of Investigational Product will be documented in the Dosing and Local tolerance diary, which the subjects participating in this trial have to maintain between the visits of each period. These diaries will be checked by the investigator (or delegated person) for completeness at each visit and collected by the investigator (or delegated person) at each visit. If IMP was not administered as per protocol, the date and reason for non-compliance is to be documented. Subjects are to be instructed to return any unused syringes to the trial site at all pre-specified visits.

From the 9 month visit onwards, double-blind medication is no longer to be used by the subject. It must be collected by the trial site personnel before handing out the open-label GTR treatment boxes. During the open-label treatment phase, compliance will be checked by standard questions at each visit, of which the results need to be entered into the eCRF.

9.4.6 Investigational Medicinal Product accountability

All Investigational Medicinal Product will be tracked and accounted for at the investigational site following receipt, dispensing and administration to subject, and ultimately including destruction or return to <CRO name redacted> as directed. In case of missing or damaged medication cartons, this is to be reported to <CRO name redacted> according to the instructions provided in the Investigational Product Handling Manual. The product accountability will be fully documented by the investigational site by filling in the applicable forms provided by the CRO. The investigational site will retain all used and

unused boxes (and outer packaging) until the drug accountability has been checked by the CRA.

9.4.7 Disposition of unused drug

All unused drug must be returned to <CRO name redacted> using the address as specified in the Investigational Product Handling Manual at the end of the trial. Returned drug can be stored and shipped in ambient conditions.

9.4.8 Subject emergency card

At first dispensing of investigational product, subjects will be handed out a Subject Emergency Card (Appendix 5). This card indicates that the subject is participating in a clinical trial and contains the subject/medication number and provides details on the IMP that is being studied in the trial. The subject is to carry the card at all occasions, so that in case of a medical event, the treating medical personnel are aware of the investigational product administration. The card also presents an emergency phone number. At the end of the trial, i.e. upon completion or premature discontinuation, the subject is to return the Subject Emergency Card. The CRA will be responsible for accountability of the Subject Emergency Cards. The Subject Emergency Card will not be used in sites in the US.

9.4.9 Treatment beyond the trial

<Information on treatment beyond the trial redacted>

10 Concomitant medication and non-drug therapies

Concomitant medication should be administered only as medically necessary during the trial. It is allowed to continue with symptomatic medication that is prescribed to a subject prior to the trial, as long as the dose is optimized and stable prior to commencing with the trial. Any concomitant medication (including herbal medication and vitamins) must be recorded in full detail (drug, dose, duration of treatment, reason for concomitant medication) in the eCRF. Note that the use of concomitant medication must relate to the documented medical history, an AE of the subject or be reported as prophylactic treatment.

<u>Treatment for relapses:</u>
Confirmed relapses can be treated with a standard course of corticosteroid therapy on an inpatient or outpatient basis. Steroid treatment should consist of a course of 3 days and up to 1.0 g i.v. methylprednisolone. In the event a different regimen is considered necessary by the investigator for a specific relapse, he/she is to contact the Medical Officer for a joint

documented approval. For treatment of non-confirmed relapses the investigator is to contact the Medical Officer for a joint documented approval. Standard of care procedures will be followed during treatment. Use of any oral tapering of corticosteroids or plasmapheresis is not allowed. If indicated, a standard regimen for proton pump inhibitors (such as omeprazole or esomeprazole) or histamine H2 receptor antagonists (such as ranitidine or famotidine) may additionally be given during the treatment cycle. The use of corticosteroid therapy should be recorded on the Concomitant Medication eCRF form.

Should a subject require corticosteroid treatment for a relapse at the same time an MRI is scheduled to be performed, corticosteroid treatment should only be initiated after the MRI scan is taken. If treatment has been initiated, the MRI is to be postponed until 14 days after the last corticosteroid dose is taken.

The following medication is not allowed in this trial:
– From screening onwards: any medication or treatments as described in the exclusion criterion number 6 except for short-term injectable corticosteroids to treat relapse(s).

The subject will be instructed by the Investigator not to take any additional medication during the trial, unless this has been discussed and approved by the Investigator (except for emergency use). Should it be unclear if a concomitant medication may be used during the trial, the Investigator should consult with the Medical Officer and/or its representatives.

11 Trial procedures and assessments

The Trial Flow Chart in Section 1.1 summarizes the trial procedures to be performed at each visit. For trial purposes, a month will be defined as 4 weeks. Individual trial procedures are described below. For details of assessment and reporting of adverse events, see Section 12 (Safety Monitoring).

Treating neurologists will be appointed who are responsible for the overall medical management and safety monitoring of the subjects. Independent examining neurologists will be appointed who will be responsible for the neurologic examination and EDSS scoring (including during relapse assessments). In order to minimize variability of evaluations, it is preferred that the same individuals perform the same types of evaluations for all subjects at each trial site. Every attempt should be made to keep subjects on visit schedules with an allowed visit window of ±7 days for the assessments in the double-blind 9 month treatment period.

Upon completion of all scheduled assessments for the 9 months visit, additional data will be collected for subjects who continue with the open-label part of the trial. A detailed assessment scheme is provided in **Table 2**. For this part of the trial, visits should occur within ±2 weeks from the specified time point.

11.1 Trial procedures

11.1.1 Obtain Informed Consent

At the screening visit 1, the investigator or authorized delegate will explain the trial to the subject, answer all of his/her questions and obtain the subject's written Informed Consent before performing any trial-related procedure. The ICF will be signed in duplicate and the subject and/or the authorised representative obtain one original of the signed ICF. The second original is filed with the trial documents at the investigational site. If the site intends to submit routinely taken MRIs as screening MRI to avoid additional burden to the subjects, it should be clearly documented in the subject's medical and/or study chart or trial site documentation that this concerns routine MRIs, as this data has been collected prior to obtaining Informed Consent.

If after ICF signing a second (and any subsequent) relapse occurs, the subject is to re-consent for further continuation in the trial. The investigator or authorized delegate will explain the risks and benefits of available alternative MS treatment to the subject, as well as the risks and benefits associated with continuation in the trial. The investigator or authorized delegate will answer all of the subject's questions and obtain the subject's signature on the Informed Consent Form for Re-consenting. A Master Informed Consent Form for Re-consenting after Second Relapse is available in Appendix 3.

11.1.2 Medical history

A medical history will be obtained by the investigator or authorized (medically qualified) delegate. The medical history will include at minimum the date of MS disease onset (i.e. the date of the first clinical event), the date of diagnosis of MS including the McDonald Criteria according to which diagnosis was made (See **Table 4**, adapted from Polman *et al.*, 2011 [1]), number of previous relapses, date(s) of relapses occurring in the 24 months prior to screening, prior MS treatment. Note: MS diagnoses established before the 2010 Mc Donald criteria were issued can retrospectively be confirmed.

Table 4: Categories of the 2010 Mc Donald Criteria for diagnosis of MS in GATE (GTR001)

	Clinical Presentation	Additional Data Needed for MS Diagnosis
1	≥2 attacks[a]; objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack[b]	None[c]
2	≥2 attacks[a]; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: - ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or - await a further clinical attack[a] implicating a different CNS site
3	1 attack[a]; objective clinical evidence of ≥2 lesions	Dissemination in time, demonstrated by: - simultaneous presence of asymptomatic GdE and Gd nonenhancing lesions at any time; or - a new T2 and/or GdE lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or - await a second clinical attack[a]
4	1 attack[a]; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For dissemination in space: - ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or - await a second clinical attack[a] implicating a different CNS site; and For dissemination in time: - simultaneous presence of asymptomatic GdE and Gd nonenhancing lesions at any time; or - a new T2 and/or GdE lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or - await a second clinical attack[a]

[a] An attack (relapse; exacerbation) is defined as patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection. It should be documented by contemporaneous neurological examination, but some historical events with symptoms and evolution characteristic for MS, but for which no objective neurological findings are documented, can provide reasonable evidence of a prior demyelinating event. Reports of paroxysmal symptoms (historical or current) should, however, consist of multiple episodes occurring over not less than 24 hours. Before a definite diagnosis of MS can be made, at least 1 attack must be corroborated by findings on neurological examination, visual evoked potential response in patients reporting prior visual disturbance, or MRI consistent with demyelination in the area of the CNS implicated in the historical report of neurological symptoms.

[b] Clinical diagnosis based on objective clinical findings for 2 attacks is most secure. Reasonable historical evidence for 1 past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristics for a prior inflammatory demyelinating event; at least 1 attack, however, must be supported by objective findings.

[c] No additional tests are required. However, it is desirable that any diagnosis of MS be made with access to imaging based on these Criteria. If imaging or other tests (for instance, cerebrospinal fluid) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS, and alternative diagnoses must be considered. There must be no better explanation for the clinical presentation, and objective evidence must be present to support a diagnosis of MS.

[d] Gadolinium-enhancing lesions are not required; symptomatic lesions are excluded from consideration in subjects with brainstem or spinal cord syndromes.

11.1.3 Inclusion and exclusion criteria

The inclusion and exclusion criteria will be reviewed by qualified trial personnel at the indicated visits to ensure that the subject qualifies for the trial. The review of inclusion and exclusion criteria and confirmation of the subject's eligibility will be noted in subject's source documents and appropriate eCRF screens.

11.1.4 Physical examination

At screening and upon completion of the 24 months assessment a complete physical examination will be performed by the investigator or a medically qualified delegate, which will involve abnormalities of at least head/neck, thorax, abdomen, extremities, skin and lymph nodes. Results of this examination should be carefully documented in the subject's medical and/or study chart. Abnormal findings at screening are to be reported in the medical history.

At later assessments, a targeted physical examination will be performed when indicated by the review of symptoms and AEs reported at each scheduled visit.

If the subject is discontinued prematurely for any reason during the treatment phase, every attempt should be made to perform a final physical examination at the discontinuation visit.

11.1.5 Vital signs, body weight, body height

At the time points indicated in the flowchart, vital signs to be obtained are blood pressure, heart rate and body temperature (axillary, orally, or intrauriculary) at the clinical site. Except for the baseline (Day 1) assessment, which needs to precede IMP injection, vital signs can be obtained independent of the injection timing. Vital signs are to be recorded with the subject in sitting position and using standardized equipment. Height will be recorded only at the Screening visit. Weight will be recorded at screening, Day 1, Months 9 and 24 and in the case of early discontinuation (to the nearest 0.1 kg in indoor clothing, but without shoes). Weight can additionally be measured and recorded at the MRI department/facility using standardized scales to allow proper calculation of the dose of contrast agent.

11.1.6 Laboratory tests: blood chemistry, haematology, urinalysis

At screening, a serum sample will be taken to assess HIV, HBsAg and HCV. In addition, a urine drug screening will be performed locally using dipsticks provided by the central laboratory to assess the subject's eligibility, including: cocaine, amphetamines,

methadone, opiates, phencyclidine, barbiturates, and benzodiazepines. A drug screen will be assessed as positive when positive for cocaine, amphetamines, methadone, opiates, or phencyclidine. If the drug screen tests positive for barbiturates and/or benzodiazepines, exposure to these medicines should be documented in the subjects' medical and/or study chart and concomitant medication eCRF pages and should be assessed by the investigator for their potential of substance abuse, i.e., whether their use would constitute an abuse pattern in the opinion of the investigator. Only when the medication is considered to be taken within the accepted prescription, the subject is considered to pass this exclusion criterion and if also meeting all other in- and exclusion criteria, the subject can be randomized.

At the time points indicated in the flow chart blood samples will be taken and analyzed for the following parameters by the central laboratory:

Haematology:	RBC, Haematocrit, Haemoglobin, full and differential WBC (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils), Platelets.
Routine blood Chemistry:	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), GGT, Calcium, Chloride, Inorganic phosphorus, LDH, Creatinine, eGFR, Potassium, Sodium, Total Bilirubin, Conjugated bilirubin, Total protein, total cholesterol, triglycerides, HDL, LDL.
Urinalysis (dipstick):	Ketones, Glucose, Protein, Blood.

Pregnancy test

To exclude pregnancy, urine of female subjects will be tested using the pregnancy tests as provided by the central laboratory at screening, at every scheduled visit and any time pregnancy is suspected. Women of childbearing potential participating in this clinical trial should be instructed to use adequate contraceptive barriers to prevent them from getting pregnant while using trial drug.

In the event a subject becomes pregnant during the trial, treatment is to be discontinued, and the procedures as documented in Section 12.9 (Reporting of pregnancies) are to be followed.

All blood samples for haematology and routine blood chemistry and urine samples for urinalysis are to be taken according to the detailed instructions in the manual of the central laboratory. Subjects with clinically significant values outside the applicable reference ranges at screening are not to be randomized in the trial (refer to exclusion criteria for further specification).

Apart from the first screening MRI, where the investigator needs to judge (based on the medical records) whether a subject's renal function is adequate to allow safe administration of contrast medium, a recent eGFR value is to be available within three months (i.e. three periods of 28 days, plus the allowed visit window) prior to each MRI scan with contrast agent and only when the eGFR is $\geq$ 50 mL/min/1.73m^2 the MRI scan

can be performed. For subjects with acceptable eGFR values (i.e. eGFR values ≥ 50 mL/min/1.73m^2) obtained at the baseline visit and subsequent visits at months 1, 3, 6, 9 and 12, the eGFR value obtained at month 12 and 18 remains valid until the month 18 and 24 MRI assessments, respectively. For subjects without stable eGFR values throughout the previous period (i.e. any eGFR value < 50 mL/min/1.73m^2), an additional (local) eGFR value needs to be obtained in order to ensure the MRI with contrast agent can safely be taken at months 18 and 24.

All laboratory samples should be collected at approximately the same time of day. The results of the analysis will be made available to each site by the central laboratory. It will be attempted to have results available 24 hours after receipt of the samples. Results will be provided by fax and published electronically on the central laboratory's website.

Extreme values will generate an alert to the investigator. Investigators will be asked to comment on these abnormalities on the laboratory report, including a notation of the clinical (in)significance of each abnormal finding in the subject's source documents. The laboratory reports will be filed with the subject's source documents. As a general rule, abnormal laboratory values as such should not be recorded as AEs; however, diagnoses, signs or symptoms associated with the abnormal laboratory findings should be recorded as AEs. If an abnormal laboratory value is not associated with a specific medical condition but nevertheless considered to be clinically significant, such abnormal value should be recorded as an AE and reported in the eCRF.

11.1.7 Anti-glatiramer antibodies

Blood samples to assess anti-glatiramer antibodies will be taken in all subjects at the time points indicated in the flow chart and handled according to the instructions in the manual of the central laboratory. Samples for the assessment of anti-glatiramer antibodies will be analysed by the Central Immunogenicity Lab using validated assays. For handling, storage and shipment of these samples refer to the central lab manual in the Investigator Site File.

<Antibody assessment details redacted>

11.1.8 Biomarker assessment

<Biomarker assessment details redacted>

11.1.9 Neurological examination & Expanded Disability Status Scale (EDSS) scoring

At screening and at the time points indicated in the flow chart, a complete neurological examination will be performed by a trained examining neurologist, which will involve mental status/cognition, cranial nerves, motor system, sensory system, reflexes and coordination/gait. Results of this examination should be carefully documented in the subject's medical and/or study chart.

The EDSS is an ordinal clinical rating scale ranging from 0 (normal neurologic examination) to 10 (death due to MS) in half-point increments [2]. Based on the standard neurological examination as reported above, the 7 functional systems (plus "other") are rated. These ratings are then used in conjunction with observations and information concerning gait and use of assistive devices to rate the EDSS. Only personnel that is medically qualified and trained to perform the neurological examination and EDSS rating are allowed to enter the EDSS ratings. Qualification and training (through Neurostatus, level A certification) will have to be documented in the TMF and Investigator Site File.

11.1.10 MRI assessment

Brain MRIs will be obtained at screening, baseline, and during selected time points on treatment as indicated in the flow charts according to an MRI protocol provided by the central neuro-imaging centre. No additional MRI scans are to be obtained outside these pre-specified time points.

MRI safety assessments

Each MRI scan performed for the study will be reviewed for safety by a local neuro-radiologist. The investigator (or delegate) will only be notified in case the local neuro-radiologist or the central MRI reader(s) detects unexpected MS-unrelated findings on the MRI scan. In addition, automated flags will be generated for all MRI scans that present with more than 15 T1-GdE lesions and notifications will be send from the central neuro-imaging centre to the investigator (or delegate). Otherwise, the site staff will be blinded regarding the MRI scanning results.

MRI efficacy assessments

A central neuro-imaging centre will serve as the MRI analysis centre. Details on the MRI assessments are provided in a separate manual as prepared by <CRO name redacted>. The manual is to be available in the TMF and Investigator Site File.

Before any centre can screen trial participants they will be required to perform test scans with use of image equipment with minimum field strength of 1.0 Tesla. In order to check imaging protocol compliance, image quality and potentially optimize the acquisition parameters at each imaging site prior to scanning the first study subject, the protocol-specific MRI sequences will need to be run on a non-study subject ("dummy run"). This subject can be any patient requiring a diagnostic MRI scan or any healthy volunteer. The patient or volunteer are not required to have any specific pathology but must be:

- willing and able to sign the MRI dry-run consent form;
- aged 18 years or more;
- without any physiological or physical limitations to undergo an MRI scan as judged by the responsible medical specialist, e.g. not claustrophobic, no metal implants or fragments, no tattoos or permanent make-up, not pregnant, not breastfeeding.

It is the investigator's and/or the local radiologist's responsibility to ensure that these requirements are met before initiating a dummy run.
Subjects undergoing these test scans will have to sign a separate Informed Consent Form (see Appendix 2 for Master Informed Consent Form for MRI test scans) after being instructed carefully by the local MRI staff on the purpose, risks and procedures of the test scan. For appropriate and safe conduct of the test scans, the MRI staff is to follow the procedures and instructions as applicable in their site. If not available, or if deemed to be inadequate as judged by the CRA in consultation with the Medical Monitor, trial specific procedures for obtaining the test scans will be prepared and filed at the MRI site, in the TMF and in the Investigator Site File.

The image quality of each scan (test scans and trial scans) will be reviewed at the MRI analysis centre with predetermined criteria; unsatisfactory images will be rejected and in such cases a repeat scan will be requested. For each subject evaluated under the current protocol, scans will be performed using the same machine and similar operational parameters throughout the trial.

The screening MRI scan is to be taken when the subject is neurologically stable and after the wash-out period for the respective MS treatments as detailed in the exclusion criteria has passed.

If a subject had an MRI performed within 3 months of signing ICF for the trial, on which one or more T1-GdE lesions are present, and this scan is to be used to base eligibility for inclusion criterion 7 and 8 on, this scan must be submitted to <CRO name redacted> for review. Together with the scan information should be provided to <CRO name redacted> (and <CRO name redacted>) to indicate whether or not the subject was

receiving immuno-modulatory therapy at the time the scan was taken, in order to assess whether an upper limit of 5 or 15 lesions should be considered. If the presence of at least one but not more than 5 or 15 T1-GdE lesions is determined by <CRO name redacted> and confirmed by <CRO name redacted> no screening MRI is to be performed for that subject.

If an eligible subject has no T1-GdE lesion at the first screening MRI, subject can be kept in screening and a repeat scan can be made at least 30 days after the first screening MRI. If this scan does not reveal T1-GdE lesions either, this procedure can be repeated once more (if this also still falls within the planned clinical trial recruitment period as communicated by the Sponsor). If none of these three scans reveal any T1-GdE lesions, the subject cannot be randomized and will be considered a screen failure.

In any case, a subject should return for the baseline visit within 30 days of signing of ICF (in the event a routine MRI is used for inclusion), or within 30 days of the screening MRI on which eligibility was based.

MRI scans are to be taken at the time points as indicated in the flow chart. During the double-blind part, the Day 1 MRI scan can be done up to two days before the other Day 1 assessments , the other MRI scans can be obtained two days before or after the other assessments of the respective visit, as long as the MRI scan is taken within the overall window of ± 7 days for the scheduled visit. In the event a scan is missed or reported to be of inadequate quality, a repeat scan should be taken at the earliest opportunity. When this turns out to be within the window of the next planned MRI scan, there is no need to repeat the scan. The planned subsequent scan is to be taken at the time point and within the allowed window of the flow chart. The Month 9 MRI scan should also be considered as the baseline assessment for the open-label part and needs to be done within the visit window and before the subject receives the first open-label IMP injection.

During the open-label part, the MRI scan can be taken up to maximally three days before or after the planned visit (which is to be performed within the window of ± 14 days), in order to allow the results of the eGFR to be available (if applicable).

Identification of T1-weighted T1-GdE lesions will be done by means of a double-blind read of two independent experienced readers. Identification of T2-hyperintense and post contrast T1 hypointense lesions will be done by a trained and certified radiology reviewer according to standard procedures at the reading center. At baseline the number of T1-GdE lesions, the number and volume of T2-hyperintense lesions, and the volume of T1-hypointense lesions will be assessed. On each follow-up scan the number of total and new T1-GdE lesions and new T2-hyperintense lesions will be assessed. T1-hypointense lesion volume and T2 lesion volume will additionally be assessed at the month 9, 12, 18 and 24 assessments, or at the discontinuation assessment. At the 9 and 18 months visits, changes in whole brain volume assessment will be performed.

To preserve subject confidentiality, the full name of the subject must not appear on the images. The scans should contain at least the following identifiers: subject number, study site number, date of investigation and visit. A comment line should specify the name and the volume of the contrast agent delivered. Further details will be provided in the manual.

Contrast agent

The contrast medium gadolinium (Gd) will be administered as an intravenous infusion of 0.1 mmol/kg. Depending on routine local practice, the dose can be calculated based on the weight as determined in the MRI facility/radiology department or as measured as the site. The administration of Gd, including the brand used and the dose given will be documented in the eCRF. To minimize the risk of occurrence of NSF the use of Gd contrast agents with a cyclical molecular structure is recommended (e.g., gadobutrol, gadoteridol, or gadoterate meglumine). Throughout the study different contrast media can be used for the same patient as long as the standard dose is adhered to and brand used is appropriately documented.

Steroid treatment

In the event of a relapse it will be attempted to have the trial-related efficacy MRI scans obtained before steroid therapy is initiated. If this cannot be met, the MRI scan is to be taken 14 days or more after the last steroid dose. Should this occur during the 9 month double-blind treatment period, and the delayed MRI scan then be taken within the window of the next planned MRI scan, this next MRI scan can be omitted, as otherwise two scans would be taken at around the same time.

11.1.11 Relapse assessment

For this protocol, a relapse is defined as the appearance of one or more new neurological symptoms or the reappearance of one or more previously experienced ones. The neurological deterioration has to last at least 24 hours, occur in the absence of fever, and should be starting at least 30 days after the onset of any previous confirmed relapse. Fever is defined as a body temperature measured either axillary, orally, or intrauriculary of > 37.5°C or 99.5°F. An event will be counted as a relapse only when the subject's symptoms will be accompanied by objective changes in the neurological examination corresponding to an increase of at least 0.5 points on the EDSS, or one grade in the score of two or more Functional Systems (FS), or two grades in one FS. A change in bowel/bladder or cognitive function cannot be solely responsible for the changes in the EDSS or the FS.

When symptoms suggestive of a relapse occur it will be assessed at that time if a relapse has occurred. Subjects will be instructed to telephone their local centre immediately if they perceive that they might be experiencing a relapse. A visit should be arranged

within 7 days of notification and a full neurological examination is to be performed by a trained examining neurologist to confirm the relapse.

For the current trial, relapses confirmed by the treating neurologist (after the examining neurologist (or authorized delegate) performed the examination) occurring during treatment will be recorded on the appropriate eCRF "New neurological events" and not be considered as (S)AEs. More specifically, hospitalization due to in-house treatment with steroids to treat the relapse will not be considered as an SAE. Individual neurological symptoms that do not belong to a relapse do need to be reported as separate AEs. Further guidance on reporting of relapses is provided in the Quick reference card – Relapse assessment that is included in Appendix 6.

Only investigator-verified relapses will be considered as valid (including those already verified by other physicians, if appropriately documented in the subject's medical chart). Follow-up visits to monitor the course of the relapse will be arranged at the investigator's discretion.

Only confirmed relapses can be treated with a standard course of corticosteroid therapy on an inpatient or outpatient basis. Steroid treatment should consist of a course of 3 days and up to 1.0 g i.v. methylprednisolone. In the event a different regimen is considered necessary by the investigator for a specific relapse, he/she is to contact the Medical Officer for a joint documented approval. For treatment of non-confirmed relapses the investigator is to contact the Medical Officer for a joint documented approval. Standard of care procedures will be followed during treatment as long as these are recorded on the appropriate eCRF. Use of any oral tapering of corticosteroids or plasmapheresis is not allowed. If indicated, a standard regimen for proton pump inhibitors (such as omeprazole or esomeprazole) or histamine H2 receptor antagonists (such as ranitidine or famotidine) may additionally be given during the treatment cycle. The use of corticosteroid therapy should be recorded on the eCRF form "Steroid Treatment of MS relapses".

If after ICF signing a second (and any subsequent) relapse occurs, the subject is to re-consent for further continuation in the trial. A Master Informed Consent Form for Re-consenting after Second Relapse is available in Appendix 3.

11.1.12 Previous and concomitant medication

At screening, previous medication taken by the subjects is to be reviewed, including the required wash-out period as defined in the in- and exclusion criteria. At minimum, all treatments taken within 30 days before signing Informed Consent is to be recorded. At each visit after screening, any medication taken by the subject is to be recorded.
In addition, as part of the MS history, previously used disease modifying medication, including any experimental (blinded) treatment taken at any time in the past should be reported.

11.1.13 (S)AEs

See Section 12.2 for details on the monitoring and evaluation of (S)AEs and to Sections 12.3 and 12.5 for instructions on reporting to <CRO name redacted>.

11.1.14 Training of self-injection, IMP dispensing and diary review

On the first treatment day, a subject will be trained to self-inject the trial medication (See training materials/instruction leaflet in Appendix 4). <Injection details redacted>. The first injection of the double-blind treatment part and the first injection of the open-label treatment part is to be self-administered in the trial site. The injection will be supervised by a health-care professional and subjects will remain under supervision for at least 30 minutes after injection. <Injection details redacted>.
Subjects will be handed out trial medication boxes, which is to be recorded on the drug accountability forms. The handout (and returning) of medication boxes is specified in Section 9.4. Used syringed can be disposed off in sharps bins, which are to be provided locally.

Adherence to trial medication will be assessed by counting the returned unused syringes, reviewing the subject's Dosing and Local tolerance diary and subject questioning at all visits during the dosing period. The information reported on the Dosing and Local tolerance diary during the double-blind treatment part will be entered into the database to assess whether the subject took trial medication per protocol in the preceding interval. During the open-label treatment phase, compliance will be checked by standard questions at each visit, of which the results need to be entered into the eCRF.

11.1.15 Local tolerance reporting

Local tolerance scoring will be conducted during four periods of 14 injections each, starting at the time points indicated in the flow chart (i.e. Day 1, Month 3, Month 9 [starting with the first injection of the open-label treatment], and Month 12). Results will be reported in the Dosing and Local tolerance diary. Of each period, the first injection will be scored under supervision and guidance of the responsible person of the medical staff at the trial site. The subsequent 13 daily injections are to be scored by the subject at home, without supervision. <Injection details redacted>.
Tolerability of the injection will be assessed by scoring: 1) presence or absence and 2) severity of Local Injection Site Reactions (LISR). Subjects will score the presence or absence of pain, redness, swelling, itching and lump at the injection site at 5 minutes, and at 24 hours (i.e. just prior to the next injection) after injection. In addition, subjects will score the severity of all LISRs over the preceding period at 5 minutes and 24 hours after injection (i.e. intensity of pain, redness, swelling, itching and lump from the moment of injection up to 5 minutes afterwards, and from 5 minutes after injection up to

24 hours after injection) as “None”, ”Mild”, “Moderate” or “Severe”. Note that when “None” is scored, this means that no reaction occurred during the entire preceding interval.

Spontaneously reported local injection site reactions during those days when the subjects are not reporting LISRs on the Dosing and Local tolerance diary, need to be reported as an AE.

11.1.16 Final status

Upon completion of the 9-month double-blind treatment period and all assessments requested for that time point, an inventory on all documentation and medication will be made, to assure that everything is complete before the subject continues with the open-label treatment part of the trial. Only thereafter, open-label medication can be handed out. Upon completion of the 24 month open-label assessments or in case of premature discontinuation of the trial (regardless the reason), the End of Trial eCRF is to be completed and a similar inventory of all documentation and medication will be made to assure everything is complete before the subject leaves the trial. The subject emergency card is to be returned. The subject is to be instructed to report any (serious) adverse events starting within 30 days after last drug intake to the investigator.

12 Safety monitoring

12.1 Safety endpoints

There are no pre-specified safety endpoints in this trial.
A detailed table including all adverse reactions, which were more frequently reported in Copaxone® vs. Placebo treated subjects is provided in the Investigator’s Brochure.

12.2 Adverse event monitoring

Investigators are responsible for monitoring the safety and for providing appropriate medical care in subjects who have entered this trial (i.e. from the signing of ICF onwards). In addition, the investigator remains responsible for following AEs that are serious or that caused the subject to discontinue before completing the trial until resolution or stabilization.
Each subject will be carefully questioned and/or examined by the investigator or a medically qualified delegate (i.e. authorized by the investigator, in a separate form, to record adverse events) to obtain information regarding adverse events (AEs, including serious AEs) at each visit until the last protocol specified visit or contact. All adverse events will be reported and documented as stated below.

12.3 Adverse events documentation

The definition of an AE is defined in Section 4.

An Adverse Event generally includes any condition that has started from the signing of the Informed Consent onward. Events present before signing the Informed Consent will be defined as medical history of the subject participating in the trial. Worsening of conditions that were present before signing of the Informed Consent will also be regarded as an AE.

Under this protocol, relapses as defined in Section 11.1.11 are not to be considered and reported as an AE, but on a separate, specific eCRF "New Neurological Events". Individual neurological symptoms that do not belong to a relapse do need to be reported as separate AEs. Further guidance is provided in Appendix 6.

In addition, LISRs as specified in Section 11.1.15 that are being reported on the Dosing and Local tolerance diary should not be reported additionally as AEs. Only LISRs that are spontaneously reported during those days when the subjects are not reporting LISRs on the Dosing and Local tolerance diary, need to be reported as an AE in the eCRF.

The investigator (or authorized delegate) is responsible for recording all AEs which have occurred during the trial in the subject's medical and/or study charts and in the eCRF, regardless of their relationship to the trial drug. This includes AEs spontaneously reported by the subject, observed by the investigator/delegate or elicited by general non-leading questioning, as well as clinically important deviations of laboratory values from normal ranges. Note that preferably symptoms or diagnoses associated with the abnormal laboratory value are reported as AE (see also section 12.1.6). The Investigator will review this data and determine the severity and causality as per the definitions provided in Sections 12.3.1 and 12.3.2.

Note that by definition AEs include but are not limited to accidents (e.g. motor vehicle accidents), the reasons for changes in concomitant medication (drug and/or dose), medical, nursing and/or pharmacy consultation, admission to hospital and surgical operations.

Planned hospital admissions and/or surgical operations/procedures for an illness or disease that existed before the investigational product was given or the participant was enrolled in a clinical trial are not to be considered AEs. This needs to be documented clearly in the subject's medical records. Note that any prolongation of hospitalization resulting from these planned admissions or procedures and/or non-planned hospitalizations resulting from these planned procedures are to be recorded as SAEs.

Clinical laboratory data collected during the course of the trial, which exceed or drop below the acceptable limits for the participant population and which, based on baseline values, are considered by the investigator to be clinically significant, will be reported as an AE. Note that if clinically significant abnormal laboratory values lead to, or are associated with clinical symptom(s), the diagnosis should be reported as an AE rather than the abnormal laboratory value to allow proper coding.

If a subject's participation is discontinued as a result of an AE, trial site personnel must clearly document the circumstances and data leading to the reason for discontinuation.

12.3.1 Adverse events severity

The following definitions are to be used to assess the severity of an event:

Mild:	Causing no limitation of usual activities; the subject may experience slight discomfort.
Moderate:	Causing some limitation of usual activities, the subject may experience annoying discomfort.
Severe:	Causing inability to carry out usual activities, the subject may experience intolerable discomfort or pain.

12.3.2 Adverse events causality

The investigator (or delegate) will determine the relationship of any AE to the trial drug according to the following definitions:

Unlikely:	a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible:	a clinical event, including laboratory test abnormality, with a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable:	a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this

definition.

12.4 Serious Adverse Events documentation

The definition of an SAE is defined in Section 4.

For the current protocol, hospitalization due to in-house treatment of relapses with steroids will not be considered as an SAE.

All SAEs must additionally be documented according to the SAE completion guidelines as available in the Investigator Site File.
The following information must be provided:
- Detailed subject data (blinded to treatment code);
- Exact documentation of the event;
- Exact description of the temporal sequence to the therapy course (chronological order);
- Documentation of the results of diagnostic and therapeutic measurements;
- Results of rechallenge after re-introducing the drug (if applicable);
- Results of dechallenge after stopping the drug (if applicable);
- Details of the development and outcome including medical judgement;
- As much other supporting data as possible which are important for the judgement concerning the relationship of the SAE to the trial drug, including but not limited to concomitant medication or medication taken to treat the (S)AE;
- Critical examination of the relationship to the trial drug.

All SAEs must be followed until resolved or stabilized. The investigator must obtain and maintain files of all pertinent medical data relating to the event. This includes medical records, information and medical judgments from any party who assists in the treatment and follow-up of the subject.

Any SAE reported after the final visit (either the Month 24 visit, or an unscheduled visit at Discontinuation) but within 30 days of stopping trial medication must also be reported to <CRO name redacted>.

12.5 Reporting of Serious Adverse Events

The occurrence of any SAEs (including death, irrespective of the reason), occurring during the trial or within 30 days after stopping the trial drug (regardless of relationship to trial drug) has to be notified immediately (within 24 hours of the investigator or delegate becoming aware of the event), to the <CRO name redacted>. The notification must include a completed serious adverse event report.

The <CRO name redacted> can be contacted at the following Email address: <CRO contact details redacted>

Other procedural and contact details on SAE reporting to the <CRO name redacted> (including country-specific numbers of toll-free fax lines) will be described in the SAE completion guidelines which will be available in the TMF and Investigator Site File.

The investigator must promptly report clinically significant follow-up information pertaining to the SAE in the form of a follow-up report to the <CRO name redacted>. The investigator is obliged to pursue and provide additional information as requested by <CRO name redacted> medical monitor or its delegate. Follow-up information about a previously reported SAE must be reported within 24 hours of receipt. The final outcome of the SAE has to be reported in the eCRF and to the <CRO name redacted>.

<CRO name redacted> will report all serious and unexpected ADRs to the appropriate Regulatory Agencies, adhering to timelines for reporting outlined as per the (inter)national and local regulatory requirements and ICH GCP Guideline. For this trial the most recent version of the Company Core Safety Information as appended to the IB is to be used to assess the expectedness of an AE for GTR and Copaxone®.

Investigators must also report all SAEs to their IEC/IRB responsible for the trial.

12.6 Adverse events requiring expedited reporting

For this protocol no non-serious adverse events have been identified that require expedited reporting.

12.7 Central safety laboratory data

Routine laboratory tests from baseline and during the double-blind as well as the open-label treatment will be performed by the central safety laboratory <CRO name redacted>. All laboratory values will be reported to the investigator for review. Copies of these signed and dated laboratory reports are to be kept in the subject's medical and/or study chart. Values outside of the reference range and notable values (as detailed in the lab manual which is available in the TMF and Investigator Site File) will generate an alert to the investigator. Investigators will be asked to comment (including a notation of the clinical (in)significance) on these abnormalities on the respective laboratory reports and, if applicable, in the eCRF. If these values are considered to be clinically significant, an AE needs to be reported in the eCRF.

12.8 Central immunogenicity laboratory data

Glatiramer acetate-reactive antibodies were detected in patients' sera during daily chronic treatment with Copaxone® and are expected to be formed similarly after GTR treatment. As there is no evidence to suggest that these glatiramer acetate-reactive antibodies are neutralising or that their formation is likely to affect the clinical efficacy of the compound, these samples will be analyzed in one or two batches (additional batches can be scheduled, should this be deemed necessary to allow a timely database lock) and only reported to the investigator and DSMB upon completion of the trial.

12.9 Reporting of pregnancies

Pregnancy information on clinical trial subjects is collected by the <CRO name redacted>. If a subject would become pregnant during the course of the trial, the investigator or qualified delegate must contact the <CRO name redacted> and <CRO name redacted> Project Leader, within 24 hours of the investigator or qualified delegate first becoming aware of, or is being notified / informed about the pregnancy. If a serious adverse event occurs in conjunction with the pregnancy, then the reporting time frame for an SAE (24 hours) remains applicable. <CRO name redacted> will provide instructions on how to collect pregnancy information. Follow-up information on the outcome of the pregnancy should also be forwarded to <CRO name redacted>.

12.10 Unblinding treatment for a subject

To properly evaluate a specific safety observation and to fulfil regulatory reporting obligations, the DSMB / <CRO name redacted> medical monitor may decide to unblind the treatment of a subject for whom an SAE or other (expedited) event is reported. Unblinding will always be done via the IXRS system.

A procedure to unblind the medication for the investigator is in place in the IXRS in case an emergency situation occurs.
Unblinding of a single subject is strongly discouraged and should occur only if doing so would dictate or alter the course of treatment for the subject. Before breaking the blind, the investigator should try to contact the sponsor to discuss the intended code break. Any unblinding and an explanation of the reason the blind was broken is to be reported in writing by the investigator to <CRO name redacted>, and is also to be documented in the eCRF.

12.11 Data Safety Monitoring Board (DSMB)

Details on the responsibilities, activities and deliverables of the external DSMB are detailed in a separate charter.

13 Additional trial evaluations

<Additional trial evaluations redacted>

14 Criteria for trial and subject completion/discontinuation

14.1 Subject completion

Subjects participating in this trial are considered to have completed the trial if they completed all protocol assessments as planned for the month 24 trial visit.

14.2 Temporary interruption of treatment

Temporary interruption of treatment is allowed at the investigators' discretion. The reason for interrupting the treatment should be documented in the subjects chart or study chart and the appropriate eCRF. The duration of temporary interruption should take the non-compliance criteria as defined in Sections 16.1.3.1 and 16.1.3.2 into consideration.

14.3 Subject discontinuation

Subjects participating in this trial have the right to withdraw from the trial at any time for any reason. A subject must be discontinued from the trial when the subject withdraws Informed Consent. From that moment onwards, no new data can be collected from that subject. Discontinuation is "permanent": once a subject discontinues the trial it is not allowed to enrol the subject again in this trial. To allow follow-up of potential ongoing AEs and to assure that the health status of the patient did not change upon discontinuation of the trial treatment, subjects who withdraw consent will be called by a medical team delegate to inquire on the subject's health status. Any new AEs or resolution of AEs ongoing at the date IMP was discontinued will be documented in the patient's chart and included in the trial report.

A subject is considered to have discontinued the trial if the subject did not complete the protocol assessments up to and including the month 24 visit. This means that patients, who stop treatment, are not considered as trial discontinuers and can continue to attend all protocol visits and assessments.

Discontinued patients are requested to return for a discontinuation visit and perform the assessments as depicted in the flowchart.

The investigator has the right and duty to stop treatment in any case in which emerging effects are of such nature that the benefit-risk ratio is unacceptable to the individual subject. In addition, the investigator is to stop treatment of any subject with unmanageable factors that may interfere significantly with the trial procedure and/or interpretation of the results. As an excessive rate of withdrawals can render the trial not interpretable, unnecessary withdrawal of subjects should be avoided.

Under the current protocol, subject's treatment must be interrupted when a pregnancy is detected and treatment must be discontinued if the pregnancy is maintained.
When a subject stops trial treatment, the investigator will make every effort to contact the subject to ask him/her to complete at least the month 7, 8 and 9 MRI assessments as per the original protocol to prevent loss of data and possible loss in statistical power. After consultation of and approval by the Medical Monitor, subjects can even continue completing further protocol assessments up to month 24, if this is deemed to be in the best interest for the subject and/or trial.

For subjects who stop taking IMP and discontinue the trial prior to month 9, a Discontinuation visit is to be scheduled 1 month after the last IMP dose was administered or one month after the last MRI scan (whichever is latest), to perform a final evaluation to ensure the safety is followed up adequately.
For subjects who stop taking IMP and discontinue the trial beyond month 9 a Discontinuation visit is to be scheduled one month after the last IMP dose was administered.

Once the final status (Study Termination) has been completed for a subject, the subject is considered to have discontinued the trial and no further assessments will be performed, nor will further data will be collected.
At the final evaluation, the reason(s) for withdrawing treatment must be recorded, the date of the last dose of IMP taken, the date of the last assessment/contact, occurrence of (S)AEs.

Upon discontinuation of a subject, one of the following criteria is to be recorded in the eCRF as the main reason:
- (Serious) Adverse Event;
- Subject withdrawal of Informed Consent;
- Non-compliance with trial medication or protocol required evaluations and follow-up visits;
- Pregnancy;
- Lost to follow-up;
- Other, *to be specified in the eCRF*.

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

14.4 Termination of the clinical trial by the sponsor

The clinical trial may be stopped if the extent (incidence or severity) of emerging effects/clinical endpoints is such that the benefit-risk ratio to the trial population as a whole is unacceptable.
In addition, further recruitment may be stopped in the trial or at (a) particular site(s) due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure related problems or the number of discontinuations for administrative reasons is too high.
In such case, all subjects will be requested to return to the clinic for a final follow-up visit, during which all medication will need to be returned and all discontinuation assessments can be conduction. Additional safety monitoring assessments may also be performed, should the reason for termination of the trial dictate such assessments.

15 Trial evaluation

15.1 Primary endpoint

The primary outcome of the trial is the mean number of Gadolinium enhancing lesions during the months 7-9 after start of treatment.

15.2 Safety endpoints

The outcomes related to safety are:
- Incidence and severity of adverse events, including local tolerability.

15.3 Other endpoints:

Other endpoints related to efficacy are:
- MRI parameters:
  - Cumulative combined unique active lesions during months 7, 8 and 9 (new gadolinium-enhanced lesions on T1-weighted, or new lesions on T2-weighted MRI scans, without double counting);
  - Change in T2 lesion number and volume from baseline to month 7;
  - Change in T2 lesion number and volume at month 9 from baseline;
  - Change in T1-hypointense lesions volume at month 9 from baseline;
  - Change in brain volume from baseline at months 9 and 18, respectively;
- Annualized relapse rate;

- EDSS change from baseline at month 9;
- Percentage subjects “Free from disease activity” at month 9.

In addition, the percentage of subjects with anti-glatiramer antibodies will be evaluated.

16 Statistical considerations and data analysis

The trial data will be evaluated and reported in two parts: a clinical trial report will be prepared including data from the double-blind part to assess the primary endpoint and another clinical trial report will be generated that reflects an evaluation of the entire trial, including the open-label treatment part.

For the double-blind part, all data collected up to 9 months will be locked separately. Prior to unblinding, a detailed statistical analysis plan will be completed and approved. This will contain a detailed explanation of the methodology used in the statistical analyses and provide rules and data handling conventions to perform the analyses and how to handle missing data.

16.1 Analysis population

16.1.1 Safety (SAF) population

Subjects participating in this trial who received at least one dose of the trial medication are considered to be included in the safety population. Subjects in this group will be analyzed as treated.

16.1.2 Full Analysis Set (FAS)

The full analysis set will include all subjects who were randomized and have received at least 1 dose of trial treatment. Subjects will be analyzed according to the treatment groups to which they were randomized.

16.1.3 Per-Protocol (PP) population

Only subjects participating in this trial for which at least one of the month 7, 8 or 9 primary outcome assessments is available and who did not have any major protocol violations are considered to be included in the Per Protocol Population.

16.1.3.1 Major protocol violations

This section lists examples for conditions currently considered as major protocol deviations. Major protocol violators will be excluded from the PP analysis.

- A complete list will be compiled before unblinding of the study and laid down in the "Protocol deviation list": <protocol violation details redacted>

16.1.3.2 Minor protocol violations

This section lists examples for conditions currently considered as minor protocol deviations. A complete list will be compiled before unblinding of the study and laid down in the "Protocol deviation list": < protocol violation details redacted>
When an individual MRI scan was possibly affected, the results of that MRI will not be used in the Per Protocol analysis. In case of non-compliance, unblinding or wrong medication, the results of all MRI assessments after the occurrence of such event will be excluded from the Per Protocol analysis.

16.2 General considerations for data analysis

All data will be listed in individual subject listings. A statistical analysis plan will be prepared prior to database lock and unblinding.

Continuous data will be summarised by their mean, standard deviation, median, minimum and maximum. Categorical and ordinal data will be summarised in frequency tables by their absolute frequency (N) and relative frequency (%).
All descriptive tabulations will be made by treatment arm and visit, where appropriate.

16.2.1 Discontinuation

All subjects participating in this trial who discontinue the trial prematurely will remain included in the FAS and SAF analyses. Premature discontinuations will be tabulated by treatment group and reason for discontinuation.

16.3 Demographic and baseline characteristics

Relevant data of important screening characteristics will be summarized by treatment group to assess treatment group comparability for the FAS (and PP group, if applicable*)*.
The following important screening characteristics will be tabulated:

- Age;
- Sex;

- Body Weight;
- Body Height;
- Body Mass index (BMI);
- Race;
- Time since diagnosis of RRMS;
- Number of relapses in the previous 12 months;
- Previous MS (disease modifying) treatment;
- EDSS score;
- Number of T1-weighted Gadolinium enhancing (T1-GdE) lesions;
- Region (<region redacted>).

16.4 Efficacy analysis

All efficacy analyses will be carried out on the Full Analysis Set. Additional analyses will be carried out on the Per Protocol group.

16.4.1 Primary analysis

The number of T1-GdE lesions during the months 7-9 will be analyzed using a random effects generalized linear model with negative binomial distribution and logarithmic link function. The fixed variables will be treatment group, month, geographical region, the logarithm of the screening lesion count, and the logarithm of the baseline lesion count. When the T1-GdE lesion count is 0, log(0.5) will be used.

In detail, when the mean number of enhancing lesions in the months 7, 8 and 9 in the GTR and Copaxone® groups is $m_{7,G}$, $m_{8,G}$, $m_{9,G}$, $m_{7,C}$, $m_{8,C}$ and $m_{9,C}$, respectively, the ratio exp(mean(log($m_{7,G}$), log($m_{8,G}$), log($m_{9,G}$)) – mean(log($m_{7,C}$), log($m_{8,C}$), log($m_{9,C}$))) will be estimated. The ratio will be converted to a relative difference (percentage difference) by subtracting 1.
The 95% confidence interval for the relative difference between GTR and Copaxone® will be calculated.

GTR will be found to be equivalent to Copaxone® when the 95% confidence interval for the ratio of GTR versus Copaxone® on the primary endpoint is between 0.73 and 1.375.

Rationale on equivalence margins
From the historical Copaxone® trial [8], it can be derived that the number of T1-GdE lesions during months 7-9 was found to be 1.75 times higher after placebo treatment as compared with Copaxone®. So the ratio for the treatment effect of placebo versus Copaxone® is calculated to be 1.75. Given the fact that higher dosages of Copaxone® have not shown increased efficacy, concern is mainly with a possible lower efficacy of GTR vs Copaxone®.

Therefore, the selected equivalence margins are primarily based on the maximum allowed decrease in efficacy for GTR and the upper limit of the equivalence margin was set at half of 1.75, i.e. 1.375. Based on the information of the historical Copaxone® trial, the upper limit of 1.375 for the confidence interval corresponds to a difference of approximately 10% between (the point estimates of) the numbers of lesions in the treatment groups.<details on equivalence margins redacted>

Assay sensitivity

Assay sensitivity will be evaluated by showing superiority of the active treatments versus placebo. The random effect model described above will be used to estimate the ratio $\exp\{\{\text{mean}[\log(m_{7,G}), \log(m_{8,G}), \log(m_{9,G})] + \text{mean}[\log(m_{7,C}), \log(m_{8,C}), \log(m_{9,C})]\}/2 - \text{mean}[\log(m_{7,P}), \log(m_{8,P}), \log(m_{9,P})]\}$. The relative difference between the active treatments and placebo and its 95% confidence interval will be calculated.

16.5 Handling of missing data

When an endpoint is missing, the subject will be excluded from the analysis of that endpoint. Hence, when a subject misses all month 7 to month 9 assessments for an MRI endpoint, the subject will not be included in the analysis of that endpoint. When a subject has at least one of the months 7 to 9 lesion counts, he or she will be included in the repeated measures analysis and is therefore part of the primary endpoint evaluation When this is the case for the primary outcome for more than 10% of the subjects in a certain treatment group, an additional sensitivity analysis will be carried out.

16.6 Sample size considerations

The power calculation assumed a lognormal distribution of the count data. It estimated the sample size that is required to compare the lesion count during the months 7 to 9, taking into account the adjustment for baseline lesion counts (analysis of covariance model).
According to the results of Comi *et al*. [8] and Tubridi *et al*. [9], the standard deviation of the endpoint $(\log(m_{7,G})+\log(m_{8,G})+\log(m_{9,G}))/3$ and $(\log(m_{7,C})+\log(m_{8,C})+\log(m_{9,C}))/3$ will be approximately 1.1, multiple correlation between the endpoint and the logarithms of the screening and baseline counts is expected to be 0.3. Simulations then showed that a study with 300 evaluable subjects in the GTR and in the Copaxone® arms will have approximately 92% power to show equivalence. A placebo group of 70 evaluable subjects will lead to approximately 98% power to show assay sensitivity. The probability (power) of showing both assay sensitivity and equivalence will be approximately 90%.

To compensate for dropouts, approximately 12% extra subjects will need to be randomized. To assure the target number of 70 evaluable subjects in the placebo group is

met, the drop-out rate in the placebo group will be monitored through an unblinded, trial-independent statistician (e.g. the DSMB statistician). Assuming equal distribution of drop-outs, approximately 750 subjects in total will be randomized.

16.7 Safety analysis

Safety analysis will be based on the SAF population. Only adverse events reported to start within the in-treatment will be considered in the analysis. The in-treatment period is defined as the period starting from the first injection of IMP onwards up to and including the last assessment. Events starting before first dosing will be presented separately.

16.7.1 Analysis of pre-specified safety endpoints

For this protocol, no pre-specified safety endpoints have been defined.

16.7.2 Analysis of commonly occurring safety events – double-blind part

The commonly occurring safety events include the AE preferred terms that are observed to be "common". For this trial, an AE is considered to be "common" if it occurs in more than 1% of the subjects during the double-blind part of the trial. Incidence rates will be provided for the commonly occurring safety events. These AEs are also part of the general AE analysis as described in Section 16.7.3.

16.7.3 Analysis of descriptive safety endpoints – double-blind part

Summary statistics and/or incidence rates will be provided for the descriptive safety endpoints.

16.7.3.1 Analysis of adverse events – double-blind part

All AEs will be summarized using the latest medical dictionary for regulatory activities (MedDRA) within 60 days of official release. An overview table of the number (percentage) of subjects with any AE, deaths, SAEs, AEs of known severe intensity and drug related AEs will be presented by treatment group.

The number (percentage) of subjects with at least one (S)AE will be summarized by MedDRA system-organ class and preferred term by treatment group. The same table will be presented by treatment group and relationship to study drug according to the investigator and by treatment group and intensity of the AE.

All deaths and other SAEs will be listed by treatment group and center. The number (percentage) of subjects with at least one SAE occurring during the in-trial period will be summarized by MedDRA system-organ class and preferred term by treatment group and relationship to study drug.

16.7.3.2 Analysis of local tolerance – double-blind part

For each local tolerance assessment period, the LISR score (i.e. the number of local tolerance parameters scored as "present") by time point will be calculated. Summary statistics and/or frequency tables will be prepared by treatment group.

16.7.3.3 Analysis of safety data from open-label treatment part

The safety of the open-label part of the trial will be evaluated using the following three treatment groups:

Subjects treated with GTR only;
Subjects treated with Copaxone® and switched to GTR;
Subjects treated with placebo and switched to GTR.

For the 15 month open-label part, safety data will be summarized similarly as described for the double-blind part of the trial. In addition, safety data for the entire 2 year period will be summarized for the GTR only group.

17 Analysis of additional trial evaluations

17.1 Analysis of antibody formation – double-blind part

The percentage of subjects with anti-glatiramer antibodies will be presented by treatment group.

17.2 Analysis of predictive value of biomarkers

<biomarker analysis redacted>

18 Trial administration

18.1 Regulatory and ethics committee considerations

The sponsor, the sponsor's representatives and the investigator as well as all other involved parties will ensure that the trial is conducted in compliance with the protocol, the ethical principles that have their [1]origin in the Declaration of Helsinki, ICH Harmonised Tripartite Guideline for Good Clinical Practice E6 (R1), (CPMP/ICH/135/95) and applicable regulatory requirements including the following:

- European Commission Directive 2001/20/EC 4 April 2001;
- European Commission Directive 2005/28/EC 8 April 2005;
- European Data Protection Directive 95/46/EC;
- US Food and Drug Administration (FDA)Regulations: Code of Federal Regulations CFR 21, - Good Clinical Practice Parts 11, 50, 54, 56 and 312;
- Other applicable local regulations.

18.1.1 Approval by competent regulatory authority

The Sponsor or the Sponsor's representatives will obtain regulatory approval from the competent authority prior to trial start. The Sponsor or the Sponsor's representatives will provide all necessary documents to obtain such approval.

If any of the documents relevant to obtain approval is amended, the sponsor or the sponsor's representatives will submit these documents for review and subsequent approval to the competent authority.

An annual safety/progress report will be provided by <CRO name redacted> to the competent regulatory authorities as required.

18.1.2 Review and approval by competent IRB or IEC

The Sponsor or the Sponsor's representatives will obtain ethical approval from the competent Independent Ethic Committee(s) (IEC) / Institutional Review Board(s) (IRB) prior to trial start. The Sponsor or the Sponsor's representatives will provide all necessary documents to obtain such approval.

If any of the documents relevant to obtain approval is amended, the Sponsor or the Sponsor's representatives will submit these documents for review and subsequent approval to the competent IEC(s) / IRB(s).

An annual safety/progress report will be provided by <CRO name redacted> to the competent IEC(s)/IRB(s) as required.

18.1.3 Informed Consent

Informed Consent will be obtained from the potential subject prior to any trial-related activities and in accordance with local laws and all applicable regulatory requirements.

The investigator and/or his/her delegate will inform the subject in addition to the written subject information about all aspects of the subject's trial participation. The delegate can be a trial nurse (to explain procedural information on the trial is provided) but all medical information must be provided by a medical doctor. When a trial nurse provides non-medical information on the trial, both the investigator and the trial nurse are required to sign the Informed Consent Form (ICF). For sites where the IEC/IRB approves that only the trial nurse signs the ICF, a separate note must be added to the patients' chart to document that adequate medical information was provided to the patient.
The written subject information and Informed Consent Form must be approved by the competent IEC/IRB and competent regulatory authority. Any amendments to these documents must be approved by the competent IEC/IRB and competent regulatory authority.

The investigator and/or his/her delegate and the subject must sign and personally date the ICF prior to any trial related activities are being performed. The subject or the authorised representative must complete the printed name and personally enter the date of signature. If an authorised representative signs the ICF, all efforts should be made to obtain an additional signature, personally dated, from the subject himself/herself.

The ICF will be signed in duplicate and the subject and/or the authorised representative obtain one original of the signed ICF. The second original is filed with the trial documents at in the Investigator Site File and/or with the patient's medical chart.

The decision to participate in the trial is entirely voluntary by the subject and/or by the authorised representative. The investigator and/or his/her delegate must emphasise to the subject and/or the authorised representative that the consent to participate can be withdrawn at any time without penalty or loss of benefits to which the subject is otherwise entitled.

18.1.4 Investigator reporting requirements

The Investigator is responsible for accuracy and completeness of all data recorded in subject's medical and/or study charts and eCRFs. All data recorded in the eCRF are derived from source data unless specifically exempted. Source data will be defined prior to trial start but consists in general of the information documented in the subject medical

and/or study chart or from information documented in original records and/or certified copies. Corrections to data should be made in a way so that the originally recorded data is still legible and traceable. Any changes should be dated, initialled and explained (if necessary) by the investigator or an authorized member of the investigator's trial staff making the correction. The Investigator will maintain a file of essential documents of the trial as defined by the regulatory requirements, ICH GCP and the sponsor (Investigator Site File).

18.1.5 Amendments to trial protocol

Amendments to the trial protocol are performed when needed and according to Standard Operating Procedures of the sponsor and/or the sponsor's representative. Except for administrative amendments, all amendments will be reviewed and approved by the competent authority and competent IEC/IRB prior to implementation.

In the event of an emergency, the investigator may institute any medical procedures deemed appropriate without prior approval by the competent authority and competent IEC/IRB. However, all such procedures must be promptly reported to the sponsor and the IEC/IRB.

18.1.6 Investigator compensation

Financial compensation of the investigator and/or his/her institution will be regulated in a financial agreement established between the sponsor or the sponsor's representative and the investigator and/or his/her institution.

18.2 Monitoring and quality assurance

18.2.1 Monitoring

In accordance with applicable regulations, ICH GCP Guideline and <CRO name redacted> procedures, monitors from <CRO name redacted> and/or Synthon BV will perform the monitoring of this trial. Investigational sites will be contacted and visited regularly by <CRO name redacted> and/or Synthon BV staff.

The investigational sites will be trained on all trial procedures at an Investigator meeting and during site initiation visit performed by <CRO name redacted> and/or Synthon staff.

During the trial, the sites will be visited by <CRO name redacted> and/or Synthon BV staff to review the progress of the trial, review the data collected, conduct source data verification, perform drug accountability, identify issues and address their resolution. The aim of the monitoring of the trial is to ensure that the data collected is authentic, accurate and complete, to ensure the safety of the subjects participating in this trial and

that the subject's rights are protected, and to ensure that the trial is performed according to the approved protocol, (inter)national and local laws and all applicable regulations and guidelines.
At trial end, the investigational sites will be closed at a final visit conducted by <CRO name redacted> and/or Synthon BV staff to ensure availability of all necessary trial documentation, return and/or destruction surplus trial material including Investigational Product, and the adequate archiving of all trial-related documentation and materials.
During the whole monitoring process, the investigator agrees to allocate his/her time and the time of his/her staff to the monitor to resolve, discuss and address any trial issues.

18.2.2 Direct access to source data/documents

The investigator agrees to allow the authorised staff from <CRO name redacted> and Synthon BV, the auditor(s), the IRB/IEC and the regulatory authorities direct access to all relevant documents and source data. Source data, recorded in original records or certified copies, will include the subject's medical and/or study charts which are maintained according to standard clinical practice, read-outs and photos, scans, laboratory reports and X-rays. The nature of source data and requirement for its maintenance will be described in a separate Source Data Location List with the investigator.

18.2.3 Quality assurance

To ensure compliance with trial protocol, ICH GCP, and applicable regulatory requirements, the sponsor or the sponsor's representative will conduct a Quality Assurance audit. Regulatory agencies may also conduct inspections of investigational sites. Such audits and/or inspections can occur at any time during or after the trial. If such an inspection or audit occurs, the Investigator and the institution agree to allow the auditor or inspector direct access to source data and all relevant documents and to allocate his/her time and the time of his/her staff to the auditor or inspector to discuss findings and any relevant issues.

18.3 Data handling and records retention

18.3.1 Collection of data, Data management

All data collected for this trial is to be recorded in the subject medical and/or study charts according to standard practice at the investigational site and according to additional requirements of the trial. The relevant data will be transcribed from the subject's medical and/or study chart into the electronic Case Report Form (eCRF). All

data that is collected in the eCRF, including the eCRF itself, will be anonymous and will not reveal the subject's name. All documents will be identified by the subject number.

The eCRFs must be kept in order and up-to-date so that they always reflect the latest observations on the subjects enrolled in the trial. ECRFs must be completed for each participant enrolled in the trial and signed-off by the investigator (or authorized delegate). This should be done as soon as possible after completion of therapy. A monitor will review the completed eCRF.

For subjects who fail screening and cannot be randomized, data are to be collected from the time the Informed Consent is signed until it is determined that the subject has failed the screening. An eCRF with minimum information is to be completed, including demographics, subjects' MS history, reason for screen failure and serious adverse events.

Upon completion of the trial, each site will receive an electronic data storage device containing all eCRFs data (including audit trial data) of all subjects screened and/or treated in that site.

Each subject's medical and/or study chart should have attached to it the original signed Informed Consent. When the trial treatment is completed, the signed Informed Consent should be kept with the archived eCRF, or a note made indicating where the Informed Consent Form is located. All source data should be kept in conformance to applicable national laws and regulations.

All original laboratory reports should be available for review in each subject's medical and/or study chart. It is important that the original reports are available for review by the investigator on the evaluation of abnormalities for clinical significance.

Data management will be performed by <CRO name redacted> in accordance with a documented data validation and data management plan.

18.3.2 Records retention

Following closure of the trial, the investigator agrees to maintain all site trial records in a safe and secure location. The sponsor will inform the investigator about the time period for retaining the documents. The minimum retention time will meet the strictest standards available to that site for the trial as given by local laws or sponsor's standard procedures. By default and if not otherwise clarified, the retention period will be at least 2 years after the last approval of marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

<CRO name redacted> and Synthon BV will be notified if the trial records are moved to an offsite archive location.

18.3.3 Information of investigators about trial results

After the clinical trial report is completed, the sponsor will provide the report of the trial to the investigator.

Information about the identity of the IMP received by the subject will be provided to the investigator upon request, and details must be entered into the subject's charts.

18.4 Publication policy and inventions

18.4.1 Publication

Synthon BV assures that the key design elements of this protocol will be posted in a publicly accessible database (www.clinicaltrials.gov). In addition, upon study completion and finalisation of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

The data resulting from this trial will be proprietary information of Synthon BV.

Synthon BV plans to publish the results from this trial in one or more manuscripts in an international journal under a group authorship, lead by the Study Steering Committee. Individual manuscripts of partial /site specific data will only be approved after the overall manuscript has been accepted for publication.

None of the data resulting from this trial will be allowed to be presented or published in any form, by the investigator or any other person, without the prior approval of Synthon BV. The investigator agrees to provide to the sponsor 60 days prior to intended 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) 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:
- Proprietary information that is protected by the provisions contained in Section 18.4.3;
- The accuracy of the information contained in the publication; and
- To ensure that the presentation is fairly balanced and in compliance with FDA or other regulatory agencies regulations.

In case of disagreement, efforts will be undertaken to organize a meeting to discuss and resolve any such issues or disagreement, but the ultimate decision remains with the Sponsor.

Authorship of planned manuscripts for submission to biomedical journals shall be determined in accordance with the International Committee of Medical Journal Editors (ICMJE) Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

18.4.2 Confidentiality

A Confidentiality Agreement will be executed between <CRO name redacted> and an investigational site representative to regulate the confidentiality of all information and data provided to and/or generated by the investigational site.

18.4.3 Ownership and copyright

All information provided by Synthon BV and/or <CRO name redacted> and all data and information generated by the sites as part of the trial (other than subject charts) are the sole property of Synthon BV.

All rights, title, and interest in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by the clinical site staff during the course of or as a result of the trial are the sole property of the sponsor.

If the financial agreement for conduct of the trial does include an ownership provision inconsistent with this statement, that agreement's ownership provision shall prevail.

19 References

<redacted references removed>

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2 Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983; 33: 1444-1452.

8 Comi G, Filippi M, and Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging--measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group. Ann. Neurol. 2001; 49: 290-297.

9 Tubridy N, Ader HJ, Barkhof F, Thompson AJ, and Miller DH. Exploratory treatment trials in multiple sclerosis using MRI: sample size calculations for relapsing-remitting and secondary progressive subgroups using placebo controlled parallel groups. J. Neurol. Neurosurg. Psychiatry 1998; 64: 50-55.

APPENDICES

<Appendices redacted>