Protocol Title:

A Phase 2/3, Multi-center, Randomized, Double-blind, Placebo-controlled (Part A) and Double-blind, Double-dummy, Active-controlled (Part B), Parallel Group Study to Evaluate the Efficacy and Safety of RPC1063 Administered Orally to Relapsing Multiple Sclerosis Patients

NCT Number: NCT02047734

Original Protocol Date: 04 October 2014

DISCLOSURE

REDACTED PROTOCOL VERSION 4.0

RPC01-201

A PHASE 2/3, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED (PART A) AND DOUBLE-BLIND, DOUBLE-DUMMY, ACTIVE-CONTROLLED (PART B), PARALLEL GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF RPC1063 ADMINISTERED ORALLY TO RELAPSING MULTIPLE SCLEROSIS PATIENTS

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A PHASE 2/3, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED (PART A) AND DOUBLE-BLIND, DOUBLE-DUMMY, ACTIVE-CONTROLLED (PART B), PARALLEL GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF RPC1063 ADMINISTERED ORALLY TO RELAPSING MULTIPLE SCLEROSIS PATIENTS

Test Drug: RPC1063

Protocol Number: RPC01-201

Study Phase: Phase 2/3

IND/EudraCT number: 109,159/2012-002714-40

Date and Version: 01 October 2014 (Final Version 4.0)

Sponsor: Receptos, Inc.

USA
Tel:
Fax:

Sponsor Medical Monitor:

Office:
Cell:

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) as set forth in the International Conference on Harmonization (ICH) guidelines on GCP (ICH E6), and applicable local regulatory requirements.

CONFIDENTIAL

1. SIGNATURES

Protocol RPC01-201, Version 4.0, was approved by:

Print Name Title

Signature Date

Print Name Title

Date

Investigator

I have read and agree to the protocol RPC01-201, entitled 'A Phase 2/3, Multi-center, Randomized, Double-blind, Placebo-controlled (Part A) and Double-blind, Double-dummy, Active-controlled (Part B), Parallel Group Study to Evaluate the Efficacy and Safety of RPC1063 Administered Orally to Relapsing Multiple Sclerosis Patients' (Final Version 4.0, dated 01 October 2014). I am aware of my responsibilities as an Investigator under the guidelines of GCP, local regulations (as applicable) and the study protocol. I agree to conduct the study according to these responsibilities and to appropriately direct and assist the staff under my control, who will be involved in the study.

Clinical Site: _____

Site Number: _____

Site Principal Investigator:

_____ _____

Print Name Title

_____ _____

Signature Date

2. SYNOPSIS

NAME OF SPONSOR: Receptos, Inc.	**PROTOCOL No.:** RPC01-201
NAME OF STUDY TREATMENT: RPC1063	
TITLE OF STUDY: A Phase 2/3, Multi-center, Randomized, Double-blind, Placebo-controlled (Part A) and Double-blind, Double-dummy, Active-controlled (Part B), Parallel Group Study to Evaluate the Efficacy and Safety of RPC1063 Administered Orally to Relapsing Multiple Sclerosis Patients	
STUDY CENTERS: It is planned to initiate approximately 100-125 sites for Part A and for Part B, and to enroll patients in North America and Europe.	
PHASE OF DEVELOPMENT: Phase 2/3	
PLANNED STUDY DATES: The planned duration of the study is from June 2012 through May 2017.	

OBJECTIVES:

Primary Objective:

Part A

To demonstrate the superior clinical efficacy of RPC1063 compared to placebo by showing a reduction in the cumulative number of total gadolinium enhancing (GdE) lesions from Week 12 to Week 24 in patients with relapsing multiple sclerosis (RMS).

Part B

To assess whether the clinical efficacy of RPC1063 is superior to interferon (IFN) β-1a in reducing the rate of clinical relapses at the end of Month 24 in patients with RMS.

Secondary Objectives:

Part A

- To assess the proportion of patients who are free of GdE lesions at Week 24
- To assess the effect of RPC1063 on the cumulative number of new/enlarging T2 lesions from Week 12 to Week 24
- To compare the clinical efficacy of RPC1063 to placebo in patients with RMS as assessed by reduction in annualized relapse rate (ARR) and proportion of relapse free patients at Week 24
- To assess the safety and tolerability of RPC1063 in patients with RMS
- To assess the pharmacokinetics (PK) and pharmacodynamics (PD) of RPC1063 in patients with RMS

Part B

- To assess the effect of RPC1063 on the proportion of patients with new/enlarging T2 lesions at Month 24
- To evaluate whether the efficacy of RPC1063 is superior to IFN β-1a in delaying the accumulation of disability, as assessed by the Multiple Sclerosis Functional Composite (MSFC), and visual function as measured by the low-contrast letter acuity test (LCLA).
- To evaluate whether the efficacy of RPC1063 is superior to IFN β-1a in delaying the accumulation of disability, as assessed by the Expanded Disability Status Scale (EDSS)
- To assess the effect of RPC1063 on brain atrophy over 24 months
- To evaluate the effect of RPC1063 on patient-reported quality of life as assessed by the Multiple Sclerosis Quality of Life-54 (MSQOL-54)
- To assess the safety and tolerability of RPC1063 in patients with RMS

Exploratory Objectives for Part A:

Exploratory Objectives for Part B:

- [redacted]

STUDY DESIGN AND METHODOLOGY:

Study RPC01-201 is a multi-center, randomized, double-blind, placebo-controlled (Part A) and double-blind, double-dummy, active-controlled (Part B), parallel group study to evaluate the efficacy and safety of RPC1063 administered orally to patients with RMS. In Part A of the study, two doses of RPC1063 will be administered daily for 24 weeks with an efficacy and safety comparison to a placebo control. This will be followed by Part B of the study, where two doses of RPC1063 will be administered daily for a 24 month period compared to an active control, IFN β-1a.

An interim analysis of Part A will be completed approximately 1 month prior to completion of Part A enrollment. Part B will commence after a Data Monitoring Committee (DMC) reviews the interim analysis data and performs a thorough safety review. Patients dosed in Part A will be ineligible for participation in Part B.

Part A

Part A is a randomized, double-blind comparison of RPC1063 to a placebo control in patients with RMS, per revised 2010 McDonald criteria. Approximately 210 patients who meet eligibility criteria as assessed during the 30-day screening period will be randomly assigned 1:1:1 to receive one of two daily doses of RPC1063 (0.5 mg or 1 mg) or matching placebo for 24 weeks. Brain MRI scans will be performed at Week 0, Week 8, and every 4 weeks thereafter, up to Week 24. Patients will be evaluated for relapses throughout the study (the definition and treatment of a relapse is further defined in Part B below).

Patients who complete the 24-week placebo-controlled treatment period will have the option of entering a blinded extension period. Patients assigned to either RPC1063 treatment group during the double-blind placebo-controlled period will continue in their respective treatment groups during the blinded extension; patients assigned to the placebo treatment group will be randomly assigned in a 1:1 fashion to one of the two RPC1063 treatment groups for the blinded extension. The blinded extension study will continue until all patients who choose to participate have received at least 48 weeks of additional treatment (total of at least 72 weeks for Part A). For patients continuing to the blinded extension, MRI scans will be performed 24 and 48 weeks after Week 24 (at approximately Weeks 48 and 72, and annually after Week 72) or at End of Study visit. All patients who successfully complete the blinded extension period may be offered the opportunity to enter a long-term extension study, which will be the subject of a separate protocol.

A "dual assessor" approach will be used to evaluate efficacy and safety to prevent potential unblinding as a result of observed efficacy, adverse events (AEs), or laboratory changes. Separate treating and examining investigators will be designated at each center prior to randomization (refer to Part B for additional details). Patients will be instructed to not disclose symptoms related to their treatment regimen to the blinded evaluator (examining investigator). The blinded evaluator should communicate with patients only as needed to complete the neurological examinations.

An analysis center with no knowledge of a patient's treatment or outcomes will perform MRI measurements.

Part B

Part B is a randomized, double-blind, double-dummy comparison of RPC1063 to an active control (IFN β-1a) in patients with RMS, per revised 2010 McDonald criteria. Approximately 1200 patients who meet eligibility criteria as assessed during the 30-day screening period will be randomly assigned 1:1:1 to receive one of two doses of daily RPC1063 (0.5 mg or 1 mg) or IFN β-1a 30 μg intramuscular (IM) weekly for 24 months.

A "dual assessor" approach will be used to evaluate efficacy and safety to prevent potential unblinding as a result of observed efficacy, AEs, or laboratory changes. Each site will have two investigators: a principal or treating investigator (treating investigator) and a blinded evaluator (examining investigator or rater). The treating investigator is the safety assessor and should be a neurologist experienced in the care of multiple sclerosis (MS) patients. The treating investigator will have access to both safety and efficacy data and will make all treatment decisions based on the patient's clinical response and laboratory findings. The blinded

evaluator is the efficacy assessor and should be a neurologist or other health care practitioner trained in administering the EDSS. The blinded evaluator will be responsible for administration of the EDSS. The treating investigator and the blinded evaluator will not be allowed to switch roles.

Patients will be instructed to contact the treating investigator for any suspected relapses during the study. The treating investigator will evaluate patients to confirm suspected relapses throughout the study as necessary. A relapse is defined as the occurrence of new or worsening neurological symptoms attributable to MS and immediately preceded by a relatively stable or improving neurological state of at least 30 days. The new or worsening neurological symptoms must be accompanied by objective neurological worsening, based on examination by the blinded evaluator, consistent with an increase of at least half a point on the EDSS, or 2 points on one of the appropriate Functional System (FS) scores, or 1 point on two or more of the appropriate FS scores. The change in FS scale scores should correspond to the patient's symptoms (e.g. patient reported change in visual acuity should correspond to a change in the vision FS score). Symptoms must persist for > 24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reactions to concomitant medications).

Part A and Part B

Study assessments will include physical examination, vital signs, blood tests and MRI (without and with Gadolinium contrast). Several of the AEs noted in fingolimod clinical studies may be a consequence of S1P1R stimulation and will therefore be closely monitored in the study. These AEs include bradycardia and heart conduction abnormalities (electrocardiogram [ECG] monitoring, Holter monitoring [Part A only], vital signs), pulmonary toxicity (forced expiratory volume at 1 second [FEV_1], forced vital capacity (FVC) measurements, and lung diffusion capacity testing [DLCO] measurements), macular edema (ophthalmic monitoring including optical coherence tomography [OCT]), cutaneous malignancy (dermatological exams) and hepatotoxicity (liver function tests [LFTs]).

Patients who experience a relapse may receive treatment with intravenous (IV) corticosteroids. The following standardized treatment regimen should be used: as warranted, 1.0 g IV methylprednisolone per day for a maximum of 5 consecutive days. A corticosteroid taper is not allowed. Any deviation from the standardized treatment regimen should be discussed in advance with the Medical Monitor. The Investigator should attempt to maintain therapies or treatments for symptoms related to MS (e.g., spasticity, incontinence, pain, fatigue) reasonably constant throughout the study. However, changes may be made if appropriate for a patient's well-being in the clinical judgment of the treating investigator.

All efforts will be made to follow patients who discontinue prematurely from the treatment due to lack of response, AEs, or other reasons, even if alternative treatment is given. These patients will be followed for collection of safety data, including lymphocyte recovery, and for the assessment of their disease status. The Cognitive Function subscale of the MSQOL-54 will be assessed to evaluate quality of life and subjective cognitive impairment.

STUDY POPULATION AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

Inclusion Criteria:

1. MS, as diagnosed by the revised 2010 McDonald criteria
2. Exhibiting a relapsing clinical course consistent with RMS and history of brain MRI lesions consistent with MS
3. Ages 18-55 years, inclusive
4. EDSS score between 0 and 5.0 at baseline
5. Meet one of the following disease activity criteria:
   a. At least 1 documented relapse within the last 12 months prior to screening
      OR
   b. At least 1 documented relapse occurred within the last 24 months prior to screening and documented evidence of at least 1 GdE lesion on brain MRI within the last 12 months prior to randomization
6. No history of relapse with onset from 30 days prior to screening until randomization; during this period, patients must have been clinically stable, without systemic corticosteroid treatment or adrenocorticotrophic hormone (ACTH)
7. Ability to provide written informed consent and to be compliant with the schedule of protocol assessments

8. Patients of reproduction potential (males and females) must practice an acceptable method of birth control (acceptable methods of birth control in this study include: surgical sterilization, intrauterine devices, oral contraceptive, contraceptive patch, long acting injectable contraceptive, vasectomy or double-barrier method [condom or diaphragm with spermicide OR condom and diaphragm]) during study participation and for 30 days after their last dose of treatment of study medication or true sexual abstinence (periodic abstinence [calendar, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception)
9. Patients must have documentation of positive Varicella Zoster virus (VZV) IgG antibody status or complete VZV vaccination at least 30 days prior to study entry

Exclusion Criteria:

1. Primary progressive MS at screening
2. Disease duration of more than 15 years in patients with an EDSS ≤ 2.0
3. Contraindications to MRI or Gadolinium contrast, such as known allergy to Gadolinium contrast dyes, renal insufficiency, claustrophobia, body size incompatible with the scanner, pacemaker, cochlear implants, intracranial vascular clips
4. Incompatibility with beta IFN use (e.g. intolerable side effects) (Part B only)

Exclusions Related to General Health:

5. Pregnancy, lactation, or a positive serum beta human chorionic gonadotropin (hCG) measured during screening
6. Clinically relevant hepatic, neurological, pulmonary, ophthalmological, endocrine, renal, or other major systemic disease making implementation of the protocol or interpretation of the study results difficult or that would put the patient at risk by participating in the study in the opinion of treating investigator
7. Clinically relevant cardiovascular conditions, outlined below:

   Part A: Clinically relevant cardiovascular conditions, including history or presence of ischemic heart disease, myocardial infarction, congestive heart failure, stroke, transient ischemic attack, sick sinus syndrome, recurrent syncope, second degree or higher AV block, prolonged QTcF interval (QTcF > 450 msec males, > 470 msec females) or relevant risk factors for QT prolongation (e.g., hypokalemia, hypomagnesemia), severe untreated sleep apnea

   Part B: Specific cardiac conditions are excluded, including history or presence of:

   i. Recent (within the last 6 months) occurrence of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, Class III/IV heart failure, sick sinus syndrome, or severe untreated sleep apnea
   ii. Prolonged QTcF interval (QTcF > 450 msec males, > 470 msec females), or at additional risk for QT prolongation (e.g., hypokalemia, hypomagnesemia, congenital long-QT syndrome, concurrent therapy with QT prolonging drugs)
   iii. Patients with other pre-existing stable cardiac conditions who have not been cleared for the study by an appropriate cardiac evaluation by a cardiologist

   Part A and B: Other clinically significant conduction abnormalities or any other significant cardiac condition that could jeopardize a patient's health or put them at significant safety risk during the course of the study in the opinion of the treating investigator.
8. Resting heart rate less than 55 bpm at Screening
9. History of diabetes mellitus
   Part A: Any history of Type 1 or Type 2 diabetes mellitus
   Part B: Diabetes mellitus type 1, or uncontrolled diabetes mellitus type 2 with hemoglobin A1c >7% , or diabetic patients with significant co-morbid conditions such as retinopathy or nephropathy
10. History of uveitis
11. Known active bacterial, viral, fungal, mycobacterial infection, or other infection (including tuberculosis [TB] or atypical mycobacterial disease [but excluding fungal infection of nail beds, minor URTI and minor skin conditions]) or any major episode of infection that required hospitalization or treatment with IV antibiotics within 30 days of screening or oral antibiotics within 14 days prior to screening
12. History or known presence of recurrent or chronic infection (e.g., hepatitis A, B, or C, human

immunodeficiency virus (HIV), syphilis, TB); recurring urinary tract infections could be allowed
13. History of cancer, including solid tumors and hematological malignancies (except basal cell and in situ squamous cell carcinomas of the skin that have been excised and resolved)
14. Suicide attempts in the past or current signs of major depression
15. History of alcohol or drug abuse within 1 year prior to randomization
16. History of or currently active primary or secondary immunodeficiency

Exclusions Related to Medications:

17. Prior use of any investigational agent within 6 months prior to enrollment
18. Receipt of a live vaccine within 4 weeks prior to randomization
19. Non-lymphocyte-depleting disease-modifying MS agents (e.g., glatiramer acetate, interferons) must be discontinued from signing of informed consent
20. Previous treatment with lymphocyte-depleting therapies (e.g., alemtuzumab, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation)
21. Treatment with other immunosuppressant agents such as azathioprine, cyclosporine, methotrexate, or mycophenolate within 6 months prior to randomization
22. Systemic corticosteroid therapy or ACTH use within 30 days prior to screening.
23. Prior treatment with lymphocyte trafficking blockers (e.g., natalizumab, fingolimod, other S1PR agonists).
24. Treatment with intravenous immune globulin (IVIg) or plasmapheresis, within 3 months prior to randomization
25. Treatment with other disease modifying therapies (e.g., dimethyl fumarate, teriflunomide, daclizumab, laquinimod) within 3 months prior to randomization
26. Intolerance of or contraindication to oral or IV corticosteroids
27. Use of therapies that are not allowed based on CYP3A4 metabolism within 4 weeks prior to randomization
28. Treatment with medications with a known impact on the cardiac conduction system are excluded (e.g., beta blockers, calcium channel blockers, Class Ia or Class III anti-arrhythmic drugs, and QT prolonging drugs with a known risk of torsades de pointes, e.g., citalopram, chlorpromazine, haloperidol, methadone, and erythromycin)

Exclusions Related to Laboratory Results:

29. Positive rapid plasma reagin
30. Serum creatinine > 1.4 mg/dL for women or > 1.6 mg/dL for men
31. Liver function impairment or persisting elevations of aspartate aminotransferase (SGOT/AST) or alanine aminotransferase (SGPT/ALT) > 1.5 times the upper limit of normal (ULN), or direct bilirubin > 1.5 times the ULN
32. Platelet count < 100,000/μL
33. Hemoglobin < 8.5 g/dL
34. Neutrophils < 1500/μL
35. Absolute white blood cell (WBC) count < 3500/μL; absolute lymphocyte count < 800/μL
36. Clinically significant findings on brain MRI scan consistent with conditions other than MS
37. ECG showing any clinically significant abnormality (e.g., acute ischemia, significant heart conduction abnormality (e.g., left bundle branch block)
38. FEV_1 or FVC < 70% of predicted values at screening
39. Presence of > 20 gadolinium-enhancing lesions on baseline brain MRI scan

NUMBER OF PATIENTS:

In Part A, approximately 210 patients (70 per treatment group) will be randomized.
In Part B, approximately 1200 patients (400 per treatment group) will be randomized.

Patients dosed in Part A will be ineligible for participation in Part B.

STUDY TREATMENT(S):

For all patients in both Part A and Part B of the study, initial study treatment will consist of a 7-day dose titration regimen. For patients randomized to receive active treatment with RPC1063 in Part A or Part B,

this regimen will consist of 0.25 mg RPC1063 starting on Day 1 for 4 days, then 0.5 mg RPC1063 starting on Day 5 for 3 days, followed by the assigned treatment level beginning on Day 8.

Part A

Patients will be randomly assigned 1:1:1 on Day 1 to 1 of 3 treatment regimens through Week 24:

- Placebo oral capsule daily
- 0.5 mg RPC1063 oral capsule daily
- 1 mg RPC1063 oral capsule daily

The randomization will be stratified by country.

In the Part A blinded extension period, RPC1063 (0.5 mg or 1 mg) patients who have completed the 24 weeks placebo-controlled treatment period and who choose to participate in the blinded extension period will continue in their respective treatment groups. Placebo patients will be randomized 1:1 to either a 0.5 mg or 1 mg RPC1063 treatment regimen. All patients will undergo a blinded dose titration regimen.

Part B

Patients will be randomized 1:1:1 to receive 1 of the following three regimens for 24 months:

- IFN β-1a 30 μg IM injection weekly
- 0.5 mg RPC1063 oral capsule daily
- 1 mg RPC1063 oral capsule daily

The randomization will be stratified by baseline EDSS (≤3.5, >3.5) and country.

Part B will use a double-dummy design. Thus, patients randomized to RPC1063 0.5 or 1 mg will also receive weekly matching placebo IM injections and patients randomized to IFN β-1a 30 μg will also receive daily matching placebo oral capsules.

RPC1063 and placebo will be provided as powder-filled capsules. RPC1063 drug substance is blended with [redacted] capsules. Three RPC1063 dosage strengths have been prepared for the clinical investigations; 0.25 mg [redacted] capsule), 0.50 mg ([redacted] capsule), and 1.0 mg [redacted] capsule).

For placebo, the same [redacted] capsules will contain the same blended excipients described above. All three doses of RPC1063 and placebo capsules are identical in appearance.

Study treatment IFN β-1a and matching placebo injections will be supplied in prefilled syringes, which will be dispensed to patients at each visit and will contain a sufficient supply of IFN β-1a (or matching placebo) for each dosing interval.

DURATION OF TREATMENT:

Part A double-blind period: 24 weeks

Part A optional blinded extension period: At least 48 weeks.

Part B: 24 months (patients participating in Part A will not participate in Part B)

STUDY EVALUATIONS:

Primary Efficacy Endpoint:

Part A: Total number of GdE lesions, assessed on brain MRIs from Week 12 to Week 24

Part B: ARR at the end of Month 24

Secondary Efficacy Endpoints:

Part A:

Key Secondary Endpoints (rank ordered):

- The number of GdE lesions at Week 24
- Total number of new or enlarging hyperintense T2-weighted brain MRI lesions from Week 12 to Week 24
- ARR at the end of Week 24

Part B:

Key Secondary Endpoints (rank ordered):

- The number of new or enlarging hyperintense T2-weighted brain MRI lesions over 24 months
- The number of GdE brain MRI lesions at Month 24
- Time to onset of disability progression as defined by a sustained worsening in EDSS of 1.0 points or more, confirmed after 3 months and after 6 months

Other Secondary Efficacy Endpoints

- Proportion of patients who are GdE lesion-free at Month 24
- Proportion of patients who are new or enlarging T2 lesion-free at Month 24
- The percent change in normalized brain volume (atrophy) on brain MRI scans from baseline to Month 24
- Change in MSFC score from Baseline to Month 24 (including the Low-Contrast Letter Acuity Test [LCLA] measurement of visual function as a component)
- Change in MSQOL-54 score from Baseline to Month 24

Exploratory Endpoints:

Part A:

Part B:

Safety (Secondary) Endpoints:

Part A

Cardiac safety and tolerability during initial dose titration will be evaluated in Part A patients according to the following monitoring schedule:

- Day 1 (all Part A patients): Observation of patients predose and for the first 6 hours following initial dose administration; ECG predose and at Hour 6; continuous Holter monitoring for 15 minutes predose and for 24 hours following dose administration.
- Day 5 (first 75 patients): Observation of patients predose and for the first 6 hours following dose administration; ECG predose and at Hour 6; continuous Holter monitoring for 15 minutes predose and for 24 hours following dose administration.
- Day 8 (first 75 patients): Continuous Holter monitoring for 15 minutes predose and for 24 hours following dose administration.

If clinically significant heart rate reductions or cardiac conduction abnormalities are not observed in the first 75 patients that are treated, Day 5 and Day 8 monitoring will be discontinued for the remaining patients enrolled in the study.

Part B

Monitoring during initial dosing for Part B will include:

Day 1 (all Part B patients): Observation of patients predose and for the first 6 hours following initial dose administration; ECG predose and at Hour 6

Monitoring during initial dosing for Part B may be modified based on safety and tolerability results observed during Part A, and will be implemented as needed in an amendment to this clinical study protocol.

Part A and Part B

Safety and tolerability will be evaluated in this study by the incidence and type of AEs, serious adverse events (SAEs), AEs leading to discontinuation of study treatment, the incidence and type of laboratory abnormalities, vital sign, ECG, and physical exam abnormalities in all patients. In addition, descriptive characterization of target AEs of interest including bradycardia and heart conduction abnormalities (ECG; continuous Holter monitoring [Part A only]), pulmonary toxicity (FEV_1, FVC, and lung diffusion capacity testing [DLCO] measurements), macular edema (ophthalmic exams), hepatotoxicity (LFTs), cutaneous malignancy (dermatological exams), and suicidality (Columbia- Suicide Severity Rating Scale [C-SSRS])

will occur in both Part A and Part B of the study.

PK and PD Endpoints:
In Part A and Part B, PK assessments will include PK sampling to determine plasma concentration of RPC1063 and active metabolites at scheduled assessments during the treatment period. PD assessments with include CBC with differential (determine degree of lymphopenia and the extent of lymphocyte recovery after cessation of dosing), and total immunoglobulins (Igs) - IgA, IgG, IgM. Additional PD assessments will include plasma protein biomarkers (cytokines, chemokines, other inflammatory proteins).

STATISTICAL METHODS:
Part A:
For the primary analysis, the cumulative number of GdE lesions from Week 12 to Week 24 will be compared between the 1 mg RPC1063 group and the placebo group using the stratified Wilcoxon-Mann-Whitney test, stratified by presence of GdE lesions at baseline (absent or present). This comparison will be assessed using a 2-sided test at the alpha=0.04944 level of significance. If the comparison between the 1 mg RPC1063 group and placebo is statistically significant, then a second primary analysis will similarly compare the 0.5 mg RPC1063 group and the placebo group, also based on a 2-sided test at the alpha=0.04944 level of significance. Sensitivity and descriptive analyses will also be presented.

An interim analysis of Part A will be completed approximately 1 month prior to completion of Part A enrollment. At this time point, it is estimated that approximately 80-90% of patients will have received treatment and approximately 45% of patients will have completed 12 weeks of treatment. The primary purpose of the interim analysis is to summarize safety endpoints and to provide a preliminary assessment of the primary efficacy endpoint. The efficacy endpoint for the interim analysis will be the number of GdE lesions using all data from patients who provide data through at least Week 12 (appropriately scaled). Based on the Lan-DeMets method for group sequential trials using O'Brien-Fleming boundaries, the significance levels at the interim and final analyses will be 0.00167 and 0.04944, respectively.

Sample Size Justification:
For a nonparametric analysis using the Wilcoxon-Mann-Whitney test, the parameter of interest for sample size/power considerations is the probability that a randomly selected patient in an active treatment arm will have fewer lesions than a randomly selected patient in the placebo arm. Although limited data are available from which to estimate this parameter, estimates of this probability range from 0.634 to 0.754 (Tubridy, 1999; Miller, 2003). Using the approach of Noether (1987), a sample size of 59 patients per group will provide 80% power to detect a difference if the true value of this probability is equal to 0.65 (Noether, 1987). Assuming a dropout rate of 15%, the planned enrollment is 210 patients (70 patients per arm).

Part B:
The primary analysis of ARR during the active treatment period will be carried out using a Poisson regression model which will include factors for treatment groups, region, age, and number of GdE lesions at baseline. To account for multiple comparisons, each of the two RPC1063 treatment group comparisons with the IFN β-1a group will be tested at the alpha = 0.025 level. Results will be expressed as unadjusted and adjusted relapse rates, odds ratios, corresponding 95% confidence intervals, and p-values.

The 3 key secondary endpoints will be tested in order in a ranking the RPC1063 1 mg dose above the RPC1063 0.5 mg dose. If both doses are significant on the primary endpoint, then the first comparison on the key secondary endpoints will be between the RPC1063 1 mg group and the IFN β-1a group at the 5% level of significance. If that comparison is successful, then the same endpoint will be tested for the RPC1063 0.5 mg group vs. the IFN β-1a group comparison at the 5% level of significance. This procedure will continue down the key secondary endpoint list until a comparison fails to reach statistical significance, . If only 1 RPC1063 dose is significant on the primary endpoint, then the will be employed on the surviving dose only, at the 2.5% level of significance for each key secondary endpoint.

The key secondary endpoints of cumulative number of new or enlarging T2 lesions between baseline and Month 24 and the number of GdE lesions at Month 24 will be analyzed using a negative binomial regression model with factors for treatment, region, age, and number of GdE lesions at baseline. The key secondary endpoint of time to onset of disability progression will be compared between treatment groups using Kaplan-Meier estimation and a Cox proportional-hazards model adjusted for region, age, and

baseline EDSS score. Disability progressions confirmed at 3 months and at 6 months will be analyzed separately.

All safety data will be listed and summarized by treatment group. All treatment-emergent AEs will be coded and tabulated by system organ class and preferred term. Incidence of AEs, SAEs, and AEs leading to discontinuation will be summarized and presented in descending order of frequency. Associated laboratory parameters such as hepatic enzymes, renal function, and hematology values will be grouped and presented together. Individual patient values will be listed and values outside of the standard reference range will be flagged. Shift tables and analyses of changes from Baseline will be produced. The change from Baseline for each of the vital signs and ECG parameters will be summarized. Incidence of abnormal vital signs parameters and outlier ECG results will be tabulated.

Sample Size Justification:

The control ARR is assumed to be equal to 0.3 (Mikol, 2008). Assuming extra-Poisson variation (σ^2=1.3) (Polman, 2011) and 24 months of follow-up per patient, a total sample size of 999 patients (333 per arm) is estimated to provide 90% power to detect a 37% reduction in the ARR (i.e., an ARR of 0.19 for RPC1063) (Nicholas, 2011). In order to account for an assumed dropout rate of 17%, approximately 1200 patients (400 per arm) will be enrolled.

DATE AND VERSION: 01 October 2014 (Final Version 4.0)

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4. LIST OF ABBREVIATIONS

ACTH	adrenocorticotrophic hormone
AE	adverse event
ALT	alanine aminotransferase
ARR	annualized relapse rate
AST	aspartate aminotransferase
CFR	Code of Federal Regulations
CNS	central nervous system
CRO	clinical research organization
C-SSRS	Columbia- Suicide Severity Rating Scale
DLCO	lung diffusion capacity testing
EAE	experimental autoimmune encephalomyelitis
EC50	half maximal effective concentration
ECG	Electrocardiogram
eCRF	electronic case report form
EDSS	Expanded Disability Status Scale
FDA	Food and Drug Administration
FEV_1	forced expiratory volume at 1 second
FS	Functional System
FT4	free thyroxine
FVC	forced vital capacity
GCP	Good Clinical Practice
GdE	gadolinium enhancing
GGT	gamma glutamyltransferase
GLP	Good Laboratory Practice
HBsAg	Hepatitis B surface antigen
HBcAg	Hepatitis B core antigen
HCV	Hepatitis C virus
hCG	Human chorionic gonadotrophin
HDL	high-density lipoprotein
HIV	Human Immunodeficiency virus
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
IFN β-1a	interferon beta-1a
Ig	Immunoglobulin
IM	Intramuscular(ly)
IRB	Independent Review Board
ITT	intent-to-treat
IV	intravenous(ly)
IVIg	intravenous immune globulin
IVRS	Interactive Voice Response System
LCLA	low-contrast letter acuity

LDL	low density lipoprotein
LFT	liver function test
LOCF	last observation carried forward
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MSFC	Multiple Sclerosis Functional Composite
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSQOL-54	Multiple Sclerosis Quality of Life-54
OCT	optical coherence tomography
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	per protocol
PT	prothrombin time
PTT	partial thromboplastin time
RBC	red blood cell
RPR	rapid plasma reagin
RMS	relapsing multiple sclerosis
S1P1R	sphingosine 1-phosphate 1 receptors
SAE	serious adverse event
SAP	statistical analysis plan
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
sTSH	sensitive thyroid stimulating hormone
TB	Tuberculosis
ULN	upper limit of normal
US/USA	United States/United Sates of America
VZV	Varicella Zoster virus
WBC	white blood cell
WMA	World Medical Association

5. ETHICS

5.1. Ethics Committee

In Europe, this study will be conducted in compliance with independent ethics committee (IEC) and ICH GCP Guidelines, in accordance with applicable regulations regarding clinical safety data management (E2A, E2B(R3)), European Community directives 2001/20, 2001/83, 2003/94 and 2005/28 as enacted into local law, and with ICH guidelines regarding scientific integrity (E4, E8, E9 and E10). In addition this study will adhere to all local regulatory requirements, and requirements for data protection.

In the United States (US), this study will be conducted in compliance with institutional review board (IRB) and ICH GCP Guidelines - including Title 21 Part 56 of the United States of America (USA) Code of Federal Regulations (CFR) relating to IRBs and GCP as described in the United States Food and Drug Administration (FDA) CFR (21 CFR § 50, 56, 312) - in accordance with applicable ICH regulations regarding clinical safety data management (E2A, E2B(R3)), and with ICH regulations regarding scientific integrity (E4, E8, E9 and E10). In addition this study will adhere to all local regulatory requirements, and requirements for data protection.

Before initiating a trial/study, the investigator/institution must have written and dated approval/favorable opinion from the IRB/IEC for the study protocol/amendment(s), written informed consent form, any consent form updates, patient recruitment procedures (e.g., advertisements), and any written information to be provided to patients and a statement from the IRB/IEC that they comply with GCP requirements. The IRB/IEC approval must identify the protocol version as well as the documents reviewed.

5.2. Ethical Conduct of the Study

This study will be conducted in accordance with the Note for Guidance on GCP (ICH Harmonized Tripartite Guideline E6 (R1); FDA CFR (21 CFR § 50, 56, 312)), Declaration of Helsinki (Seoul 2008) (Section 18.1) and all applicable regulatory requirements.

5.3. Patient Information and Consent

The Investigator will explain the benefits and risks of participation in the study to each patient, the impartial witness and obtain written informed consent. Written informed consent must be obtained prior to the patient entering the study and before initiation of any study related procedure (including administration of study drug).

The Sponsor or their designee will provide a sample informed consent form, based on the elements of informed consent in Section 18.2. The final, version dated, form must be agreed to by the IRB/IEC and will contain all elements in the sample form, in language readily understood by the patient. In case the patient is unable to read or write, an impartial witness should be present during the entire informed consent discussion. After the patient has orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. The Investigator

will retain each patient's original consent form, signed and dated by the patient or witness, and by the person who conducted the informed consent discussion. The Investigator will supply all enrolled patients with a copy of their signed informed consent.

The consent form may need to be revised during the study due to a protocol amendment or should important new information become available that may be relevant to the safety of the patient. In this instance, approval should always be given by the IRB/IEC and existing patients informed of the changes and reconsented, as directed by the IRB/IEC and in accordance with its policies and procedures. However, in some instances where an immediate change is necessary to eliminate an apparent hazard to patients, then it would not be necessary for a protocol amendment to receive IRB/IEC review and approval before being implemented (21CFR 56.108(a)(4)). Those patients who are presently enrolled and actively participating in the study should be informed of the change if it might relate to the patients' willingness to continue their participation in the study (21CFR 50.25(b)(5)). The FDA does not require reconsenting of patients that have completed their active participation in the study, or of patients who are still actively participating when the change will not affect their participation, for example when the change will be implemented only for subsequently enrolled patients.

With the consent of the patient, the Investigator should inform the patient's primary physician about participation in the clinical study.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Principal Investigator(s):

This is a multi-center study.

Monitoring and Evaluation Committee(s):

This study will use an independent Data Monitoring Committee (DMC) (see Section 13.6.8).

Clinical Laboratories:

Central laboratories will be used for this study:

Tel.
Fax

Tel:
Fax

Tel:
Fax:

Tel:

Central Magnetic Resonance Imaging (MRI) Evaluation:

Independent central evaluation will be performed for this study by:

Central Electrocardiogram (ECG) Reading:

Central ECG reading will be performed for this study by:

Clinical Research Organization (CRO):

Tel:

Fax:

Tel:

Central IRB:

Study Medical Monitor/Medical Expert:

Europe

Phone:

Fax:

North America

Phone:

Fax:

Safety Contact (Serious Adverse Event [SAE] reporting):

Europe and US

Phone:

Fax:

Clinical Study Supply Management:

Europe:

North America:

7. INTRODUCTION

7.1. Disease Review

Multiple sclerosis (MS) is a chronic autoimmune and neurodegenerative disease of the central nervous system (CNS), characterized by inflammation, demyelination, neuronal and oligodendrocyte loss, and disruption of the blood-brain barrier. The disease has a prevalence estimated at greater than 400,000 patients in the US and over 2.5 million individuals worldwide (Noseworthy, 2000). Currently there is no cure for MS. Pathophysiologically, MS is driven by autoreactive lymphocytes that attack and destroy the myelin sheath surrounding nerve cells, resulting in demyelination and axonal damage. The utility of treating MS with immune modulating drugs has been well-established. The goal of current treatment strategies for MS involves improving the quality of life of patients by managing symptoms and treating relapses.

Currently approved first-line immune-modulating therapies include several interferon (IFN)-β products, glatiramer acetate (GA or Copaxone®) and fingolimod. The IFN and GA are disease-modifying therapies that have moderate efficacy, reduce the relapse rate by approximately 30% and reduce disability accumulation compared to placebo (IFNB Multiple Sclerosis Study Group, 1993; Jacobs, 1996; PRISMS, 1998; Johnson, 1995; Goodin 2002). Natalizumab (Tysabri®), a humanized monoclonal antibody, is another approved immune-modulating therapy that has been shown to reduce relapse rates by 68% and reduces the risk of sustained progression of disability by 42% compared to placebo (Polman, 2006). Natalizumab acts by blocking leukocyte recruitment to inflammatory sites in the CNS. Each of these drugs is characterized by a combination of limited therapeutic utility, safety concerns and/or drug compliance issues, suggesting the need for the development of effective, well tolerated orally active MS therapies.

7.2. Compound Review

RPC1063 is a small molecule compound that selectively and potently activates the sphingosine 1-phosphate 1 receptor (S1P1R), resulting in sequestration of lymphocytes in peripheral lymphoid organs and maintenance of endothelial barrier integrity.

7.2.1. S1PR Experience in MS

Clinical experience with fingolimod (FTY720, Gilenya®) strongly supports the rationale for therapeutically targeting S1PR in MS. Fingolimod, an oral drug recently approved for the treatment of MS, has demonstrated a superior efficacy profile compared to IFN-β, reducing relapse rates by 52% (Cohen, 2010; Kappos, 2010). Fingolimod stimulates S1P1R, resulting in lymphocyte subset sequestration in peripheral lymphoid organs and reversible systemic lymphopenia (Mandala, 2002). An inability of sequestered autoreactive lymphocytes to traffic to and exacerbate inflammation in the CNS is thought to be the primary mode of action of fingolimod (Kappos, 2006). Therefore, this peripheral lymphocyte response represents a clearly defined pharmacodynamic (PD) effect of S1P1R stimulation (Sanna, 2006). S1P1R stimulation also supports maintenance of blood-brain barrier integrity by enhancing

endothelial barrier function, thereby potentially contributing to fingolimod's efficacy profile (Sanna, 2006; Sanchez, 2003).

Fingolimod is not specific for S1P1R. The compound also stimulates three other related receptors: S1P3R, S1P4R, and S1P5R (Mandala, 2002; Brinkmann, 2002). Several toxicities associated with fingolimod treatment may be a consequence of the drug lacking specificity for S1P1R and potentially having pharmaceutics liabilities related to the drug's structural class (Cohen, 2010; Kappos, 2006). Also, due to a long half-life, the PD effect of fingolimod treatment (lymphopenia) is also long-lasting. Circulating lymphocytes typically take 4 to 6 weeks to return to normal levels in patients following cessation of treatment (Kovarik, 2004), thus raising clinical safety concerns, particularly if patients develop infections.

7.2.2. Overview of RPC1063

RPC1063 is a small molecule compound that selectively and potently activates S1P1R (half maximal effective concentration [EC50] of). RPC1063 is also active on the S1P5 receptor (EC50 of) although it is 353-fold selective towards S1P1R over S1P5R. RPC1063 has little activity on the other S1P receptors, showing greater than 20,000-fold selectivity over S1P2R, S1P3R and S1P4R. The RPC1063 metabolites, and , show a similar potency and selectivity profile to RPC1063. RPC1063 and metabolites were also shown to be highly selective for binding to S1P1R relative to a G-protein coupled receptors enriched panel of 55 non-target receptors in vitro; no pharmacologically relevant receptor interactions were observed in this study.

The S1P1R target of RPC1063 is a G protein-coupled receptor whose natural ligand is sphingosine 1-phosphate. Many cell types express S1P1R, including vascular endothelial cells, brain cells and lymphocytes (Rosen, 2009). Stimulation (agonism) of this receptor results in biological activities that are likely to ameliorate pathological processes associated with MS.

These include:

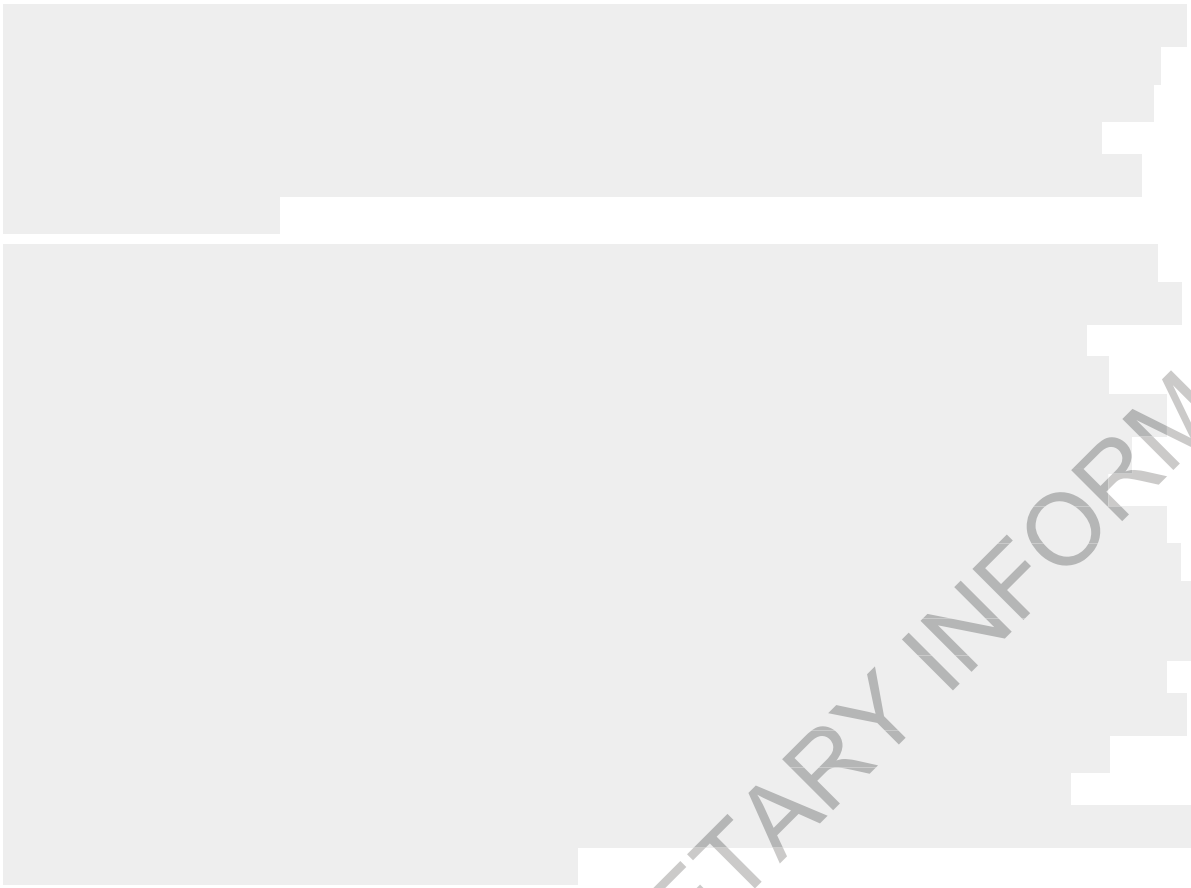
1. Lymphocyte sequestration in peripheral lymphoid organs (e.g. lymph nodes and gastrointestinal Peyer's patches), resulting in reversible systemic lymphopenia (Mandala, 2002). Since MS is an autoimmune -driven inflammatory disease, prevention of trafficking of disease-exacerbating, self-reactive lymphocytes to the CNS is likely to have immunomodulatory effects with a consequent dampening of disease processes (Kappos, 2006).
2. Enhancement of endothelial barrier function. MS is characterized by a breakdown in the vascular endothelium associated with the blood-brain barrier, resulting in easier access of proinflammatory cells (including self-reactive lymphocytes) into the brain. S1P1R stimulation strengthens endothelial cell association (Sanna, 2006; Sanchez, 2003) and supports the integrity of the blood-brain barrier.
3. Several brain tissue cell types express S1P1R and modulation of the receptor may exert neuroprotective and regenerative responses in the CNS (Soliven, 2011).

7.2.3. Non-Clinical Studies

RPC1063 is an orally available, potent and selective S1P1R agonist that induces rapid, reversible lymphopenia in rodents, dogs and nonhuman primates.

Comprehensive pre-clinical pharmacology, pharmacokinetic (PK), and toxicology programs were conducted in mice, rats, dogs, and cynomolgus monkeys. The potency and selectivity of RPC1063 has been investigated in a series of *in vitro* cellular studies. The *in vivo* pharmacological activity of RPC1063, resulting in lymphocyte sequestration in peripheral lymphoid organs and reversible systemic lymphopenia, was investigated in several animal species.

In vivo pharmacology efficacy studies in experimental autoimmune encephalomyelitis (EAE), a mouse model of MS,



Collectively, the results have shown that RPC1063 is well tolerated in animals at doses that generate robust PD effects, suggesting that the compound has a broad therapeutic window.

Additional information is provided in the Investigator's Brochure.

7.2.4. Clinical Studies

RPC1063 was studied in two Phase 1 studies that have been completed. RPCS 001 was a first-in-human Phase 1 clinical study administered orally in normal healthy volunteers, that evaluated the safety, tolerability, PK and PD effects of RPC1063 compared to placebo, and included single and multiple dose cohorts (7 and 28 days). In addition, the effects of dose titration on mitigating cardiac effects following initial dose administration were studied. A summary of the major findings is presented below. Further details are provided in the Investigator's Brochure.

Overall, 88 unique subjects were enrolled in the study. All cohorts were initially administered treatment with study drug in the fasted condition for one treatment period; 66 were randomized to receive RPC1063 and 22 were randomized to receive placebo. All subjects completed the study with the exception of 1 subject who discontinued the study due to an adverse event (AE) after receiving a single dose of RPC1063 at 1.5 mg (described below).

The preliminary assessment of RPC1063 PK in healthy volunteers demonstrated dose linear changes in C_{max} and AUC following both single and multiple doses, favorable inter-subject variability, and an elimination half-live consistent with once daily administration

(approximately 18-21 hours). In the analysis of PD, dose related decreases in lymphocyte count were observed following single dose administration of RPC1063. Upon multiple dose administration for 28 days, trough lymphocyte counts continue to decrease throughout dosing. Following the last dose, lymphocyte counts change from baseline was -48.1% and -71.1% at dose levels of 0.3 and 1 mg, respectively, and PD responses appeared to reach close to steady state by Day 28 at these dose levels.

Most AEs were considered unrelated to study drug by the Investigator. The most common AEs (occurring in >1 subject) that were assessed as related to RPC1063 (probably or possibly related) by the Investigator were: headache (6 subjects); somnolence and nausea (5 subjects); dizziness, nausea, and fatigue (3 subjects); decreased appetite, sinus arrest, obstructive airways disorder, and dry mouth, (2 subjects each). Most AEs (132) were evaluated as Grade 1 (mild); some AEs (38) were evaluated as Grade 2 (moderate) in severity. No Grade 3 (severe) or higher AEs were reported, thus no dose-limiting toxicities occurred at any dose or schedule of administration.

Target AEs of interest in study RPCS 001 were closely monitored and included bradycardia and other heart conduction abnormalities, pulmonary toxicity, hepatotoxicity, macular edema, and suicidal ideation. No AEs were reported for LFT elevation, macular edema, or suicidal ideation. Two subjects who received 2 mg RPC1063 for 7 days had Grade 1 pulmonary-related adverse events of obstructive airways disorder. For the two subjects, forced vital capacity (FVC) and forced expiratory volume at 1 second (FEV_1) declined to >20% below their baseline values on Day 7 (last dosing day) and Day 14 (last post-dose follow-up visit). Subjects were followed and values returned to baseline off therapy.

Four subjects had Grade 2 cardiac-related AEs of bradycardia and/or conduction abnormality. One subject experienced a Grade 2 second degree AV block and associated nausea after receiving a single dose of 1.5 mg RPC1063 that led to study discontinuation. At a dose of 3 mg RPC1063, 2 subjects reported AEs of Grade 2 sinus arrest, and 1 subject reported an AE of sinus bradycardia. These events resolved within 24 hours with no medical intervention.

All subjects, including those administered placebo, showed an initial reduction in HR following dosing on Day 1. Subjects who received RPC1063 had a greater decrease in HR compared to placebo subjects, and there was evidence of a dose-dependent decrease in absolute heart rate. Lower doses of RPC1063 led to less change in absolute heart rate over time, with the greatest change from baseline during the first 12 hours following treatment of -5.2 bmp and -13.2 bpm for doses of 0.3 mg and 1 mg, respectively. In general, most of the decrease in HR was observed within the first 6 hours after study drug was administered.

Dose titration was studied, consisting of doses of 0.3 to 2 mg that were increased over a 10 day dosing period, to evaluate the effect on mitigating effect on HR. The nadir HR on each dosing day decreased more on Day 1 among subjects who received RPC1063 (-7.6 bpm) than for placebo (-2.8 bpm). With continued dosing, there was an additional mean decrease of approximately 1-2 bpm per day in RPC1063-treated subjects over Days 2 to 4, with negligible further reduction observed after Day 4 despite administration of higher doses of RPC1063. Smaller change from baseline HR was observed during titration to the 1 and 2 mg doses than change that was observed on Day 1 in the fixed dose regimen. These data suggest that dose titration of RPC1063 does attenuate effects on HR observed at higher doses of RPC1063 treatment.

A second Phase 1 study that was completed, RPC01-102, was a a single-center, double-blind, randomized, placebo- and positive-controlled, parallel-group, nested crossover for positive control, thorough QT/QTc (TQT) study in healthy men and women aged 18-45 years. The study tested the effects of RPC1063 at the intended therapeutic dose (1 mg/day) and at a supratherapeutic dose (2 mg/day) compared with matching placebo. A dose of 400 mg moxifloxacin will be included as a positive control.

The study ruled out a clinically relevant effect on cardiac relevant repolarization at both the 1 mg and 2 mg doses. No new safety signals were identified and adverse events were generally similar to those observed in the previous Phase 1 study (RPCS 001). Further details are provided in the current Investigator Brochure.

Overall, the safety experience with RPC1063 supports its continual development in relapsing multiple sclerosis (RMS) patients.

7.3. Clinical Study Rationale

MS is a serious, life-threatening and disabling disease that is prevalent in young and middle-aged adults. The progressively debilitating nature of the disease has an enormous impact, not only on the quality of life of the patient, but also on their families, health systems and the national economy. New drugs are needed to positively impact the lives of patients and reduce the healthcare cost burden associated with relapses.

Clinical experience with fingolimod (recently approved for the treatment of RMS) strongly supports the rationale for therapeutically targeting S1P1R in MS. Fingolimod is an agonist of four of the five S1P receptors: S1P1R, S1P3R, S1P4R, and S1P5R (Mandala, 2002; Brinkmann, 2002). Fingolimod induces lymphocyte sequestration in peripheral lymphoid organs, resulting in lymphopenia in several animal species and in humans; this response represents a clearly defined PD effect of S1P1R stimulation and a likely mechanism of fingolimod's clinical efficacy (Kappos, 2006; Sanna, 2006). In a head-to-head clinical study, fingolimod displayed superior efficacy compared to IFN β-1a [redacted] (Cohen, 2010). Thus, fingolimod has provided clinical evidence for the effectiveness of a drug that targets S1P1R.

There are a number of AEs associated with fingolimod treatment that may limit its use in the RMS population. Cardiac AEs such as bradycardia and other heart conduction abnormalities have been observed with fingolimod in the clinical development program and in the post-marketing setting, which increased the need for more intensive cardiac monitoring for RMS patients when receiving the first dose of fingolimod. Elevations in liver enzymes (3 times the upper limit of normal [ULN]) have also been observed in the range of 8-12%, consistent with liver pathology (Cohen, 2010; Kappos, 2006). These toxicities may be a consequence of the drug lacking specificity for S1P1R, from having higher than necessary exposures, or from having pharmaceutic liabilities related to fingolimod's structural class. Additionally, due to complex absorption, distribution, metabolism and excretion properties including an extremely long half-life (89 to 157 hours), the PD effects of fingolimod are prolonged, with patients requiring several weeks before the number of circulating lymphocytes return to normal following cessation of treatment (Kovarik, 2004; Budde, 2002). This may have clinical safety consequences, particularly if patients develop infections or other treatment-related complications.

All of the currently approved drugs have therapeutic, safety and/or logistical limitations. All but fingolimod are administered by injection, presenting challenges associated with injection-related AEs, compliance and convenience. First-line therapies have modest efficacy coupled with side effect profiles that affect patient quality of life and adherence to therapy. Second- and third-line therapies have better efficacy profiles but significant safety issues. There is a pressing need for an MS treatment that is highly effective, well tolerated, and orally active.

A clinical development program for RPC1063 is being pursued in MS because: (i) it is a potent and selective orally bioavailable S1P1R agonist, (ii) it has a short half-life allowing for rapid clearance of the drug in the setting of potential treatment related complications, (iii) it may allow for a more rapid recovery of lymphocytes into the normal range in RMS patients, and (iv) RPC1063 may have an improved safety and tolerability profile over existing RMS therapies including other S1PR agonists.

The objective of the RPC1063 clinical development program in RMS is to demonstrate that RPC1063 administered orally as monotherapy is safe and effective in reducing the frequency of clinical exacerbations and in delaying the accumulation of physical disability exacerbations in RMS patients.

This Phase 2/3 clinical trial consisting of a placebo-controlled (Part A, Phase 2) and active comparator trial (Part B, Phase 3) versus IFN β-1a is the first pivotal study of the RPC1063 clinical development program. Part A is a randomized, double-blind comparison of RPC1063 to a placebo control in patients with RMS to characterize the short-term efficacy and safety of RMS in improving disease activity as measured by MRI parameters. Part B characterizes the efficacy and safety profile of RPC1063 on longer-term clinical outcomes (e.g., relapse rate and disability progression) in RMS patients.

Both of these parts will provide substantial data characterizing the clinical effects of RPC1063 in RMS patients. An active comparator design was chosen based on the significant challenges in conducting long-term placebo-controlled studies in which patients are at increased risk for experiencing irreversible disability progression from placebo treatment. IFN β-1a was chosen based upon its wide use in many global regions as a standard of care therapy, its acceptability as a reference comparator based on other trials in RMS over the last 5 years, and its relative lower frequency of administration (weekly) compared to other therapies.

8. STUDY OBJECTIVES AND ENDPOINTS

8.1. Study Objectives

8.1.1. Primary Study Objectives

Part A

To demonstrate the superior efficacy of RPC1063 compared to placebo by showing a reduction in the cumulative number of total gadolinium enhancing (GdE) lesions from Week 12 to Week 24 in patients with RMS.

Part B

To assess whether the clinical efficacy of RPC1063 is superior to IFN β-1a in reducing the rate of clinical relapses at the end of Month 24 in patients with RMS.

8.1.2. Secondary Study Objectives

Part A

- To assess the proportion of patients who are free of GdE lesions at Week 24
- To assess the effect of RPC1063 on the cumulative number of new/enlarging T2 lesions from Week 12 to Week 24
- To compare the clinical efficacy of RPC1063 to placebo in patients with RMS as assessed by reduction in annualized relapse rate (ARR) and proportion of relapse free patients at Week 24
- To assess the safety and tolerability of RPC1063 in patients with RMS
- To assess the pharmacokinetics (PK) and PD of RPC1063 in patients with RMS

Part B

- To assess the effect of RPC1063 on the proportion of patients with new/enlarging T2 lesions at Month 24
- To evaluate whether the efficacy of RPC1063 is superior to IFN β-1a in delaying the accumulation of disability, as assessed by the Multiple Sclerosis Functional Composite (MSFC), and visual function as measured by the low contrast visual acuity test (LCLA) (Balcer, 2000).
- To evaluate whether the efficacy of RPC1063 is superior to IFN β-1a in delaying the accumulation of disability, as assessed by the Expanded Disability Status Scale (EDSS)
- To assess the effect of RPC1063 on brain atrophy over 24 months
- To evaluate the effect of RPC1063 on patient-reported quality of life as assessed by the Multiple Sclerosis Quality of Life-54 (MSQOL-54)
- To assess the safety and tolerability of RPC1063 in patients with RMS

8.1.3. Exploratory Study Objectives

Part A

Part B

8.2. Endpoints

8.2.1. Efficacy Endpoints

Part A

Primary Efficacy Endpoint:

- Total number of GdE lesions, assessed on brain MRIs from Week 12 to Week 24

Key Secondary Efficacy Endpoints (rank ordered):

- The number of GdE lesions at Week 24
- Total number of new or enlarging hyperintense T2-weighted brain MRI lesions from Week 12 to Week 24
- ARR at the end of Week 24

Exploratory Endpoints:

Part B

Primary Efficacy Endpoint:

- ARR at the end of Month 24

Key Secondary Efficacy Endpoints (rank ordered):

- The number of new or enlarging hyperintense T2-weighted brain MRI lesions over 24 months
- The number of GdE brain MRI lesions at 24 months
- Time to onset of disability progression as defined by a sustained worsening in EDSS of 1.0 points or more, confirmed after 3 months and after 6 months

Other Secondary Efficacy Endpoints

- Proportion of patients who are GdE lesion-free at Month 24
- Proportion of patients who are new or enlarging T2 lesion-free at Month 24
- The percent change in normalized brain volume (atrophy) on brain MRI scans from baseline to 24 months
- Change in MSFC score from Baseline to Month 24 (including the Low-Contrast Letter Acuity Test [LCLA] measurement of visual function as a component)
- Change in MSQOL-54 score from Baseline to 24 months

Exploratory Endpoints:

8.2.2. Safety (Secondary) Endpoints

Part A

Cardiac safety and tolerability during initial dose titration will be evaluated in Part A patients according to the following monitoring schedule:

- Day 1 (all Part A patients): Observation of patients predose and for the first 6 hours following initial dose administration; ECG predose and at Hour 6; continuous Holter monitoring for 15 minutes predose and for 24 hours following dose administration.
- Day 5 (first 75 patients): Observation of patients predose and for the first 6 hours following dose administration; ECG predose and at Hour 6; continuous Holter monitoring for 15 minutes predose and for 24 hours following dose administration.

- Day 8 (first 75 patients): Continuous Holter monitoring for 15 minutes predose and for 24 hours following dose administration.

If clinically significant heart rate reduction or cardiac conduction abnormalities are not observed in the first 75 patients that are treated, Day 5 and Day 8 monitoring will be discontinued for the remaining patients enrolled in the study.

Part B

Monitoring during initial dosing for Part B will include:

Day 1 (all Part B patients): Observation of patients predose and for the first 6 hours following initial dose administration; ECG predose and at Hour 6

Monitoring during initial dosing for Part B may be modified based on safety and tolerability results observed during Part A, and will be implemented as needed in an amendment to this clinical study protocol.

Part A and Part B

Safety and tolerability will be evaluated in this study by the incidence and type of AEs, SAEs, AEs leading to discontinuation of study treatment, the incidence and type of laboratory abnormalities, vital sign, ECG, and physical exam abnormalities in all patients. In addition, descriptive characterization of target AEs of interest including bradycardia and heart conduction abnormalities (ECG, vital signs, continuous Holter monitoring [Part A only]), pulmonary toxicity (FEV_1, FVC measurements), and lung diffusion capacity testing [DLCO] measurements), macular edema (optical coherence tomography [OCT]), hepatotoxicity (LFTs), cutaneous malignancy (dermatological exams), and suicidality (Columbia- Suicide Severity Rating Scale [C-SSRS]) will occur in both Part A and Part B of the study.

Safety assessments will include the following:

- AEs
- Laboratory evaluations
- Vital sign measurements
- ECG results
- Continuous Holter monitoring
- Physical and neurological examination
- OCT
- Pulmonary function tests
- Dermatological examination
- Columbia-Suicide Severity Rating Scale (C-SSRS)

8.2.3. PK and PD Endpoints

PK and PD assessments will include the following:

- Standard PK sampling to determine plasma concentration of RPC1063 and active metabolites
- CBC with differential (differential will be blinded)
- Plasma protein biomarker analysis (e.g., cytokines, chemokines, other inflammatory proteins)
- Total immunoglobulins (Igs) - IgA, IgG, IgM

PK data from this study may be integrated with PK data from other clinical trials to further enhance a population PK analysis. Results from any population PK analysis will be documented in a separate pharmacometric report.

9. INVESTIGATIONAL PLAN

9.1. Overall Study Design and Plan

Study RPC01-201 is a multi-center, randomized, double-blind, placebo-controlled (Part A) and double-blind, double-dummy, active-controlled (Part B) parallel group study to evaluate the efficacy and safety of RPC1063 administered orally to patients with RMS.

In Part A of the study, two doses of RPC1063 will be administered daily for 24 weeks with an efficacy and safety comparison to a placebo control. This will be followed by Part B of the study, where two doses of RPC1063 will be administered daily for a 24 month period compared to an active control, IFN β-1a.

An interim analysis of Part A will be completed approximately 1 month prior to completion of Part A enrollment. Part B will commence after a DMC reviews the interim analysis data and performs a thorough safety review. Patients dosed in Part A will be ineligible for participation in Part B.

It is anticipated that the study will be performed at approximately 100-125 sites for Part A and for Part B in North America and Europe.

The study designs for Part A and Part B are shown in Figure 1.

Tests and assessments are outlined in Table 1 and Table 2 (Part A), Table 3 and Table 4 (Part B), and Table 5 (cardiac monitoring during dose titration), additional details regarding procedures are included in Section 10. Assessments are described in Section 11.

Part A

Part A is a randomized, double-blind comparison of RPC1063 to a placebo control in patients with RMS, per revised 2010 McDonald criteria (McDonald, 2010; Polman, 2011). Approximately 210 patients who meet eligibility criteria as assessed during the 30-day screening period will be randomly assigned 1:1:1 to receive one of the three following regimens, up to Week 24:

- Placebo oral capsule daily
- 0.5 mg RPC1063 oral capsule daily
- 1 mg RPC1063 oral capsule daily

The randomization will be stratified by country.

Brain MRI scans will be performed at Week 0, Week 8, and every 4 weeks thereafter, up to Week 24. Patients will be evaluated for relapses throughout the study.

Patients who complete the 24 weeks placebo-controlled treatment period will have the option of entering a blinded extension period. During the blinded extension period, the sponsor and CRO will be blinded until the Week 24 primary endpoint is reached by all patients and the data through Week 24 are final, after which the sponsor and CRO will be unblinded to treatment assignment. Investigators and patients will remain blinded throughout the blinded extension period. Patients assigned to either RPC1063 treatment group during the double-

blind placebo-controlled period will continue in their respective treatment groups during the blinded extension; patients assigned to the placebo treatment group will be randomly assigned in a 1:1 fashion to one of the two RPC1063 treatment groups for the blinded extension. The blinded extension study will continue until all patients who choose to participate have received at least 48 weeks of treatment (total of at least 72 weeks for Part A, 24 weeks in placebo-controlled period and at least 48 weeks additional weeks in the blinded extension). For patients continuing to the blinded extension, MRI scans will be performed 24 and 48 weeks after Week 24 (at approximately Weeks 48 and 72 and annually after Week 72) or at End of Study visit. All patients who successfully complete the blinded extension period will be offered the opportunity to enter a long-term extension period, which will be the subject of a separate protocol.

A "dual assessor" approach will be used to evaluate efficacy and safety to prevent potential unblinding as result of observed efficacy, AEs, or laboratory changes. Separate treating and examining investigators will be designated at each center prior to randomization (refer to Section 9.1.2.1 for additional details). Patients will be instructed to not disclose symptoms related to their treatment regimen to the blinded evaluator (examining investigator). The blinded evaluator should communicate with patients only as needed to complete the neurologic examinations.

The MSQOL-54 will also be assessed during Part A.

An analysis center with no knowledge of a patient's treatment or outcomes will perform MRI evaluations.

Part B

Part B is a randomized, double-blind, double-dummy comparison of RPC1063 to IFN β-1a in patients with RMS, per revised 2010 McDonald criteria (McDonald, 2010; Polman, 2011). Part B will commence after the DMC reviews the Part A interim analysis data and performs a thorough safety review. Patients dosed in Part A will be ineligible for participation in Part B.

Approximately 1200 patients who meet eligibility criteria as assessed during the 30-day screening period will be randomly assigned 1:1:1 to receive one of the three following regimens for 24 months:

- IFN β-1a 30 µg intramuscular (IM) weekly
- 0.5 mg RPC1063 oral capsule daily
- 1 mg RPC1063 oral capsule daily

The randomization will be stratified by baseline EDSS (≤ 3.5, > 3.5) and country.

A "dual assessor" approach will be used to evaluate efficacy and safety to prevent potential unblinding as result of observed efficacy, AEs, or laboratory changes (refer to Section 9.1.2.1 for additional details). The treating investigator will evaluate patients every 3 months throughout the study and, if necessary, at unscheduled visits for relapses occurring between scheduled visits.

The blinded evaluator will assess the EDSS. Blinded study coordinators or EDSS evaluators will perform the MSFC and LCLA assessments. The Cognitive Function subscale of the

MSQOL-54 will also be assessed to evaluate subjective cognitive impairment. The Paced Auditory Serial Addition Test (PASAT-3) of the MSFC will also be used to evaluate cognitive function.

All efforts will be made to follow patients who discontinue from the treatment due to lack of response, AEs, or other reasons, even if alternative treatment is given. These patients will be followed for collection of safety data, including lymphocyte recovery, and for the assessment of their disease status.

9.1.1. Study Schematic and Schedule of Events

Figure 1 Study Schematic

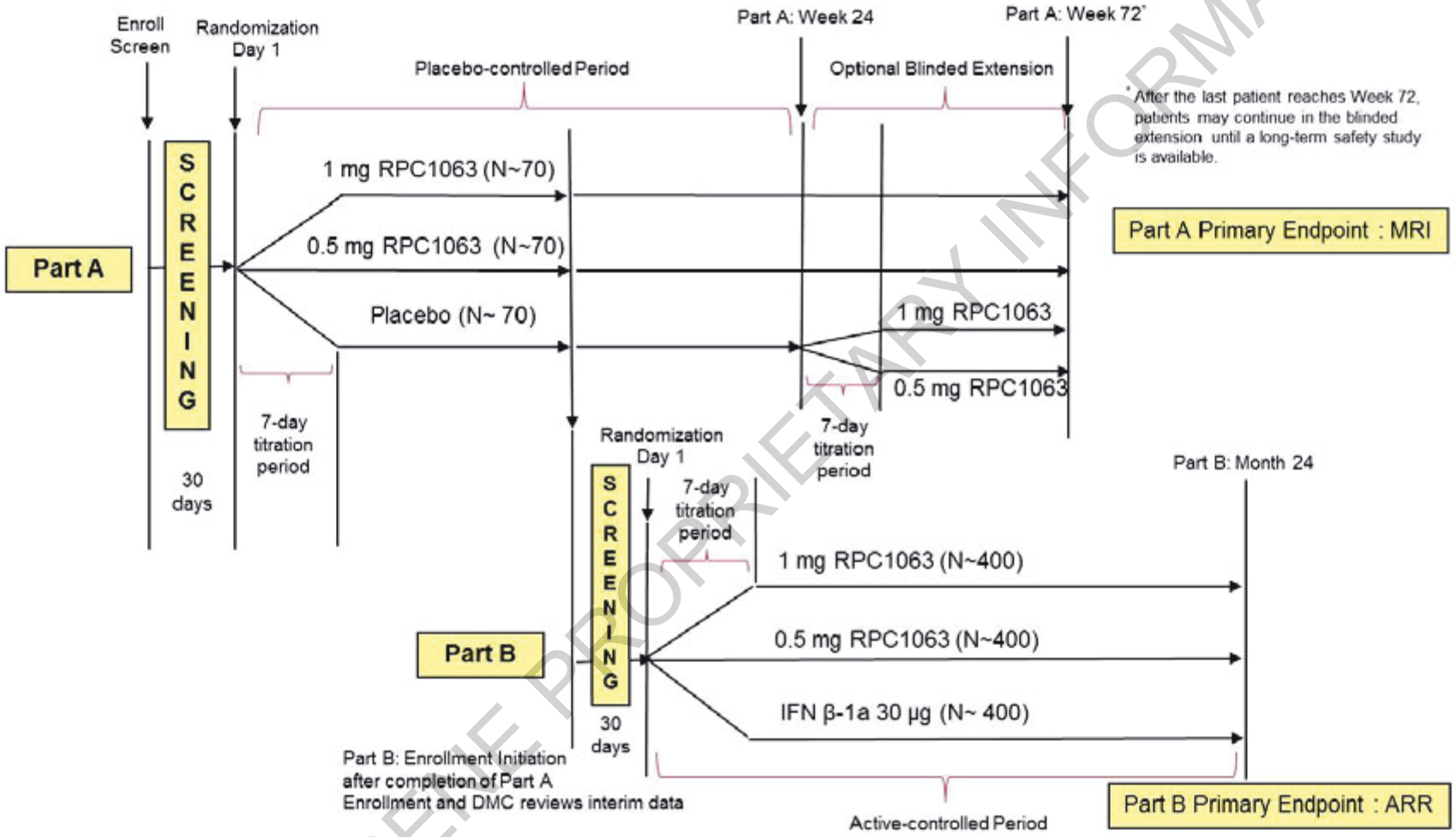


Table 1 Schedule of Assessments – Part A: Screening, Baseline, and Treatment Period Visits

	Screening	Baseline	Double-Blind Placebo-Controlled Period							
Procedure	**Initial (-30 days)**	**D1 (W1)**	**D5[1] (W1)**	**D8[1] (W1)**	**D29 (W4)** (±3d)	**D57 (W8)** (±3d)	**D85 (W12)** (±3d)	**D113 (W16)** (±3d)	**D141 (W20)** (±3d)	**D169 (W24)[2,12]** (±3d)
Informed consent	X									
Inclusion/exclusion criteria	X	X								
Medical history	X	X[3]								
Clinical laboratory tests[4]	X	X			X		X			X
Urine/serum pregnancy (women of childbearing potential only)[5]	X	X			X	X	X	X	X	X
Coagulation panel	X									X
sTSH	X									X
Total Ig (IgA, IgG, IgM)										
Viral serology[6], and syphilis RPR	X									
TB testing[7]	X									
Complete physical examination	X									X
Height[8] and weight	X	X								X
Vital Signs	X	X[10]	X[10]		X	X	X	X	X	X[11]
Chest X-ray[9]	X									
12-lead ECG	X	X[10]	X[10]		X		X			X[11]
Holter monitoring		X[10]	X[10]	X[10]						
Enroll patient, contact IVRS	X									
Randomization		X								X[12]
Study drug administration		X	X	X	X	X	X	X	X	X[12]
Administer study drug at clinic		X	X	X			X			X[12]
Dispense study drug and patient diary		X			X	X	X	X	X	X[12]
Study drug accountability and compliance check					X	X	X	X	X	X
Brain MRI	X					X	X	X	X	X
EDSS and neurological examination	X						X			
MSFC and LCLA	X[13]	X					X			

Procedure	Screening	Baseline	Double-Blind Placebo-Controlled Period							
	Initial (-30 days)	**D1 (W1)**	**D5[1] (W1)**	**D8[1] (W1)**	**D29 (W4)** (±3d)	**D57 (W8)** (±3d)	**D85 (W12)** (±3d)	**D113 (W16)** (±3d)	**D141 (W20)** (±3d)	**D169 (W24)[2,12]** (±3d)
MSQOL-54		X								X
Pulmonary function tests[14]	X						X			X
OCT[15]	X									X
Dermatological (skin) examination	X									X
C-SSRS	X	X			X	X	X	X	X	X
Standard PK sampling[16]		X			X		X			X
Plasma biomarkers										
Prior/Concomitant therapy										
AEs/SAEs[3]	X	X	X	X	X	X	X	X	X	X

TSH = Thyroid stimulating hormone, RPR = rapid plasma reagin; TB = tuberculosis, ECG = electrocardiogram, IVRS = interactive voice response system, MRI = magnetic resonance imaging, EDSS = Expanded Disability Status Scale, MSFC = Multiple Sclerosis Functional Composite, LCLA = low-contrast letter acuity test; MSQOL = Multiple sclerosis quality of life, OCT = optical coherence tomography, C-SSRS = Columbia- Suicide Severity Rating Scale, PK = pharmacokinetics, AE/SAE = adverse events/serious AE

Footnotes to Table 1

1 If clinically significant heart rate reductions or cardiac conduction abnormalities are not observed in the first 75 patients that are treated, Day 5 and Day 8 monitoring will be discontinued for the remaining patients enrolled in the study.
2 Week 24 visit is the End of Treatment visit of the double-blind placebo-controlled period.
3 At Day 1 an interim medical history will be performed to complete the screening medical history. Medical events that occur between screening and first dose will be recorded as medical history. All SAEs must be reported from the time of signing the informed consent; AEs are collected after the first dose.
4 Laboratory tests include Hematology and Chemistry. Urinalysis is only performed at Screening and Week 24 only.
5 Serum beta human chorionic gonadotrophin (hCG) at screening, urine beta hCG at each visit. If the urine pregnancy test is positive, do not dose and confirm with a serum pregnancy test.
6 Serology testing will be performed at screening to determine the patient's immune status with respect to the following viruses: Human immunodeficiency virus (HIV) antibodies, anti-hepatitis A virus IgM, hepatitis B surface antigen (HBsAg) and anti-hepatitis B core antigen (HBcAg) IgM, anti-hepatitis C virus (HCV) IgG or IgM. In addition, patients must have documentation of positive Varicella Zoster Virus (VZV) IgG antibody status or complete VZV vaccination at least 30 days prior to first dose of study medication.
7 The TB screening (purified protein derivative) should be performed during the screening period and all testing must be completed prior to administration of study drug on Day 1. As available locally, an interferon gamma release assay such as QuantiFERON Gold test may be used as an alternative screening TB test, or as a confirmatory test to rule out a false positive result using purified protein derivative.
8 Height at screening only.
9 A chest X-ray is not required if performed within 60 days prior to randomization and if documentation is on file.
10 Refer to Table 5 for details of cardiac monitoring.
11 At the Week 24 visit (Day 169), cardiac monitoring procedures will also be performed on the first day of dosing for patients who continue in the optional extension period following the first dose of that period. Refer to Table 5 for details of cardiac monitoring.
12 At Week 24, patients will be given the option to enter an extension period. The blinded extension study will continue until all patients who choose to participate have received at least 48 weeks of treatment in the extension. Patients assigned to either RPC1063 treatment group during the double-blind placebo-controlled period will continue in their respective treatment groups during the blinded extension; patients assigned to the placebo treatment group will be re-randomized in a 1:1 fashion to receive one of the two RPC1063 treatment groups for the blinded extension. For all patients in the blinded extension, the first dose of study medication will be administered on a separate day after the Week 24 visit procedures are completed, and may be performed up to 7 days after the Week 24 visit date. Upon randomization, the 7-day dose titration regimen will be administered, study medication will be dispensed, and first dose cardiac monitoring procedures will be performed. (See Table 5)
13 Three MSFC practice assessments must be performed before baseline. These may be performed at the screening visit, or at any time between the screening and baseline visit.
14 Pulmonary function tests will include FEV_1 and FVC measurements at all the above indicated visits. In addition, DLCO (if available locally) will be assessed at screening and Week 24. If any abnormalities occur, they will be followed until such time as resolution is confirmed or no further improvement is expected by the investigator (based on a follow-up period of not less than 3 months).
15 If abnormal OCT findings, or visual signs or symptoms of macular edema are observed, a general ophthalmologic examination including eye history, visual acuity, and dilated ophthalmoscopy will also be performed.
16 PK samples on Day 1 and Week 12 will be taken predose. PK samples at Week 4 and Week 24 will be taken 2 to 6 hours following study drug administration; patients should record the time of study drug administration for these visits. An additional PK sample will be obtained for patients with any AE resulting in unblinding, discontinuation, or SAE.

Table 2 Schedule of Assessments – Part A: Optional Blinded Extension, Early Termination, and Follow-up Visits

Procedure	Blinded Extension[1]			Un-scheduled Relapse Visit[4]	Early Term[5]	Follow Up Visit
	Day 183 (W26)[2] (±1d)	Every 12 weeks[3] (±5d)	End of Study[3]			4 weeks after last dose (±5d)
Clinical laboratory tests[6]		X	X	X	X	X
Urine/serum pregnancy (women of childbearing potential only)[7]		X	X		X	X
Coagulation panel			X		X	
Total Ig (IgA, IgG, IgM)						
Complete physical examination			X		X	
Weight			X		X	
Vital Signs	X	X	X	X	X	X
12-lead ECG	X	X	X		X	X
Study drug administration	X	X	X			
Administer study drug at clinic						
Dispense study drug and patient diary		X				
Study drug accountability and compliance check	X	X	X		X	
Brain MRI		X[8]	X[8]		X	
EDSS and neurological examination		X	X	X	X	
MSFC and LCLA		X	X	X	X	
MSQOL-54			X		X	
Pulmonary function tests[9]		X	X		X	
OCT[10]			X		X	
Dermatological (skin) examination			X			
C-SSRS	X	X	X	X	X	X
Standard PK sampling[11]					X	
Plasma biomarkers						
Prior/Concomitant therapy	X	X	X	X	X	X
AEs/SAEs	X	X	X	X	X	X

ECG = electrocardiogram, MRI = magnetic resonance imaging, EDSS = Expanded Disability Status Scale, MSFC = Multiple Sclerosis Functional Composite, LCLA = low-contrast letter acuity test; MSQOL = Multiple sclerosis quality of life, OCT = optical coherence tomography, C-SSRS = Columbia- Suicide Severity Rating Scale, PK = pharmacokinetics, AE/SAE = adverse events/serious AE

Footnotes to Table 2

1 The blinded extension is optional.
2 A visit for safety assessments will be performed 14 days after the first dose of study medication.
3 Patients will continue in the optional Blinded Extension period at least until the last patient reaches Week 72 and may continue on blinded therapy until a long-term safety study is available. For patients who continue in the Blinded Extension period beyond the nominal Week 72 visit, the assessments indicated will be repeated at 12-week intervals (with the exception of MRI which will be repeated annually). The End of Study visit will be performed 12 weeks after the previous scheduled visit and after all active patients have received at least 48 weeks of treatment in the Blinded Extension.
4 The Unscheduled Relapse Assessment Visit will be conducted in case of a suspected of possible relapse (see Section 9.1.2.3). After the Unscheduled Relapse Assessment Visit, patients should return to their usual visit schedule.
5 Patients who prematurely discontinue study treatment will be asked to complete an Early Termination visit.
6 Laboratory tests include Hematology, Chemistry, and Urinalysis
7 Urine beta hCG at each visit. If the urine pregnancy test is positive, do not dose and confirm with a serum pregnancy test.
8 For patients continuing to the blinded extension, MRI scans will be performed at approximately Weeks 48 and 72, and annually after Week 72. End of Study visit will include an MRI if it corresponds with this schedule.
9 Pulmonary function tests will include FEV_1 and FVC measurements at all the above indicated visits. In addition, DLCO will be assessed at the Early Termination visit if the patient prematurely discontinues the study. If any abnormalities occur, they will be followed until such time as resolution is confirmed or no further improvement is expected by the investigator (based on a follow-up period of not less than 3 months).
10 If abnormal OCT findings, or visual signs or symptoms of macular edema are observed, a general ophthalmologic examination including eye history, visual acuity, and dilated ophthalmoscopy will also be performed.
11 An additional PK sample will be obtained for patients with any AE resulting in unblinding, discontinuation, or SAE.

Table 3 Schedule of Assessments – Part B: Screening, Baseline, and Treatment Period Visits

Visit	Screening	Baseline	Active-Comparator Treatment Period								
		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
Month	**M -1**	**M1**	**M1**	**M3 (W13)**	**M6 (W26)**	**M9 (W39)**	**M12 (W52)**	**M15 (W65)**	**M18 (W78)**	**M21 (W91)**	**M24 (W104)**
Study Day	-30 to -1	1	15 (±1)	92 (±5)	183 (±5)	274 (±5)	365 (±5)	456 (±5)	547 (±5)	638 (±5)	729 (±5)
Procedure											
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Medical history	X	X[1]									
Clinical laboratory tests[2]	X	X		X	X	X	X	X	X	X	X
Urine/serum pregnancy test (women of childbearing potential only)[3]	X	X		X	X	X	X	X	X	X	X
Coagulation panel	X						X				X
sTSH	X						X				X
Total Ig (IgA, IgG, IgM)											
Viral serology[4], and syphilis RPR	X										
TB testing[5]	X										
Complete physical examination	X						X				X
Height[6] and weight	X	X					X				X
Vital signs, body temp[15]	X	X[8]	X	X	X	X	X	X	X	X	X
Chest X-ray[7]	X										
12-lead ECG	X	X[8]	X				X				X
Enroll patient, contact IVRS	X										
Randomization		X									
Study drug administration[9]		X	X	X	X	X	X	X	X	X	X
Administer study drug at clinic		X					X				
Dispense study drug and patient diary		X		X	X	X	X	X	X	X	
Study drug accountability and compliance check			X	X	X	X	X	X	X	X	X
Brain MRI[10]	X						X				X
EDSS and neurological examination	X			X	X	X	X	X	X	X	X
MSFC and LCLA	X[11]	X			X		X		X		X
MSQOL-54		X			X		X		X		X
Pulmonary Function Tests[12]	X			X	X		X				X
OCT[13]	X				X		X				X

Visit	Screening	Baseline	Active-Comparator Treatment Period								
		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
Month	**M -1**	**M1**	**M1**	**M3 (W13)**	**M6 (W26)**	**M9 (W39)**	**M12 (W52)**	**M15 (W65)**	**M18 (W78)**	**M21 (W91)**	**M24 (W104)**
Study Day	-30 to -1	1	15 (±1)	92 (±5)	183 (±5)	274 (±5)	365 (±5)	456 (±5)	547 (±5)	638 (±5)	729 (±5)
Procedure											
Dermatological (skin) examination	X						X				X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X
Standard PK sampling[14]		X			X		X				X
Plasma biomarkers											
Prior/Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X
AEs/SAEs[1]	X	X	X	X	X	X	X	X	X	X	X

sTSH = sensitive Thyroid stimulating hormone, RPR = rapid plasma reagin; TB = tuberculosis, ECG = electrocardiogram, IVRS = interactive voice response system, MRI = magnetic resonance imaging, EDSS = Expanded Disability Status Scale, MSFC = Multiple Sclerosis Functional Composite, LCLA = low-contrast letter acuity test; MSQOL = Multiple sclerosis quality of life, OCT = optical coherence tomography, C-SSRS = Columbia- Suicide Severity Rating Scale, PK = pharmacokinetics, AE/SAE = adverse events/serious AE

Footnotes to Table 3

1 At Visit 1 an interim medical history will be performed to complete the screening medical history. Medical events that occur between screening and first dose will be recorded as medical history. All SAEs must be reported from the time of signing the informed consent; AEs are collected after the first dose.

2 Laboratory tests include Hematology, Chemistry, and Urinalysis.

3 Serum beta-hCG at screening, urine beta-hCG at each visit. If the urine pregnancy test is positive, do not dose and confirm with a serum pregnancy test.

4 Serology testing will be performed at screening to determine the patient's immune status with respect to the following viruses: Human immunodeficiency virus (HIV) antibodies, anti-hepatitis A virus IgM, hepatitis B surface antigen (HBsAg) and anti-hepatitis B core antigen (HBcAg) IgM, anti-hepatitis C virus (HCV) IgG or IgM. In addition, patients must have documentation of positive Varicella Zoster Virus (VZV) IgG antibody status or complete VZV vaccination at least 30 days prior to first dose of study medication.

5 The TB screening test (purified protein derivative) should be performed during the screening period and all testing must be completed prior to administration of study drug on Day 1 As available locally, an interferon gamma release assay such as QuantiFERON Gold test may be used as an alternative screening TB test or as a confirmatory test to rule out a false positive result using purified protein derivative.

6 Height at screening only.

7 A chest X-ray is not required if performed within 60 days prior to randomization and if documentation is on file.

8 Refer to Table 5 for details of cardiac monitoring.

9 RPC1063 (0.5 or 1 mg) will be administered daily for the study duration; IFN β-1a 30 μg will be administered by IM injection weekly.

10 Brain MRI scans will include a T2 and T1 scan (with and without Gadolinium) and will be performed at screening and then yearly.

11 Three MSFC practice assessments must be performed before baseline. These may be performed at the screening visit, or at any time between the screening and baseline visit.

12 Pulmonary function tests will include FEV_1 and FVC measurements at all the above indicated visits. In addition, DLCO will be assessed at screening, Month 12, and Month 24. If any abnormalities occur, they will be followed until such time as resolution is confirmed or no further improvement is expected by the investigator (based on a follow-up period of not less than 3 months).

13 If abnormal OCT findings, or visual signs or symptoms of macular edema are observed, a general ophthalmologic examination including eye history, visual acuity, and dilated ophthalmoscopy will also be performed.

14 PK sample on Day 1 and Month 12 will be taken predose. PK samples at Month 6 (Visit 4) and Month 24 (Visit 10) will be taken 2 to 6 hours following study drug administration; patients should record the time of study drug administration for these visits. An additional PK sample will be obtained for patients with any AE resulting in unblinding, discontinuation, or SAE.

15. Body temperature is recorded at screening, EOT or early term visits only.

Table 4 Schedule of Assessments – Part B: Unscheduled Relapse, Early Termination, and Follow-up Visits

Procedure	**Unscheduled Relapse Visit[1]**	**Early Termination[2]**	**Follow Up Visit** 4 weeks after last dose
Clinical laboratory tests[3]	X	X	X
Urine/serum pregnancy test (females of childbearing potential only)[4]		X	X
Coagulation panel		X	
Total Ig (IgA, IgG, IgM)			
Complete physical examination		X	
Weight		X	
Vital signs	X	X	X
12-lead ECG		X	X
Study drug accountability and compliance check		X	
Brain MRI[5]		X	
EDSS and neurological examination	X	X	
MSFC and LCLA	X	X	
MSQOL-54		X	
Pulmonary Function Tests[6]		X	
OCT[7]		X	
Dermatological (skin) examination		X	
C-SSRS	X	X	X
Standard PK sampling		X	
Plasma biomarkers			
Prior/Concomitant therapy	X	X	
AEs/SAEs	X	X	X

ECG = electrocardiogram, MRI = magnetic resonance imaging, EDSS = Expanded Disability Status Scale, MSFC = Multiple Sclerosis Functional Composite, LCLA = low-contrast letter acuity test; MSQOL = Multiple sclerosis quality of life, OCT = optical coherence tomography, C-SSRS = Columbia- Suicide Severity Rating Scale, PK = pharmacokinetics, AE/SAE = adverse events/serious AE

Footnotes to Table 4

1 The Unscheduled Relapse Assessment Visit will be conducted in the case of a suspected relapse (see Section 9.1.2.3). After the Unscheduled Relapse Assessment Visit, patients should return to their usual visit schedule.
2 Patients who prematurely discontinue study treatment will be asked to complete an Early Termination visit.
3 Laboratory tests include Hematology, Chemistry, and Urinalysis.
4 Urine beta-hCG. If the urine pregnancy test is positive, do not dose and confirm with a serum pregnancy test.
5 Brain MRI scans will include a T2 and T1 scan (with and without Gadolinium).
6 Pulmonary function tests will include FEV_1 and FVC measurements, and DLCO. If any abnormalities occur, they will be followed until such time as resolution is confirmed or no further improvement is expected by the investigator (based on a follow-up period of not less than 3 months).
7 If abnormal OCT findings, or visual signs or symptoms of macular edema are observed, a general ophthalmologic examination including eye history, visual acuity, and dilated ophthalmoscopy will also be performed.

Table 5 Cardiac Monitoring During Dose Titration – Days 1, 5, and 8

	Cardiac Monitoring								
	Day 1/Part A Day 169 (W24)				Day 5[1]				Day 8[1]
Procedure	Predose	Hourly for 6 hours	At Hour 6	Continuous Monitoring for 24 hours	Predose	Hourly for 6 hours	At Hour 6	Continuous Monitoring for 24 hours	Continuous Monitoring for 24 hours
Vital signs	X	X			X	X			
12-lead ECG	X[2]		X		X[2]		X		
Holter monitoring[3]				X[4]				X	X
Assess Discharge Criteria[5]			X[5]				X[6,7]		

ECG = electrocardiogram

1 Day 5 and Day 8 procedures will be conducted in the first 75 patients
2 Baseline or predose ECG should be provided by the site and be available for comparison to the postdose ECG in order to determine if discharge criteria are met.
3Begin 15 minutes predose and continue for 24 hours after dose.
4 Holter monitoring will be performed on Day 1 for Part A patients only, and will not be performed in Part B or on the Week 24 (Day 169) visit for Part A.
5 See Section 10.2.1.1 for discharge criteria. Additional observation should be instituted until the finding has resolved in the following situations: heart rate 6 hours post-dose is < 45 bpm; heart rate 6 hours post-dose is at the lowest value post-dose; ECG 6 hours post-dose shows new onset second degree or higher AV block; the ECG 6 hours post-dose shows a prolonged QTcF interval (>450 msec males, >470 msec females).
6 If any safety issues are identified, then the monitoring guidelines in Section 10.2.1.1 should be followed.
7 The first-dose monitoring strategy should be repeated at Day 8 if any cardiac safety issues were observed at Day 5. See the monitoring guidelines in Section 10.2.1.1 for further details.

9.1.2. Additional Information

9.1.2.1. Definition of Study Staff

At each study site the staff will consist at minimum of the following:

- A treating investigator
- A blinded evaluator
- A blinded MSFC assessor (if MSFC is not performed by the blinded evaluator)
- A treating nurse or study coordinator
- An MRI technician
- A pulmonary function testing center
- A pharmacist or authorized designee

Back-ups for all personnel should be selected at each site in case of absence.

Requirements and responsibilities of the treating investigator and the blinded evaluator are described in Section 9.1.2.2 below.

The treating nurse (or study coordinator) will be responsible for assisting the treating investigator in patient management, including the treatment of AEs, the treatment and assessment of disease relapses, and the recording of AEs and concomitant medication, collection of blood samples and obtaining vital signs.

The MRI Technician will be responsible for performing a brain MRI scan with and without Gadolinium at all protocol-required timepoints. Study-specific MRI procedures and protocols must be followed. MRI evaluations will be performed centrally. Refer to the MRI Manual for details.

Pulmonary function tests will be performed at high quality pulmonary function laboratory with the appropriate certification.

The Pharmacist (or authorized designee) will be responsible for storage, distribution, and accountability of study treatment.

9.1.2.2. Blinded Evaluator

A "dual assessor" approach will be used to evaluate efficacy and safety to prevent potential unblinding as result of observed efficacy, AEs, or laboratory changes. Each site will have two investigators: a principal or treating investigator and a blinded evaluator (examining investigator or rater).

The treating investigator is the safety assessor and should be a neurologist experienced in the care of MS patients. The treating investigator will have access to both safety and efficacy data and will make all treatment decisions based on the patient's clinical response and laboratory findings. The treating investigator will be responsible of the management of the routine neurological care of the patient, assessment (including assignment of causality) and treatment of

AEs including suspected neurological worsening and MS relapses, and review of central laboratory results.

The blinded evaluator is the efficacy assessor and should be a neurologist or other health care practitioner trained in administering the Neurostatus version of the EDSS. The examining investigator will be responsible for administration of the EDSS and will not have access to other patient data or to prior EDSS data when performing exams. The blinded evaluator may also perform the MSFC and LCLA, or these may be performed by a separate, blinded MSFC assessor trained in administering the MSFC and LCLA. The blinded evaluator (and MSFC assessor, if applicable) must not be involved with any other aspect of patient care and management and must remain blinded to AEs, concomitant medications, laboratory data, MRI data, and any other data that have the potential of revealing the treatment assignment. There should be no communication about the study patients between the treating investigator and the blinded evaluator or any other information flow about the study patients that could potentially unblind the blinded evaluator.

The treating investigator and the blinded evaluator will not be allowed to switch roles. Back-ups for all personnel should be selected at each site in case of absence. However, whenever possible, the blinded evaluator (and MSFC assessor, if applicable) should remain constant for all EDSS, MSFC and LCLA assessments performed for a given patient.

Patients will be instructed to not disclose their treatment assignment or symptoms related to their treatment regimen, injection sites should be covered. Blinded evaluators and MSFC assessors should communicate with patients only as needed to complete the neurologic examinations and to assess the EDSS, MSFC and LCLA scores.

Central blinded examiners who have no knowledge of a patient's treatment or outcome will perform MRI evaluations.

9.1.2.3. Identification and Treatment of MS Relapse

A relapse is defined as the occurrence of new or worsening neurological symptoms attributable to MS and immediately preceded by a relatively stable or improving neurological state of at least 30 days. The new or worsening neurological symptoms must be accompanied by objective neurological worsening, based on examination by the blinded evaluator, consistent with an increase of at least half a point on the EDSS, or 2 points on one of the appropriate Functional System (FS) scores, or 1 point on two or more of the appropriate FS scores.

The change in FS scale scores should correspond to the patient's symptoms (e.g. patient reported change in visual acuity should correspond to a change in the vision FS score). Symptoms must persist for > 24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reactions to concomitant medications). EDSS and FS scores documented by the blinded evaluator at the time of the relapse will be verified by that the treating investigator who will determine whether change in EDSS and FS scores meet the protocol defined relapse definitions and determine whether relapse treatment will be administered.

When a patient experiences new or worsening symptoms that may indicate a possible relapse, he/she should telephone the treating investigator within 48 hours of symptoms onset. The treating investigator will conduct a telephone questionnaire and, as necessary, will arrange an unscheduled relapse assessment visit. The treating physician will then assess whether the

symptoms had onset in the presence of fever or infection. If fever or infection can be excluded, a neurological examination by the independent evaluating physician must be arranged as soon as possible, preferably within 7 days of the onset of symptoms. The blinded evaluator should perform the EDSS, and the blinded evaluator or blinded MSFC assessor should perform the MSFC and LCLA.

If no neurological worsening is observed, the patient will continue to attend the next scheduled study visit.

If a non-MS related disease is suspected, the treating investigator should perform additional assessments to determine the cause of worsening. The Medical Monitor should be contacted as needed to discuss any question regarding eligibility for further treatment or study participation.

The treating investigator will be responsible for the diagnosis and treatment of the patient's symptoms; the blinded evaluator will only be responsible for performing the EDSS.

Patients who experience a relapse may receive treatment with IV corticosteroids, if judged to be clinically appropriate by the investigator. The following standardized treatment regimen should be used: as warranted, 1.0 g IV methylprednisolone per day for a maximum of 5 consecutive days. Any deviation from the standardized treatment regimen should be discussed in advance with the Medical Monitor.

The investigator should attempt to maintain therapies or treatments for symptoms related to MS (e.g., spasticity, incontinence, pain, fatigue) reasonably constant throughout the study. However, changes may be made if appropriate for a patient's well-being in the clinical judgment of the treating investigator.

After a MS relapse occurred the treating investigator will discuss with the patient the treatment alternatives outside of the study. If the patient decides to continue with the study, the patient will have to re-consent for the study and the Investigator will document that an adequate discussion about treatment alternatives took place.

9.1.2.4. MS Disease Progression

The MS disease progression is defined as a sustained worsening in EDSS of 1.0 points or more, confirmed after a 3 and 6 month period. Confirmation of MS disease progression must not occur at the time of a relapse. If the patient is scheduled to be evaluated to confirm their disability at the time of a relapse, the disability event must be assessed at a later visit, which may be the next scheduled visit, or an unscheduled visit conducted after the relapse has resolved. In case of MS disease progression the treating investigator will discuss with the patient the treatment alternatives outside of the study. If the patient decides to continue with the study, the patient will have to re-consent for the study and the Investigator will document that an adequate discussion about treatment alternatives took place.

9.1.2.5. Adverse Events of Special Interest

There are a number of potential safety risks associated with RPC1063 administration that are based on the general concerns around immunosuppression (serious and opportunistic infections, malignancies), the safety findings from the Phase 1 clinical study, and the safety profile of the approved s1pr agonist fingolimod and other S1PR agonists. These include serious infections as well as the clinical consequences of its effect on the various organ systems including cardiac and

pulmonary organ systems. Other potential risks observed in the fingolimod experience, although not observed in the Phase 1 clinical trial, include hepatic, ophthalmological and dermatological effects.

Therefore, target AEs of special interest will be closely monitored in the RPC01-201 study. These AEs include infections, malignancies, cardiac (bradycardia and heart conduction abnormalities), pulmonary function (decline in FEV_1, FVC, and DLCO measurements), ophthalmic (macular edema), hepatic (LFTs elevation), and dermatologic (cutaneous malignancy) abnormalities. If any abnormalities occur, they will be followed until such time as resolution is confirmed or no further improvement is expected by the investigator (based on a follow-up period of not less than 3 months). Further details on monitoring of these AEs are provided in Section 12.4.

9.2. Discussion of Dose Rationale

Previous nonclinical pharmacology, toxicology, and clinical experience were considered for the selection of RPC1063 doses in this study. In the nonclinical and clinical setting, the human doses of RPC1063 were assessed by benchmarking with fingolimod and other S1P1R agonists. The reduction in peripheral absolute lymphocyte counts was employed as a PD marker for the mechanism of drug action and for the selection of potential efficacious RPC1063 doses.

Based upon publically available clinical efficacy data and PD data for other S1P1 modulators evaluated in multiple sclerosis (fingolimod and BAF312), the high dose (1 mg) of RPC1063 to be used in this study should produce a target steady state lymphocyte decrease of -70%. For fingolimod, an approximately 70% decrease in lymphocyte count was associated with the marketed dose of 0.5 mg; significant reductions in the ARR and in the rate of disability progression with respect to placebo and reductions in the ARR with respect to interferon beta-1have been reported at this dose level (Cohen, 2010; Kappos, 2010). In addition, it does not appear that doses that produce greater than a 70% peripheral lymphocyte count reduction are necessary as the fingolimod higher doses of 1.25 mg and 5 mg demonstrated similar efficacy to 0.5 mg.

In the case of the S1P1 and S1P5 receptor modulator BAF312, statistically significant reduction in ARR at 6 months and/or meaningful reductions in combined active lesions at 3 months were observed at doses of 1.25, 2 and 10 mg, but not at doses of 0.25 and 0.5 mg, indicating that a certain threshold of lymphocyte reduction is required to observe clinical efficacy (Selmaj, 2011). Based upon 28 day lymphocyte dose response data for BAF312, the threshold lymphopenia decrease at which a therapeutic benefit was measurable was ~-50% (i.e. estimated lymphopenia at a dose of 1.25 mg) (Nuesslein-Hildesheim, 2011). Consistent with the fingolimod PD response versus efficacy relationship, the BAF312 data suggest that -70% lymphocyte reduction would also be associated with maximal efficacy for this compound in MS (Wallström, 2011). The BAF312 data described above suggests that a 50% reduction in lymphocyte count was associated with measurable, but less than maximal efficacy, and therefore this could be a reasonable PD target upon which to select the low dose for this study.

Therefore, two dose levels will be selected for RPC1063, both administered as a daily oral capsule. The first dose level will be a high dose (1 mg) targeting ~70% peripheral lymphopenia and a lower dose (0.5 mg) targeting ~50% peripheral lymphopenia.

Based upon Phase 1 findings, an RPC1063 dose of 1 mg is predicted to produce a 70% decrease in the lymphocyte count at steady state and therefore this is an appropriate high dose for the study that will produce a clinical response level in a similar range of what has been observed in the clinical studies of fingolimod. An RPC1063 dose of ~0.5 mg is predicted to produce a 50% decrease in lymphocyte count at steady state and therefore this is an appropriate low dose for the study that will likely be clinically effective and potentially further improve the safety profile of RPC1063therapy. Nonclinical and clinical data to date supports the evaluation of both the 0.5 and 1 mg doses in longer-term clinical studies.

Dose titration data from the RPC1063 Phase 1 clinical study provided evidence that the use of dose titration (gradual increasing doses of RPC1063 administered over a 7 day period) seemed to attenuate the reduction in heart rate observed with higher doses of RPC1063 administered without titration. Thus, in order to further improve the cardiac AE profile of RPC1063, an initial 7-day dose titration regimen will be employed for all patients in both Part A and Part B of the study. For patients randomized to receive active treatment with RPC1063 in Part A or Part B, this regimen will consist of 0.25 mg RPC1063 on Days 1-4, 0.5 mg RPC1063 on Days 5-7, and the assigned treatment dose of 0.5 mg or 1 mg RPC1063 starting on Day 8.

9.3. Study Duration

Part A: 24 weeks with an optional blinded extension of at least 48 weeks (total at least 72 weeks)

Patients will have up to a 30-day screening period, followed by a 24-week treatment period (RPC1063 or placebo). A follow-up visit will be performed 4 weeks after the last dose. In addition, patients who complete the 24-week treatment period of Part A will have the option of entering a blinded extension period for at least 48 additional weeks of treatment.

Part B: 24 months

Patients will have up to a 30-day screening period, followed by 24 months of treatment (RPC1063 or IFN β-1A). A follow-up visit will be performed 4 weeks after the last dose.

9.4. Study Population

Eligible patients will be 18 to 55 years of age, inclusive, with a diagnosis of MS according to revised 2010 McDonald criteria (McDonald, 2010; Polman, 2011), with a relapsing course (Lublin, 1996), who had at least one relapse within the last 12 months prior to screening or, if at least one documented relapse occurred within the last 24 months, evidence of at least one GdE lesion on brain MRI should be documented within the last 12 months prior to randomization. Eligible patients should have a baseline EDSS score between 0 and 5.0.

9.4.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following inclusion criteria:

1. MS, as diagnosed by the revised 2010 McDonald criteria
2. Exhibiting a relapsing clinical course consistent with RMS and history of brain MRI lesions consistent with MS
3. Ages 18-55 years, inclusive

4. EDSS score between 0 and 5.0 at baseline
5. Meet one of the following disease activity criteria:
    a. At least 1 documented relapse within the last 12 months prior to screening

    OR

    b. At least 1 documented relapse occurred within the last 24 months prior to screening and evidence of at least 1 GdE lesion on brain MRI within the last 12 months prior to randomization
6. No history of relapse with from 30 days prior to screening until randomization; during this period, patients must have been clinically stable, without systemic corticosteroid treatment or adrenocorticotrophic hormone (ACTH)
7. Ability to provide written informed consent and to be compliant with the schedule of protocol assessments
8. Patients of reproduction potential (males and females) must practice an acceptable method of birth control (acceptable methods of birth control in this study include: surgical sterilization, intrauterine devices, oral contraceptive, contraceptive patch, long acting injectable contraceptive, vasectomy, or double-barrier method [condom or diaphragm with spermicide OR condom and diaphragm]) during study participation and for 30 days after their last dose of treatment of study medication or true sexual abstinence (periodic abstinence [calendar, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception)
9. Patients must have documentation of positive Varicella Zoster virus (VZV) IgG antibody status or complete VZV vaccination at least 30 days prior to study entry

9.4.2. Exclusion Criteria

Candidates will be excluded from entering the study if any of the following exclusion criteria exist at time of enrollment or at the timepoint specified in the individual criterion listed:

1. Primary progressive MS at screening
2. Disease duration of more than 15 years in patients with an EDSS ≤ 2.0
3. Contraindications to MRI or Gadolinium contrast, such as known allergy to Gadolinium contrast dyes, renal insufficiency, claustrophobia, body size incompatible with the scanner, pacemaker, cochlear implants, intracranial vascular clips
4. Incompatibility with beta IFN use (e.g. intolerable side effects) (Part B only), including:
    a. Prior cessation of IFN β-1a therapy due to poor tolerability
    b. Prior cessation of IFN β-1a therapy due to liver function abnormalities or other toxicities
    c. Prior cessation of other IFN-β therapy due to poor tolerability or toxicity that is likely to recur with IFN β-1a therapy

Exclusions Related to General Health - Patients who meet the following criteria related to their general health will be excluded:

5. Pregnancy, lactation, or a positive serum beta hCG measured during screening
6. Clinically relevant hepatic, neurological, pulmonary, ophthalmological, endocrine, renal, or other major systemic disease making implementation of the protocol or interpretation of the study results difficult or that would put the patient at risk by participating in the study in the opinion of the treating investigator
7. Clinically relevant cardiovascular conditions, outlined below

   Part A: Clinically relevant cardiovascular conditions, including history or presence of ischemic heart disease, myocardial infarction, congestive heart failure, stroke, transient ischemic attack, sick sinus syndrome, recurrent syncope, second degree or higher AV block, prolonged QTcF interval (QTcF >_ 450 msec males, > 470 msec females) or relevant risk factors for QT prolongation (e.g., hypokalemia, hypomagnesemia), severe untreated sleep apnea

   Part B: Specific cardiac conditions are excluded, including history or presence of:

   i. Recent (within the last 6 months) occurrence of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, Class III/IV heart failure, sick sinus syndrome, or severe untreated sleep apnea

   ii. Prolonged QTcF interval (QTcF > 450 msec males, > 470 msec females), or at additional risk for QT prolongation (e.g., hypokalemia, hypomagnesemia, congenital long-QT syndrome, concurrent therapy with QT prolonging drugs)

   iii. Patients with other pre-existing stable cardiac conditions who have not been cleared for the study by an appropriate cardiac evaluation by a cardiologist

   Part A and B: Other clinically significant conduction abnormalities or any other significant cardiac condition that could jeopardize a patient's health or put them at significant safety risk during the course of the study in the opinion of the treating investigator.
8. Resting heart rate less than 55 bpm at Screening
9. History of diabetes mellitus

   Part A: Any history of Type 1 or Type 2 diabetes mellitus

   Part B: diabetes mellitus type 1, or uncontrolled diabetes mellitus type 2 with hemoglobin A1c > 7%, or diabetic patients with significant co-morbid conditions such as retinopathy or nephropathy
10. History of uveitis
11. Known active bacterial, viral, fungal, mycobacterial infection, or other infection (including TB or atypical mycobacterial disease [but excluding fungal infection of nail beds, minor URTI and minor skin conditions]) or any major episode of infection that required hospitalization or treatment with IV antibiotics within 30 days of screening or oral antibiotics within 14 days prior to screening

12. History or known presence of recurrent or chronic infection (e.g., hepatitis A, B, or C, HIV, syphilis, TB); recurring urinary tract infections could be allowed
    - Testing for viral serology and syphilis will be performed during screening
13. History of cancer, including solid tumors and hematological malignancies (except basal cell and in situ squamous cell carcinomas of the skin that have been excised and resolved)
14. Suicide attempts in the past or current signs of major depression
15. History of alcohol or drug abuse within 1 year prior to randomization
16. History of or currently active primary or secondary immunodeficiency

Exclusions Related to Medications:

17. Prior use of any investigational agent within 6 months prior to enrollment
18. Receipt of a live vaccine within 4 weeks prior to randomization
19. Non-lymphocyte-depleting disease-modifying MS agents (e.g., glatiramer acetate, interferons) must be discontinued from signing of informed consent
20. Previous treatment with lymphocyte-depleting therapies (e.g., alemtuzumab, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation)
21. Treatment with other immunosuppressant agents such as azathioprine, cyclosporine, methotrexate, or mycophenolate within 6 months prior to randomization
22. Systemic corticosteroid therapy or ACTH use within 30 days prior to screening
23. Prior treatment with lymphocyte trafficking blockers (e.g., natalizumab, fingolimod, other S1P1R agonists)
24. Treatment with intravenous immune globulin (IVIg), plasmapheresis, within 3 months prior to randomization
25. Treatment with other disease modifying therapies (e.g., dimethyl fumarate, teriflunomide, daclizumab, laquinimod) within 3 months prior to randomization
26. Intolerance of or contraindication to oral or IV corticosteroids
27. Use of therapies that are not allowed based on CYP3A4 metabolism within 4 weeks prior to randomization
28. Treatment with medications with a known impact on the cardiac conduction system are excluded (e.g., beta blockers, calcium channel blockers, Class Ia or Class III anti-arrhythmic drugs, and QT prolonging drugs with a known risk of torsades de pointes, e.g., citalopram, chlorpromazine, haloperidol, methadone, and erythromycin)

Exclusions Related to Laboratory Results:

29. Positive rapid plasma reagin
30. Serum creatinine > 1.4 mg/dL for women or > 1.6 mg/dL for men

31. Liver function impairment or persisting elevations of aspartate aminotransferase (SGOT/AST) or alanine aminotransferase (SGPT/ALT) > 1.5 times the ULN, or direct bilirubin > 1.5 times the ULN)
32. Platelet count < 100,000/μL
33. Hemoglobin < 8.5 g/dL
34. Neutrophils < 1500/μL
35. Absolute white blood cell (WBC) count < 3500/μL; absolute lymphocyte count < 800/μL
36. Clinically significant findings on brain MRI scan consistent with conditions other than MS
37. ECG showing any clinically significant abnormality (e.g., acute ischemia, significant heart conduction abnormality (e.g. left bundle branch block))
38. FEV_1 or FVC < 70% of predicted values at screening
39. Presence of > 20 gadolinium-enhancing lesions on baseline brain MRI scan

9.4.3. Considerations for Patients with Co-morbid Conditions

9.4.3.1. Patients with Type 2 Diabetes Mellitus

In Part A of the study, all patients with type 2 diabetes mellitus are excluded. In addition, in both Part A and Part B, patients with type 1 diabetes mellitus are excluded.

Patients with type 2 diabetes mellitus are permitted in Part B of the study if their disease is controlled, with hemoglobin A1c ≤ 7% at screening. Such patients should receive appropriate diabetes management during the study, with treatment as deemed appropriate, with the goal of maintaining stable disease with hemoglobin A1c ≤ 7% throughout the trial.

Gestational diabetes and steroid induced diabetes occurring in the past and resolved prior to screening are not exclusionary.

The treating investigator should ensure that diabetic patients that are included in the study are closely monitored for signs or symptoms of macular edema. (See Section12.4) Patients with diabetic uveitis or retinopathy or other co-morbid conditions due to their diabetes are excluded.

Duration of disease and medication history for 3 months prior to randomization and throughout the study will be recorded in source documents and in the eCRF.

9.4.3.2. Patients with History of Cardiac Disease

In Part A of the study, patients with any clinically relevant cardiovascular conditions, as listed out in the exclusion criteria (Section 9.4.2), are excluded from participating in the study.

In Part B, patients with some pre-existing cardiac conditions, who have stable disease and would not be placed at significant safety risk by participating in the study, may be considered for participation in Part B of the study. Please refer to Section 9.4.2 for a list of cardiac exclusion criteria for Part B. These patients should have a cardiology consultation to determine whether it is appropriate for them to participate in Part B of the study and whether they need additional

cardiac monitoring, such as being monitored for an extended period of time and/or possible extended continuous ECG monitoring overnight in a medical facility.

If more intensive monitoring is not deemed necessary by the consulting cardiologist, these patients will follow the detailed first dose monitoring procedures as outlined in Section10.2.1.1. The treating investigator should ensure these patients included in the study are closely monitored for signs of any bradycardia or other rhythm disturbances after the first dose of RPC1063, as these patients may be at higher risk for cardiac adverse events.

9.4.4. Withdrawal of Patients from Study Medication and/or the Study

9.4.4.1. Discontinuation of Study Medication

Reasons for discontinuation include, but are not limited to the following:

- Investigator decision

  The Treating Investigator may discontinue study medication if it is determined that it is not safe or in the patient's best interest to receive further treatment. The Medical Monitor should be promptly notified of the decision.

- Noncompliance: after consultation between the investigator, the Medical Monitor, or Study Monitor, and the sponsor when appropriate, a patient may be discontinued from study medication for failure to comply with protocol requirements
- Intercurrent illness: A patient may be discontinued from study medication if, in the judgment of the treating investigator, the patient develops an intercurrent illness or complication that is not consistent with the protocol requirements or that, in any way, justifies discontinuation of study medication.
- Protocol-defined adverse events of special interest (see Section 12.4):
  - Confirmed AST or ALT >5 times the upper limit of the normal range, confirmed upon retest within 14 days of the original lab value (unless determined by the investigator to not be of hepatic origin)
  - A diagnosis of macular edema, which is new or worsening since baseline
  - FEV1 or FVC <50% of predicted values
- If the patient becomes pregnant
- Sponsor termination or suspension of the study

All patients who discontinue study medication should complete an Early Termination Visit (see Table 2 [Part A] and Table 4 [Part B]). Unless the patient withdraws consent or is lost to follow-up, they will be asked to undergo a follow-up visit 4 weeks after the last dose for the collection of safety data including lymphocyte recovery and to assess their disease status. Alternative treatment for multiple sclerosis (with the exception of medication given in the context of another clinical trial) can be started, if needed, after the early termination visit.

The reason for discontinuation of study medication will be recorded in the clinical records and the patient's eCRF.

9.4.4.2. Withdrawal of Patients From the Study

Patients must be withdrawn from the study for any one of the following reasons:

- The patient is lost to follow up (i.e., those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show due diligence by documenting in the source documents steps taken to contact the patient (e.g., dates of telephone calls, registered letters).
- Patient withdrawal of consent. Every effort should be made within the bounds of safety and patient choice to have each patient complete the study. If a patient withdraws consent, the only additional study data to be collected will be the follow up of SAEs as mandated by the protocol.

The reason for the patient's withdrawal from the study must be recorded in the clinical records and the patient's eCRF.

9.5. Treatment

9.5.1. Treatments Administered

The Investigator must ensure that the investigational product will be used only in accordance with the protocol.

Part A of the study is randomized and double-blinded with regard to treatment with RPC1063 and matching placebo in order to prevent bias in treatment allocation and in the assessment of effect. The Investigator site personnel, as well as the Sponsor and their representatives involved in the monitoring or conducting the study, and the patients will all be blinded to the study drug codes.

Part B of the study is randomized and double-blind, double-dummy with regards to treatment with RPC1063 or IFN β-1a and their corresponding matching placebo in order to prevent bias in treatment allocation and in the assessment of effect. The prolonged treatment period (24 months) will provide additional safety and efficacy data; information that is relevant to RMS, a chronic, highly variable, slowly progressing disease.

In both Part A and Part B of the study, a "dual assessor" approach will be used to evaluate efficacy and safety to prevent potential unblinding as result of observed efficacy, AEs, or laboratory changes

Part A

In Part A, patients will be randomly assigned 1:1:1 on Day 1 to one of following 3 treatment regimens:

- Placebo oral capsule daily for 24 weeks
- 0.5 mg RPC1063 oral capsule daily for 24 weeks
- 1 mg RPC1063 oral capsule daily for 24 weeks

For all patients in Part A, initial study treatment will consist of a 7-day dose titration regimen as follows (see Table 6): for patients randomized to receive active treatment with RPC1063, this regimen will consist of 0.25 mg RPC1063 starting on Day 1 for 4 days and 0.5 mg RPC1063

starting on Day 5 for 3 days. All patients will be dosed with their assigned treatment level beginning on Day 8.

Table 6 Titration Schedule for the RPC1063 Treatment Groups in Part A

	RPC1063/Placebo dose (# capsules)		
Assigned treatment	**Days 1 to 4**	**Days 5 to 7**	**From Day 8 on**
RPC1063 0.5 mg	0.25 mg (1 x 0.25 mg capsule)	0.5 mg (2 x 0.25 mg capsules)	0.5 mg (1 x 0.5 mg capsule)
RPC1063 1 mg	0.25 mg (1 x 0.25 mg capsule)	0.5 mg (2 x 0.25 mg capsules)	1 mg (1 x 1 mg capsule)
Placebo	Placebo (1 capsule)	Placebo (2 capsules)	Placebo (1 capsule)

Study medication will begin following randomization (Section 13.4) on Day 1. Patients will take capsule(s) daily through Week 24.

Capsule dosing: dosing will be once daily in the morning in fasting conditions (before breakfast).

On days of study visits on which a pre-dose PK sample will be obtained (Day 1 and Week 12 in Part A, Day 1 and Month 12 in Part B), patients should be instructed to withhold the dose and their morning meal until the office visit, and dose will be administered during the visit.

Part A Blinded Extension Period

In the blinded extension period of Part A, patients will receive 1 of the 2 following treatment regimens:

- 0.5 mg RPC1063 oral capsule daily beginning on Week 25
- 1 mg RPC1063 oral capsule daily beginning on Week 25

RPC1063 0.5 mg or 1 mg patients who have completed the 24-week placebo-controlled treatment period and who choose to participate in the blinded extension period will continue in their respective treatment groups.

Placebo patients who have completed the 24-week placebo-controlled treatment period and who choose to participate in the blinded extension period will be randomized 1:1 to either the 0.5 mg or 1 mg RPC1063 treatment regimen.

All patients who participate in the optional blinded extension period will have an initial 7-day dose titration period as shown in Table 6: 0.25 mg RPC1063 starting on Day 1 for 4 days and 0.5 mg RPC1063 starting on Day 5 for 3 days. Day 1 cardiac monitoring procedures will also be performed on the first day of dose titration, as shown in Table 5. (Holter monitoring will not be included in these cardiac monitoring procedures.) Patients will be dosed with their assigned treatment level beginning on Day 8.

Patients who opt to enter the optional, blinded extension period will continue to receive study drug until all patients who choose to participate have received at least 48 weeks of treatment (total of at least 72 weeks, 24 weeks in the placebo-controlled period and at least 48 weeks in the blinded extension).

Treatment in case of relapse is described in Section 9.1.2.3.

Part B

In Part B, patients will be randomized 1:1:1 to receive one of the following 3 regimens:

- IFN β-1a 30 μg IM injection weekly for 24 months
- 0.5 mg RPC1063 oral capsule daily for 24 months
- 1 mg RPC1063 oral capsule daily for 24 months

Dosing will begin following randomization on Day 1.

Part B will be use a double-dummy design. Thus, patients randomized to RPC1063 0.5 or 1 mg will also receive weekly matching placebo IM injections and patients randomized to IFN β-1a 30 μg will also receive daily matching placebo oral capsules.

For all patients in Part B, initial study treatment will consist of a 7-day dose titration regimen as shown in Table 7: for patients randomized to receive treatment with RPC1063, this regimen will consist of 0.25 mg RPC1063 starting on Day 1 for 4 days, and 0.5 mg RPC1063 starting on Day 5 for 3 days. All patients will be dosed with their assigned RPC1063 treatment level beginning on Day 8. Patients randomized to IFN β-1a 30 μg will receive RPC1063-matching placebo titration kits.

Table 7 Titration Schedule for the RPC1063 Treatment Groups in Part B

	RPC1063/IFN β-1a dose (# RPC1063/Placebo capsules)			
Assigned treatment	**Day 1**	**Days 2 to 4**	**Days 5 to 7**	**Day 8***
RPC1063 0.5 mg	0.25 mg RPC1063 (1 x 0.25 mg capsule) + Placebo IM injection	0.25 mg RPC1063 (1 x 0.25 mg capsule)	0.5 mg RPC1063 (2 x 0.25 mg capsules)	0.5 mg RPC1063 (1 x 0.5 capsule) + Placebo IM injection
RPC1063 1 mg	0.25 mg RPC1063 (1 x 0.25 mg capsule) + Placebo IM injection	0.25 mg RPC1063 (1 x 0.25 mg capsule)	0.5 mg RPC1063 (2 x 0.25 mg capsules)	1 mg RPC1063 (1 x 1 mg capsule) + Placebo IM injection
IFN β-1a 30 μg	IFN β-1a 30 μg- IM injection + Placebo (1 capsule)	Placebo (1 capsule)	Placebo (2 capsules)	IFN β-1a 30 μg- IM injection + Placebo (1 capsule)

* From Day 8 on, patients will continue receiving weekly IM injections (IFN β-1a/ placebo) and daily capsules (RPC1063/placebo) according to the assigned treatment level

IFN β-1a 30 μg (and matching placebo) will be supplied in sealed plastic trays containing one prefilled syringe for IM injection for each dosing interval. Patients will be instructed by a nurse or physician how to self-administer injections. The first injection will be self-administered under the supervision of a nurse or physician. Thereafter, patients will self-administer their study treatment (IFN β-1a or matching placebo) once weekly. Further instructions on how patients

should self-inject are provided in the study injection guide (information for the user) that will be provided to the patients.

RPC1063 and matching placebo capsules will be taken in fasting conditions as described above in Part A.

Treatment in case of relapse is described in Section 9.1.2.3.

On the days of IFN β-1a/placebo IM injection administration, prophylactic treatment of flu-like symptoms is recommended as follows:

- Acetaminophen (paracetamol) or ibuprofen within 1 hour prior to each IFN β-1a injection, and then approximately every 6 hours for the 24 hours following each injection.

If the patient cannot take either acetaminophen (paracetamol) or ibuprofen, then the patient may take:

- Naproxen within 1 hour prior to IFN β-1a injection, and then approximately every 12 hours for the 24 hours following each injection.

If the patient cannot take acetaminophen (paracetamol), ibuprofen, or naproxen, then:

- Aspirin may be administered within 1 hour prior to each IFN β-1a injection and then approximately every 4 to 6 hours for the 24 hours following each injection.

Patients may take additional doses of acetaminophen (paracetamol), ibuprofen, naproxen, or aspirin within a 24-hour period as necessary for the relief of IFN-related flu-like symptoms.

Patients should be told to refer to the medication label/packaging for the recommended individual and maximum total doses within any 24-hour period.

Instructions for Missed Dose(s) of RPC1063/Placebo Capsules

Patients should be instructed that if they forget to take a dose, they can take the dose within 4 hours of the normal dosing time; otherwise they should take their next dose at the regular time on the following day. If the patient vomits the capsule, he/she should be instructed not to take another capsule on the same day, but to take the next dose at the regular time on the following day. If the patient is ill and unable to take a dose, 2 days without treatment is acceptable, otherwise the patient will contact the Investigator.

If a patient misses a dose during dose titration, the Medical Monitor should be contacted to discuss completing the dose titration schedule.

If the patient misses more than 7 consecutive doses for any reason, Day 1 cardiac monitoring procedures will be performed on the first day that the patient resumes dosing (Holter monitoring will not be performed). If a patient misses more than 14 consecutive doses for any reason, the Medical Monitor must be contacted to discuss procedures for resuming therapy, which may include an additional dose titration schedule if deemed appropriate.

Instructions for Missed Dose of IFN β-1a/Placebo Injection

Patients should be instructed that if they forget to take a dose, they can administer the injection within 2 days of the scheduled weekly dosing day. Prophylactic treatment should be administered prior to injection as described above. If the patient does not administer the

injection within 2 days of the scheduled injection day, they should take their next dose on the next scheduled weekly injection day.

9.5.2. Study Treatment Formulation

RPC1063 Capsules and Placebo

The drug substance will be manufactured, quality control checked and released in accordance with good manufacturing practices at will supply the study medication (RPC1063 capsules and matching placebo).

RPC1063 and placebo will be provided as powder-filled capsules. RPC1063 drug substance is blended with

capsules. Three RPC1063 dosage strengths have been prepared for the clinical investigations; 0.25 mg (capsule), 0.50 mg (capsule), and 1.0 mg (capsule).

For placebo, the same capsules will contain the same blended excipients described above. All three doses of RPC1063 and placebo capsules are identical in appearance.

The capsules will be orally administered singularly, or in varying combinations, to achieve the desired dose for clinical studies.

IFN β-1a and Matching Placebo

IFN β-1a is commercially available and is manufactured by . Stocks of IFN β-1a will be purchased directly from the supplier and supplied by

IFN β-1a matching placebo will be manufactured, quality control checked and released in accordance with good manufacturing practices at
IFN β-1a matching placebo for injection will contain 0.9% Sodium Chloride.

Study treatment IFN β-1a and matching placebo will be supplied in prefilled syringes, which will be dispensed to patients at each visit and will contain a sufficient supply of IFN β-1a 30 μg/0.5 mL for IM injection at each dosing interval.

Study treatment (IFN β-1a or matching placebo) prefilled syringes and needles are for one-time use only; any study treatment remaining should not be used for another dose.

All study medication must only be dispensed by a Pharmacist or medically qualified staff and is to be dispensed only to patients enrolled in this study.

9.5.3. Study Treatment Labeling and Packaging

RPC1063 capsules will be packaged in
(35 capsules per bottle, apart from the titration kits), closed with a child resistant screw-cap that is induction sealed.

The labeling will be in accordance with GCP and any other local regulatory requirements.

Details unique to Parts A and B are described below.

Part A

Similar to RPC1063 capsules, placebo capsules will be packaged in [redacted] (35 capsules per bottle for treatment medication capsules, and 12 capsules per bottle in the titration kits), closed with a [redacted] child resistant screw-cap that is induction sealed. The cap on the treatment bottles will be white, and the cap on the titration bottles will be blue.

The labeling will be in accordance with GCP and any other local regulatory requirements.

Part B

IFN β-1a and matching placebo injections will be supplied in prefilled syringes, which will be dispensed to patients at each visit and will contain a sufficient supply of IFN β-1a (or matching placebo) for each dosing interval. Treatment kits must be stored in a secure location. Accountability for study treatment is the responsibility of the Investigator. More details concerning this responsibility are included in Section 9.5.5.

9.5.4. Blinding of Study Medication

In Parts A and B, a "Dual Assessor" approach (described in Section 9.1.2.2) will be used to evaluate efficacy and safety.

Details unique to Parts A or B are described below.

Part A

Part A is a randomized, double-blind, placebo-controlled study with limited access to the randomization code. RPC1063 and placebo capsules will be identical in physical appearance. The treatment each patient will receive will not be disclosed to the Investigator, Evaluator, study center personnel, patient, Sponsor and their representatives. The treatment codes will be held according to an IVRS. Further instructions will be provided in a separate IVRS manual.

Part B

Part B is a randomized, double-blind, double-dummy, active-controlled study. RPC1063 and IFN β-1a and their respective matching placebo capsules/injections will be identical in physical appearance. The treatment each patient will receive will not be disclosed to the Investigator, Evaluator, study center personnel, patient, Sponsor and their representatives. The treatment codes will be held according to an IVRS. Further instructions will be provided in a separate IVRS manual.

For details of the emergency procedure for unblinding of individual patients see Section 9.5.11, below.

9.5.5. Study Treatment Storage and Accountability

Study medication should not be used for purposes other than as defined in this protocol.

9.5.5.1. Study Treatment Storage

Part A

RPC1063 and placebo capsules should be stored at room temperature (approximately 25° C, excursions permitted to 15-30°C [59-86°F]) in a dry location. The inactive ingredients used in

the formulations are slightly hygroscopic; therefore, all bottles contain a ½-gram desiccant canister and should be kept tightly sealed when drug product is not being dispensed.

Part B

IFN β-1a prefilled syringes (and matching placebo) must be stored in a secure location. They must be stored at 2-8ºC.

RPC1063 capsules will be stored as described for study medication capsules in Part A.

9.5.5.2. Study Treatment Accountability

All supplies of study medication and placebo will be accounted for in accordance with GCP. There will be an individual study drug accountability record for each patient and the Investigator should maintain accurate records of the disposition of all study medication supplies received during the study. These records should include the amounts and dates clinical drug supplies were received, dispensed to the patient, returned by the patient and returned to the Sponsor. If errors or damages in the clinical drug supply shipments occur, the Investigator should contact and the Study Monitor immediately. Each Investigator will provide copies of the study medication accountability records for inclusion in the Trial Master File after database lock. The Study Monitor will periodically check the supplies of study medication held by the Investigator or pharmacist to verify accountability of all medication used.

The Investigator will provide the medication only to the identified patients of this study, according to the procedures described in this study protocol. After the end of the study, the Study Monitor will perform final accountability, package, seal, and prepare for shipment. Medication and all medication containers will be returned to and documentation will be returned to the CRO. The CRO will verify that a final report of drug accountability is prepared and maintained in the Investigator's Study Center File.

9.5.6. Dose Adjustments and Dose Escalation

There is no provision for dose adjustments in this study. Patients who cannot tolerate investigational drug must be withdrawn from the study

9.5.7. Prior and Concomitant Therapy

All treatments being taken by the patients on entry to the study or at any time during the study in addition to the investigational product are regarded as concomitant treatments and must be documented on the appropriate section of the eCRF. A history of all prior medications needs to be documented to at least 4 weeks prior to study participation, and a history of previous treatments for MS needs to be documented for at least the prior 2 years.

Concomitant treatment with any of the medications listed below is not allowed during the study or some time prior to randomization.

Medications that must be discontinued prior to randomization and cannot be used during the study:

- Non-lymphocyte-depleting disease-modifying MS agents (e.g., glatiramer acetate, interferons) must be discontinued from signing of informed consent until randomization for a minimum of 2 weeks;

- Treatment with medications with a known impact on the cardiac conduction system (e.g., beta blockers, calcium channel blockers, Class Ia or Class III anti-arrhythmics). A list with examples of prohibited cardiac medications is provided in Table 8 (note that this is not a comprehensive list and other drugs in these classes are also excluded. Refer to the Study Reference Manual and contact the Medical Monitor for further guidance if needed.

Medications that must be discontinued at least 4 weeks prior to randomization and cannot be used during the study:

- Systemic corticosteroid therapy or ACTH is not allowed within 30 days prior to screening, except for treatment of protocol-defined treatment of relapses (Section 9.1.2.3). Corticosteroids that are by non-systemic routes (e.g., topical, inhaled, intraarticular) are allowed.
- Inducers or inhibitors of CYP3A4 metabolism. A list with examples of medications that may affect the metabolism of RPC1063 is provided in Table 9 (note that this is not a comprehensive list and other drugs in these classes are also excluded. The Medical Monitor should be contacted for further guidance as needed.
- Live vaccines.

Medications that must be discontinued 3 months prior to randomization and cannot be used during the study:

- Treatment with IVIg or plasmapheresis
- Treatment with other disease modifying therapies (e.g., daclizumab, dimethyl fumarate, laquinimod)
- Teriflunomide. Treatment with teriflunomide is not permitted within 3 months prior to randomization. In addition, if a patient has received teriflunomide treatment within 6 months of randomization either of the two following accelerated elimination procedures must be followed, according to the manufacturer's protocol (Genzyme, 2012).
    - Administration of cholestyramine 8 g every 8 hours for 11 days. If cholestyramine 8 g three times a day is not well tolerated, cholestyramine 4 g three times a day can be used.
    - Administration of 50 g oral activated charcoal powder every 12 hours for 11 days.

  If either elimination procedure is poorly tolerated, treatment days do not need to be consecutive.

Medications that must be discontinued 6 months prior to randomization and cannot be used during the study:

- Immunosuppressive agents (e.g., azathioprine, cyclosporine, methotrexate, or mycophenolate)
- Any other investigational agent

Medications that cannot be used at any time prior to randomization (i.e. are exclusionary and any prior use is prohibited):

- Lymphocyte-trafficking inhibitors (fingolimod, natalizumab)
- Immunosuppressive agents that deplete lymphocytes (e.g., alemtuzumab, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone)

Table 8 Examples of Prohibited Cardiac Medications

Pharmaceutical Class	Example Medications
Beta blockers	acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propranolol, sotalol, timolol
Calcium channel blockers	diltiazem, verapamil
Anti-arrhythmic drugs	amiodarone, bepridil hydrochloride, disopyramide, dofetilide, dronedarone, flecainide, ibutilide, lidocaine, procainamide, propafenone, quinidine, tocainide
QT prolonging drugs	Citalopram (>20 mg/day), chlorpromazine, haloperidol, methadone, erythromycin

Table 9 Examples of Prohibited Inducers or Inhibitors of CYP3A4

Pharmaceutical Class	Example Medications
HIV protease inhibitors	indinavir, nelfinavir, ritonavir, atazanavir, saquinavir
Antibiotics	clarithromycin, telithromycin, rifampin, rifamycin
Antifungals	itraconazole, ketoconazole, fluconazole
Anticonvulsants	phenobarbital, phenytoin, carbamazepine
Others medications	nefazodone, pioglitazone, troglitazone, amiodarone, cyclosporine
Foods and herbal supplements	grapefruit juice, Seville orange juice, St. John's Wort

Treatment for symptoms related to MS (e.g., spasticity, incontinence, pain, fatigue, and depression) is not restricted but investigators should attempt to keep therapies or treatments reasonably constant throughout the study. Patients should have been on a stable dose for 3 months prior to screening. Changes may be made if appropriate for a patient's well-being in the clinical judgment of the treating investigator.

Administration of concomitant medications must be reported in the appropriate section of the eCRF along with dosage information, dates of administration, and reasons for use. For medications with a single active ingredient, generic names for concomitant medication should be used, if possible. For combination products, brand names should be used. The total daily dose should be filled in whenever possible.

9.5.8. Concomitant Procedures

Immunosuppressive procedures that deplete lymphocytes (e.g., total body irradiation, bone marrow transplantation) are not allowed during the study or at any time prior to the study.

Concomitant procedures must be reported in the appropriate section of the eCRF. AEs related to these therapies or procedures must be documented on the patient's eCRF.

9.5.9. Treatment Compliance

It is the Investigator's responsibility to ensure that patients are correctly instructed on how to take their study medication and that each patient is fully compliant with their assigned dosage regimen. Records of study medication used and intervals between visits will be kept during the study. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused medication at the end of the study. The study treatment should be dispensed by the Investigator, or by a qualified individual under the Investigator's supervision. An up-to-date treatment inventory/dispensing record must be maintained as described above in Section 9.5.5.2.

Overall study non-compliance is defined as taking less than 80% or more than 120% of study medication during the entire treatment period.

Details unique to Parts A or B are described below.

Part A

At each visit, previously dispensed study medication capsules will be collected by the Investigator and compliance assessed. Patients will record capsules intake in a dosing diary that will be reviewed periodically by site staff and the Clinical Monitor. Patients exhibiting poor compliance as assessed by medication counts (i.e., 2 or more missed medication days in 1 week) and response to the question "Did you take your medication regularly?" should be counseled on the importance of good compliance to the study dosing regimen. Patients who are persistently non-compliant (< 80% or > 120%) should be discussed with the Medical Monitor to determine whether they should be withdrawn from the study.

Part B

Compliance with IFN β-1a dosing is to be monitored and recorded by site staff. Patients will record IFN β-1a treatment in a dosing diary that will be reviewed periodically by site staff and the Clinical Monitor.

Compliance with RPC1063 capsules will be assessed as described above for Part A.

9.5.10. Assignment to Treatment

Patients must provide proper informed consent before any study procedures are performed (refer to Section 5.3 for further details regarding obtaining patients informed consent). At the time of consent the patient is enrolled in the study. In Parts A and B patients will be randomized into the study on Day 1 after all screening and baseline assessments have been completed and the Investigator has verified that the patient is eligible per the inclusion (Section 9.4.1) and exclusion criteria (Section 9.4.2).

Randomization will be performed through an IVRS (Section 13.4). Treatment groups are described in Section 9.5.1. Details unique to Parts A or B are described below.

Part A

Patients will be stratified by country and will be randomized 1:1:1 to receive placebo, 0.5 mg RPC1063, or 1 mg RPC1063.

Part B

Patients will be stratified by baseline EDSS (≤ 3.5, > 3.5) and country and will be randomized 1:1:1 to receive IFN β-1a 30 μg, or 0.5 mg RPC1063, or 1 mg RPC1063.

9.5.11. Unblinding Procedures for Individual Patients

A patient's treatment group assignment blind will not be broken until the end of the study unless medical treatment of that patient depends upon knowing whether the patient is receiving active drug. In the event that the blind needs to be broken because of a medical emergency, the investigator may unblind an individual patient's treatment allocation. The investigator should attempt to contact the Medical Monitor as soon as practicable to discuss the medical emergency and the reason unblinding. The treatment assignment will be unblinded through an IVRS. Reasons for treatment unblinding must be clearly explained and justified in the eCRF. The date on which the code was broken together with the identity of the person responsible must also be documented.

A PK sample will be obtained whenever possible for patients with any AE resulting in unblinding, discontinuation or SAE.

10. STUDY SCHEDULE

The study design is shown in . Tests and Assessments are outlined in Table 1 and Table 2 (Part A), Table 3 and Table 4 (Part B), and Table 5 (cardiac monitoring during dose titration). Methods of assessment are described in Section 11.

It is recommended that the study visits are scheduled in the morning. At the Baseline visit, and on days of study visits on which a predose PK sample is to be obtained (Part A Week 12 and Part B Month 12), patients should be instructed to withhold the dose and the morning meal until the office visit, and dose will be administered during the visit.

Whenever possible, the sequence of when the efficacy assessments are done (EDSS, MSFC) should remain constant and at approximately the same time of day throughout the study. Assessment of the MSFC should start with walking, and it should be done before walking for EDSS.

Predose blood samples for PK evaluation are to be taken 5 to 30 minutes prior to study treatment administration. Actual sampling times must be accurately recorded in the source document and appropriate eCRF. On days of study visits with collection of predose PK blood samples, patients must arrive at the site in fasting conditions.

On days of study visits on which a postdose PK sample is to be obtained, patient visits should be scheduled so a sample can be obtained 2 to 6 hours after the patient's usual dosing time. The patient should also be instructed to ensure that the dosing time is accurately recorded in the dosing diary.

It is recommended that procedures are performed in the following order (note that not all procedures are performed at every visit):

- Spontaneous or solicited AE reporting
- ECG
- Vital signs
- Clinical laboratory tests, including predose PK sampling
- Physical examination
- Efficacy assessments.

Specified visit windows (other than visits during dose titration) may be extended on a case by case basis if needed to accommodate scheduling *except* for the following procedures:

- Brain MRI
- EDSS and neurological examination

10.1. Screening Period (Part A and Part B)

Every effort should be made to complete all screening procedures within 30 days prior to receiving the first dose of study treatment in Part A or B of the study. If necessary, the Principal Investigator (or designee) may extend the Screening Period if needed to a maximum of 45 days

to accommodate scheduling of screening and baseline procedures. If screening procedures cannot be completed within 45 days, the Medical Monitor must be contacted for approval for any further extension, and to discuss whether any Screening procedures must be repeated prior to randomization. All screening assessments and procedures are to be performed by the Principal Investigator or a qualified designee.

Written, signed, and dated informed consent from the patient prior to the performance of any study-related procedures must be obtained by the Principal Investigator or designee (refer to Section 5.3 for further details regarding obtaining patients informed consent). A copy of the signed informed consent must be given to the patient for his/her records.

Screening Period

During the screening period, the following procedures will be performed:

- Obtain patient's informed consent
- Inclusion/exclusion criteria
- Complete medical history
- Blood/urine sampling for the following laboratory tests:
  - Hematology: red blood cell (RBC) count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC)
  - Blood chemistry: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, random glucose, albumin, alkaline phosphatase, creatinine, SGPT/ALT, SGOT/AST, gamma glutamyltransferase (GGT), amylase, total bilirubin, conjugated bilirubin, hemoglobin A1c. Abnormal laboratory parameters inconsistent with clinical presentation of MS or suspicious of underlying medical condition should be repeated for accuracy.
  - Urinalysis: leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, and urobilinogen
  - Serum beta-human chorionic gonadotrophin (β-hCG) (women of childbearing potential only)
  - Coagulation panel: prothrombin time (PT) and partial thromboplastin time (PTT)
  - Sensitive thyroid stimulating hormone (sTSH)
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  - Viral serology: HIV antibodies, anti-hepatitis A virus IgM, HBsAg and HBcAg IgM, anti-HCV IgG or IgM. In addition, patients must have documentation of positive VZV IgG antibody status. Patients who are negative for VZV IgG antibodies at screening can undergo vaccination and be enrolled 30 days after appropriate VZV vaccination has been completed. Patients testing positive for HIV or for serological markers of acute or chronic hepatitis A, B, or C will be

excluded from the study unless they are indicative of prior hepatitis B vaccination or cured hepatitis A or B and accompanied by normal liver transaminase values.

– Syphilis RPR. Patients must have a negative result to be enrolled.

- TB testing. TB testing will include the purified protein derivative test. All testing must be completed prior to administration of study drug on Day 1. As available locally, an interferon gamma release assay such as QuantiFERON Gold test or other comparable interferon gamma release assay test (e.g., T-SPOT) may be used as an alternative TB screening test. Patients testing positive for TB with the purified protein derivative skin test or interferon gamma release assay will be excluded from the study unless there is (1) a history of either prior TB vaccination or well-documented cured TB/treatment of tuberculin conversion that is (2) accompanied by a chest x-ray negative for active infection, taking into account the subject's risk for TB based on history of contact, symptoms and physical signs. The investigator should consult an infectious disease physician if needed
- Complete physical examination: including evaluation of heart, lung, head and neck, abdominal, neurological, skin, and extremities. Note: Neurological evaluation should include fundoscopic examination to rule out uveitis and other clinically significant ophthalmologic abnormalities, which should be recorded in source documents.
- Height and weight
- Vital signs: body temperature, blood pressure and heart rate
- Chest X-ray: not required if performed within 60 days prior to randomization and if documentation is on file
- 12-lead ECG: the screening ECG report from the central reader must be available to confirm patient eligibility before randomization
- Enroll patient, contact IVRS
- EDSS and neurological examination
- Brain MRI
- MSFC practice. Three MSFC practice assessments must be performed before baseline: MSFC Practice 1 is to be performed at the screening visit, MSFC Practice 2 and MSFC Practice 3 may also be performed at the screening visit, or on other days between the screening and baseline visit).
- LCLA
- Pulmonary function tests including FEV_1 and FVC measurements, and DLCO
- OCT evaluation
- Dermatological examination.
- Suicidality assessment using the C-SSRS

- Record relevant prior and current therapy. A history of all prior medications needs to be documented to at least 4 weeks prior to study participation, and a history of previous treatments for MS needs to be documented for the prior 2 years
- SAEs to be recorded from the time of signing the informed consent; AEs to be recorded from the first dose of study drug.

10.1.1. Screen Failure

A screen failure is defined as a patient who has given informed consent, and failed to meet the inclusion and/or exclusion criteria.

10.1.2. Rescreening of Patients

Patients who fail to meet the inclusion/exclusion criteria can be rescreened. The Medical Monitor should be contacted prior to rescreening to discuss whether any prior screening results may still be used for rescreening.

10.2. Part A Treatment Period

10.2.1. Baseline/Day 1 Visit

Eligible patients will be randomized to treatment group on Day 1.

The following assessments will be performed at the baseline/Day 1 visit:

- Review of inclusion/exclusion criteria
- An interim medical history will be performed to complete the screening medical history. Medical events that occur between screening and first dose will be recorded as medical history.
- Blood/urine sampling for the following laboratory tests:
  - Hematology: RBC count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, MCV, MCH, and MCHC
  - Blood chemistry: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, random glucose, albumin, alkaline phosphatase, creatinine, SGPT/ALT, SGOT/AST, GGT, amylase, total bilirubin, conjugated bilirubin.
  - Urine beta-hCG (females of childbearing potential only). If the urine pregnancy test is positive, do not dose and confirm with a serum pregnancy test.
  - Standard PK sampling: PK sample is to be taken prior to dose administration
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  -
- Weight

- Vital signs: body temperature, blood pressure and heart rate. See the special monitoring procedures below that will be performed on Day 1
- 12-lead ECG. See the special monitoring procedures below that will be performed on Day 1
- Continuous Holter monitoring (15 minutes predose and for 24 hours following dose). See the special monitoring procedures below that will be performed on Day 1
- Randomization
- Dispense study drug (with titration kit) and patient diary, and administer first dose of study drug at the site
- MSFC AND LCLA
- MSQOL-54
- Suicidality assessment using the C-SSRS
- Record concomitant therapy
- Record AEs/SAEs

10.2.1.1. Guidelines for Monitoring Patients Taking Their First Dose of RCP1063

On Day 1 of treatment, careful cardiac monitoring of the patients is required. The treating physician is responsible for monitoring the patient following the first intake of the study drug, as well as managing bradycardia symptoms should they occur. He or she must review the baseline predose ECG, vital signs during the 6-hour monitoring period, post-dose ECG, and assess discharge status at 6 hours after dosing. Baseline predose ECG should be provided by the site and be available for comparison to the postdose ECG in order to determine if criteria requiring extended monitoring are met. In addition, continuous Holter monitoring will be performed beginning 15 minutes predose and for 24 hours after dose administration. Further details on ECG and Holter monitoring procedures are provided in the Holter Manual.

Heart rate, blood pressure, and other vital signs will be measured before the first dose of study drug, then every hour for at least 6 hours thereafter (by the treating physician or an assisting nurse). Blood pressure and heart rate will be measured in the supine position and then the standing position at each time point. When obtaining the predose heart rate before the first dose, the patient should be allowed to rest in the supine position for 10 to 15 minutes before taking the heart rate. The supine heart rate and blood pressure measurements should be repeated 2 additional times to produce 3 readings for both heart rate and blood pressure (before the first dose of study drug only). The lowest predose value of supine heart rate and blood pressure (based on systolic blood pressure) will be recorded in the case report form and should be used for comparison to the postdose values. Orthostatic blood pressure will then be measured once with the patient in the standing position (after standing for 2 minutes) before the first dose of study drug.

Patients should receive the first dose of study drug in a fasted condition before 12:00 pm (noon) in the clinic. The first dose of RPC1063 should be administered in a setting in which resources to appropriately manage symptomatic bradycardia are available. A member of the Investigator team

should be available to monitor the patient for the 6 hours monitoring period and will need to report any abnormalities to the treating neurologist. Atropine needs to be readily available to the site personnel.

Additional extended monitoring should be instituted until the finding has resolved in the following situations:

- The heart rate 6 hours post-dose is < 45 bpm
- The heart rate 6 hours post-dose is at the lowest value post-dose (suggesting that the maximum PD effect on the heart may not have occurred)
- The ECG 6 hours post-dose shows new onset second degree or higher AV block
- The ECG 6 hours post-dose shows a prolonged QTcF interval (>450 msec males, >470 msec females).

Should post-dose symptomatic bradycardia occur, the treating neurologist should be notified and he or she should initiate appropriate management, begin continuous ECG monitoring, and continue observation until the symptoms have resolved.

Should a patient require pharmacologic intervention for symptomatic bradycardia, continuous overnight ECG monitoring in a medical facility should be instituted, and the first dose monitoring strategy should be repeated the following day (Day 2). The first dose monitoring strategy should also be repeated at Day 5 if any cardiac safety issues were observed on Day 1.

Patients should have written instruction on when to return to clinic and a 24-hour contact phone number to call in the event of any new or warranted symptoms (e.g., chest pain, dizziness, palpitations, syncope, nausea, vomiting). Patients should be instructed not to drive on the same day after the first dose of study drug administration.

First dose monitoring procedures will also be followed at the Week 24 visit in Part A for patients who elect to continue in the blinded extension study, or for any patient who resumes treatment after missing more than 7 consecutive doses.

10.2.2. Day 5 Visit

This visit will be performed for safety purposes. Patients will be instructed that they must take the Day 5 study drug dose at the clinic before 12:00 pm (noon), after the Holter monitor has been placed. The following assessments will be performed at the Day 5 visit for the first 75 randomized patients:

- Observation of patients predose and for the first 6 hours following dose administration, including hourly vital sign monitoring
- ECG predose and at Hour 6
- Continuous Holter monitoring 15 minutes predose and for 24 hours following dose administration

If clinically significant cardiac conduction abnormalities are not observed in the first 75 patients that are treated, Day 5 monitoring will be discontinued for the remaining patients enrolled in the study. After that time, the first-dose monitoring strategy should be repeated at Day 5 if any

cardiac safety issues were observed at Day 1. If any safety issues are identified during Day 5 monitoring, then the monitoring guidelines in Section 10.2.1.1 should be followed.

10.2.3. Day 8 Visit

This visit will be performed for safety purposes. Patients will be instructed that they must take the Day 8 study drug dose at the clinic before 12:00 pm (noon), after the Holter monitor has been placed. Continuous Holter monitoring will be performed for 15 minutes predose and for 24 hours following dose administration for the first 75 randomized patients.

If clinically significant cardiac conduction abnormalities are not observed in the first 75 patients that are treated, Day 8 monitoring will be discontinued for the remaining patients enrolled in the study. The first-dose monitoring strategy should be repeated at Day 8 if any cardiac safety issues were observed at Day 5. See the monitoring guidelines in Section 10.2.1.1 for further details.

10.2.4. Day 29 (Week 4 ± 3 days) Visit

The following assessments will be performed at the Week 4 visit:

- Blood/urine sampling for the following laboratory tests:
  - Hematology: RBC count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, MCV, MCH, and MCHC.
    Note: All total WBC and differential WBC counts will be blinded during the study.
  - Blood chemistry: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, random glucose, albumin, alkaline phosphatase, creatinine, SGPT/ALT, SGOT/AST, GGT, amylase, total bilirubin, conjugated bilirubin. Abnormal laboratory parameters inconsistent with clinical presentation of MS or suspicious of underlying medical condition should be repeated for accuracy. If an increase of amylase above the clinically notable value (≥ 300 U/L) is observed at any post randomization visit, lipase should be tested to determine the origin of elevated amylase (pancreatic versus extra pancreatic).
  - Urine beta-hCG (females of childbearing potential only). If the urine pregnancy test is positive, do not dose and confirm with a serum pregnancy test.
  - Standard PK sampling: PK samples are to be taken 2 to 6 hours following administration
- Vital signs: body temperature, blood pressure and heart rate
- 12-lead ECG
- Dispense study drug and patient diary
- Review study drug accountability and compliance
- Suicidality assessment using the C-SSRS
- Record concomitant therapy

- Record AEs/SAEs

10.2.5. Day 57 (Week 8 ± 3 days) Visit

The following assessments will be performed at the Week 8 visit:

- Urine beta-hCG (females of childbearing potential only). If the urine pregnancy test is positive, do not dose and confirm with a serum pregnancy test.
- Vital signs: body temperature, blood pressure and heart rate
- Dispense study drug and patient diary
- Review study drug accountability and compliance
- Brain MRI
- Suicidality assessment using the C-SSRS
- Record concomitant therapy
- Record AEs/SAEs

10.2.6. Day 85 (Week 12 ± 3 days) Visit

Note: Subjects are to be instructed not to take their dose of study drug at home, and will be administered study drug at the clinic after laboratory procedures have been completed. Subjects should arrive at the clinic in a fasted state.

The following assessments will be performed at the Week 12 visit:

- Blood/urine sampling for the following laboratory tests:
  - Hematology: RBC count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, MCV, MCH, and MCHC
    Note: All total WBC and differential WBC counts will be blinded during the study.
  - Blood chemistry: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, random glucose, albumin, alkaline phosphatase, creatinine, SGPT/ALT, SGOT/AST, GGT, amylase, total bilirubin, conjugated bilirubin. Abnormal laboratory parameters inconsistent with clinical presentation of MS or suspicious of underlying medical condition should be repeated for accuracy. If an increase of amylase above the clinically notable value (≥ 300 U/L) is observed at any post randomization visit, lipase should be tested to determine the origin of elevated amylase (pancreatic versus extra pancreatic)
  - Urine beta-hCG (females of childbearing potential only). If the urine pregnancy test is positive, do not dose and confirm with a serum pregnancy test.
  - Standard PK sampling: PK sample is to be taken prior to dose administration
- Administer study drug
- Vital signs: body temperature, blood pressure and heart rate

- 12-lead ECG
- Dispense study drug and patient diary
- Review study drug accountability and compliance
- Brain MRI
- EDSS and neurological examination
- MSFC AND LCLA
- Pulmonary function tests including FEV_1 and FVC measurements
- Suicidality assessment using the C-SSRS
- Record concomitant therapy
- Record AEs/SAEs

10.2.7. Day 113 (Week 16 ± 3 days) Visit and Day 141 (Week 20) Visit

The same assessments will be performed at the Week 16 visit and the Week 20 visit, as follows:

- Urine beta-hCG (females of childbearing potential only). If the urine pregnancy test is positive, do not dose and confirm with a serum pregnancy test.
- Vital signs: body temperature, blood pressure and heart rate
- Dispense study drug and patient diary
- Review study drug accountability and compliance
- Brain MRI
- Suicidality assessment using the C-SSRS
- Record concomitant therapy
- Record AEs/SAEs

10.2.8. Day 169 (Week 24 ± 3 days) Visit

The Week 24 visit will be the end of study visit for patients who do not choose to continue participating in the optional blinded extension period. After all Week 24 visit procedures have been completed, patients who choose to continue will be re-consented and re-randomized in a blinded fashion to receive the RPC1063 dose titration regimen (if on placebo) or continue on their RPC1063 treatment assignment. First dose monitoring procedures will be followed in all patients as described in Section 10.2.1. Patients participating in the optional blinded extension period will be instructed that they must take the first study drug dose at the clinic before 12:00 pm (noon). The first dose and cardiac monitoring procedures for the blinded extension treatment will be performed on a separate day up to 7 days following the Week 24 visit.

The following assessments will be performed at the Day 169 (Week 24) visit:

- Blood/urine sampling for the following laboratory tests:

  - Hematology: RBC count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, MCV, MCH, and MCHC
    Note: All total WBC and differential WBC counts will be blinded during the study.
  - Blood chemistry: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, random glucose, albumin, alkaline phosphatase, creatinine, SGPT/ALT, SGOT/AST, GGT, amylase, total bilirubin, conjugated bilirubin,. Abnormal laboratory parameters inconsistent with clinical presentation of MS or suspicious of underlying medical condition should be repeated for accuracy. If an increase of amylase above the clinically notable value (≥ 300 U/L) is observed at any post randomization visit, lipase should be tested to determine the origin of elevated amylase (pancreatic versus extra pancreatic)
  - Urinalysis: leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, and urobilinogen
  - Urine beta-hCG (females of childbearing potential only). If the urine pregnancy test is positive, do not dose and confirm with a serum pregnancy test.
  - Coagulation panel: PT and PTT
  - sTSH
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  - Standard PK sampling: PK samples are to be taken 2 to 6 hours following administration

- Complete physical examination: including evaluation of heart, lung, head and neck, abdominal, neurological, skin, and extremities
- Weight
- Vital signs: body temperature, blood pressure and heart rate. For patients who choose to continue on the blinded extension period, the first dose monitoring procedures must be performed, including recording of baseline (predose) heart rate and blood pressure (see Section 10.2.1)
- 12-lead ECG. For patients who choose to continue on the blinded extension period, the Day 1 first dose monitoring procedures must be performed (see Section 10.2.1).
- Review study drug accountability and compliance
- Randomize in case patient chooses to continue on the blinded extension period
- If the patient chooses to continue in the study to the blinded extension period, dispense study drug (including titration kit) and patient diary, and administer dose of study drug at the site

- Brain MRI
- and neurological examination.
-
- MSQOL-54
- Pulmonary function tests including FEV_1 and FVC measurements, and DLCO
- OCT evaluation
- Dermatological examination
- Suicidality assessment using the C-SSRS
- Record concomitant therapy
- Record AEs/SAEs

Patients who terminate study at this visit will be scheduled for a follow-up visit 4 weeks (± 5 days) after last dose.

Patients who choose to continue on the blinded extension period will be scheduled for a safety visit 14 days after first dose of the blinded extension period.

10.2.9. Day 183 (Week 26 ± 1 day) Visit of the Blinded Extension

This visit will be performed for safety purposes. The following assessments will be performed at the Week 26 visit of the optional blinded extension:

- Vital signs: body temperature, blood pressure and heart rate
- 12-lead ECG
- Review study drug accountability and compliance
- Suicidality assessment using the C-SSRS
- Record concomitant therapy
- Record AEs/SAEs

10.2.10. Visits Every 12 Weeks of the Blinded Extension

Patients will continue in the optional Blinded Extension period at least until the last patient reaches ExtensionWeek 48 (nominal Week 72). After the last patient reaches Week 72, patients may continue on blinded therapy until a long-term safety study is available. The following assessments will be performed every 12 weeks of the optional blinded extension, if indicated:

- Blood/urine sampling for the following laboratory tests:
  - Hematology: RBC count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, MCV, MCH, and MCHC
    Note: All total WBC and differential WBC counts will be blinded during the study.

  - Blood chemistry: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, random glucose, albumin, alkaline phosphatase, creatinine, SGPT/ALT, SGOT/AST, GGT, amylase, total bilirubin, conjugated bilirubin,. Abnormal laboratory parameters inconsistent with clinical presentation of MS or suspicious of underlying medical condition should be repeated for accuracy. If an increase of amylase above the clinically notable value (≥ 300 U/L) is observed at any post randomization visit, lipase should be tested to determine the origin of elevated amylase (pancreatic versus extra pancreatic)
  - Urine beta-hCG (females of childbearing potential only). If the urine pregnancy test is positive, do not dose and confirm with a serum pregnancy test.

- Vital signs: body temperature, blood pressure and heart rate
- 12-lead ECG
- Dispense study drug and patient diary
- Review study drug accountability and compliance
- EDSS and neurological examination
- MSFC AND LCLA
- Pulmonary function tests including FEV_1 and FVC measurements
- Suicidality assessment using the C-SSRS
- Record concomitant therapy
- Record AEs/SAEs

MRI assessments during the blinded extension:

- Brain MRI at approximately Weeks 48 and 72
- After Week 72, brain MRI will be performed annually

10.2.11. End of Study Visit of the Blinded Extension

When the last active patient who entered the optional blinded extension period has reached at least Week 72 and a long-term safety study is available, the End of Study assessments will be performed at the next scheduled visit. The following assessments will be performed:

- Blood/urine sampling for the following laboratory tests:
  - Hematology: RBC count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, MCV, MCH, and MCHC
    Note: All total WBC and differential WBC counts will be blinded during the study.
  - Blood chemistry: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, random glucose, albumin, alkaline phosphatase, creatinine,

SGPT/ALT, SGOT/AST, GGT, amylase, total bilirubin, conjugated bilirubin,. Abnormal laboratory parameters inconsistent with clinical presentation of MS or suspicious of underlying medical condition should be repeated for accuracy. If an increase of amylase above the clinically notable value (≥ 300 U/L) is observed at any post randomization visit, lipase should be tested to determine the origin of elevated amylase (pancreatic versus extra pancreatic)

- Urine beta-hCG (females of childbearing potential only). If the urine pregnancy test is positive, do not dose and confirm with a serum pregnancy test.
- Coagulation panel: prothrombin time (PT) and partial thromboplastin time (PTT)
- sTSH
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- Complete physical examination: including evaluation of heart, lung, head and neck, abdominal, neurological, skin, and extremities
- Weight
- Vital signs: body temperature, blood pressure and heart rate
- 12-lead ECG
- Review study drug accountability and compliance
- Brain MRI (if End of Study corresponds to a scheduled MRI visit)
- EDSS and neurological examination
- MSFC AND LCLA
- MSQOL-54
- Pulmonary function tests including FEV_1 and FVC measurements
- OCT evaluation
- Dermatological examination
- Suicidality assessment using the C-SSRS
- Record concomitant therapy
- Record AEs/SAEs

Patients will be scheduled for a follow-up visit 4 weeks (± 5 days) after last dose.

10.3. Part B Treatment Period

Part B will commence after the DMC reviews the Part A interim analysis data and performs a thorough safety review. Patients dosed in Part A will be ineligible for participation in Part B.

10.3.1. Visit 1 (Baseline/Month 1)

Eligible patients will be randomized to treatment group on Visit 1.

The following assessments will be performed at the Visit 1 (Baseline/Month 1):

- Review of inclusion/exclusion criteria
- An interim medical history will be performed to complete the screening medical history. Medical events that occur between screening and first dose will be recorded as medical history
- Blood/urine sampling for the following laboratory tests:
  - Hematology: RBC count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, MCV, MCH, and MCHC
    Note: All total WBC and differential WBC counts will be blinded during the study.
  - Blood chemistry: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, random glucose, albumin, alkaline phosphatase, creatinine, SGPT/ALT, SGOT/AST, GGT, amylase, total bilirubin, conjugated bilirubin, hemoglobin A1c, and total cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL).
  - Urinalysis: leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, and urobilinogen.
  - Urine beta-hCG (females of childbearing potential only). If the urine pregnancy test is positive, do not dose and confirm with a serum pregnancy test.
  - Standard PK sampling: PK sample is to be taken prior to dose administration
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- Weight
- Vital signs: body temperature, blood pressure and heart rate. The special first dose monitoring procedures must be performed (see below and Guidelines for Monitoring Patients Taking Their First Dose in Section 10.2.1.1)
- 12-lead ECG. The special first dose monitoring procedures must be performed (see below and Guidelines for Monitoring Patients Taking Their First Dose in Section 10.2.1.1)
- Randomization
- Dispense study drug (with titration kit) and patient diary, and administer first dose of study drug at the site
- MSFC AND LCLA
- MSQOL-54

- Suicidality assessment using the C-SSRS
- Record concomitant therapy
- Record AEs/SAEs

On Day 1 of treatment, careful cardiac monitoring of the patients is required. The first dose of RPC1063 should be administered in a setting in which resources to appropriately manage symptomatic bradycardia are available. A member of the Investigator team should be available to monitor the patient for the 6 hours monitoring period and will need to report any abnormalities to the treating neurologist. Atropine or Epinephrine need to be readily available to the site personnel.

Additional observation should be instituted until the finding has resolved in the following situations:

- The heart rate 6 hours post-dose is < 45 bpm
- The heart rate 6 hours post-dose is at the lowest value post-dose (suggesting that the maximum PD effect on the heart may not have occurred)
- The ECG 6 hours post-dose shows new onset second degree or higher AV block
- The ECG 6 hours post-dose shows a prolonged QTcF interval (>450 msec males, >470 msec females).

Should post-dose symptomatic bradycardia occur, initiate appropriate management, begin continuous ECG monitoring, and continue observation until the symptoms have resolved.

Should a patient require pharmacologic intervention for symptomatic bradycardia, continuous overnight ECG monitoring in a medical facility should be instituted, and the first dose monitoring strategy should be repeated at Day 5 if any cardiac safety issues were observed on Day 1.

Refer to Guidelines for Monitoring Patients Taking Their First Dose in Section 10.2.1.1 for further details.

10.3.2. Visit 2 (Day 15 ± 1 day)

This visit will be performed for safety purposes. The following assessments will be performed at Visit 2 (Day 15):

- Vital signs: blood pressure and heart rate
- 12-lead ECG
- Review study drug accountability and compliance
- Suicidality assessment using the C-SSRS
- Record concomitant therapy
- Record AEs/SAEs

10.3.3. Visit 3 (Month 3/Week 13) ± 5 days)

The following assessments will be performed at Visit 3 (Month 3):

- Blood/urine sampling for the following laboratory tests:
  - Hematology: RBC count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, MCV, MCH, and MCHC
    Note: All total WBC and differential WBC counts will be blinded during the study.
  - Blood chemistry: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, random glucose, albumin, alkaline phosphatase, creatinine, SGPT/ALT, SGOT/AST, GGT, amylase, total bilirubin, conjugated bilirubin, hemoglobin A1c. Abnormal laboratory parameters inconsistent with clinical presentation of MS or suspicious of underlying medical condition should be repeated for accuracy. If an increase of amylase above the clinically notable value (≥ 300 U/L) is observed at any post randomization visit, lipase should be tested to determine the origin of elevated amylase (pancreatic versus extra pancreatic)
  - Urinalysis: leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, and urobilinogen.
  - Urine beta-hCG (females of childbearing potential only). If the urine pregnancy test is positive, do not dose and confirm with a serum pregnancy test.
- Vital signs: blood pressure and heart rate
- Dispense study drug and patient diary
- Review study drug accountability and compliance
- EDSS and neurological assessment
- Pulmonary function tests including FEV_1 and FVC measurements
- Suicidality assessment using the C-SSRS
- Record concomitant therapy
- Record AEs/SAEs

10.3.4. Visit 4 (Month 6/Week 26 ± 5 days)

The following assessments will be performed at Visit 4 (Month 6):

- Blood/urine sampling for the following laboratory tests:
  - Hematology: RBC count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, MCV, MCH, and MCHC
    Note: All total WBC and differential WBC counts will be blinded during the study.

  - Blood chemistry: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, random glucose, albumin, alkaline phosphatase, creatinine, SGPT/ALT, SGOT/AST, GGT, amylase, total bilirubin, conjugated bilirubin, hemoglobin A1c, and total cholesterol, triglycerides, HDL and LDL. Abnormal laboratory parameters inconsistent with clinical presentation of MS or suspicious of underlying medical condition should be repeated for accuracy. If an increase of amylase above the clinically notable value (≥ 300 U/L) is observed at any post randomization visit, lipase should be tested to determine the origin of elevated amylase (pancreatic versus extra pancreatic)
  - Urinalysis: leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, and urobilinogen
  - Urine beta-hCG (females of childbearing potential only). If the urine pregnancy test is positive, do not dose and confirm with a serum pregnancy test.
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  - Standard PK sampling: PK samples are to be taken 2 to 6 hours following administration
- Vital signs: blood pressure and heart rate
- Dispense study drug and patient diary
- Review study drug accountability and compliance
- EDSS and neurological examination
- MSFC AND LCLA
- MSQOL-54
- Pulmonary function tests including FEV_1 and FVC measurements
- OCT evaluation
- Suicidality assessment using the C-SSRS
- Record concomitant therapy
- Record AEs/SAEs

10.3.5. Visit 5 (Month 9/Week 39 ± 5 days)

The following assessments will be performed at Visit 5 (Month 9):

- Blood/urine sampling for the following laboratory tests:
  - Hematology: RBC count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, MCV, MCH, and MCHC
    Note: All total WBC and differential WBC counts will be blinded during the study.

  - Blood chemistry: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, random glucose, albumin, alkaline phosphatase, creatinine, SGPT/ALT, SGOT/AST, GGT, amylase, total bilirubin, conjugated bilirubin, hemoglobin A1c. Abnormal laboratory parameters inconsistent with clinical presentation of MS or suspicious of underlying medical condition should be repeated for accuracy. If an increase of amylase above the clinically notable value (≥ 300 U/L) is observed at any post randomization visit, lipase should be tested to determine the origin of elevated amylase (pancreatic versus extra pancreatic)
  - Urinalysis: leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, and urobilinogen.
  - Urine beta-hCG (females of childbearing potential only). If the urine pregnancy test is positive, do not dose and confirm with a serum pregnancy test.
- Vital signs: blood pressure and heart rate
- Dispense study drug and patient diary
- Review study drug accountability and compliance
- EDSS and neurological examination
- Suicidality assessment using the C-SSRS
- Record concomitant therapy
- Record AEs/SAEs

10.3.6. Visit 6 (Month 12/Week 52 ± 5 days)

Note: Subjects are to be instructed not to take their dose of study drug at home, and will be administered study drug at the clinic after laboratory procedures have been completed. Subjects should arrive at the clinic in a fasted state.

The following assessments will be performed at Visit 6 (Month 12):

- Blood/urine sampling for the following laboratory tests (to be performed predose):
  - Hematology: RBC count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, MCV, MCH, and MCHC
    Note: All total WBC and differential WBC counts will be blinded during the study.
  - Blood chemistry: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, random glucose, albumin, alkaline phosphatase, creatinine, SGPT/ALT, SGOT/AST, GGT, amylase, total bilirubin, conjugated bilirubin, hemoglobin A1c, and total cholesterol, triglycerides, HDL and LDL. Abnormal laboratory parameters inconsistent with clinical presentation of MS or suspicious of underlying medical condition should be repeated for accuracy. If an increase of amylase above the clinically notable value (≥ 300 U/L) is observed at any post

randomization visit, lipase should be tested to determine the origin of elevated amylase (pancreatic versus extra pancreatic)

- Urinalysis: leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, and urobilinogen
- Urine beta-hCG (females of childbearing potential only). If the urine pregnancy test is positive, do not dose and confirm with a serum pregnancy test.
- Coagulation panel: PT and PTT
- sTSH
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- Standard PK sampling: PK sample is to be taken prior to dose administration

- Administer study drug
- Complete physical examination: including evaluation of heart, lung, head and neck, abdominal, neurological, skin, and extremities
- Weight
- Vital signs: blood pressure and heart rate
- 12-lead ECG
- Dispense study drug and patient diary
- Review study drug accountability and compliance
- Brain MRI
- EDSS and neurological examination
- MSFC AND LCLA
- MSQOL-54
- Pulmonary function tests including FEV_1 and FVC measurements, and DLCO
- OCT evaluation
- Dermatological examination
- Suicidality assessment using the C-SSRS
- Record concomitant therapy
- Record AEs/SAEs

10.3.7. Visit 7 (Month 15/Week 65 ± 5 days)

The following assessments will be performed at Visit 7 (Month 15):

- Blood/urine sampling for the following laboratory tests:

  - Hematology: RBC count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, MCV, MCH, and MCHC
    Note: All total WBC and differential WBC counts will be blinded during the study.
  - Blood chemistry: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, random glucose, albumin, alkaline phosphatase, creatinine, SGPT/ALT, SGOT/AST, GGT, amylase, total bilirubin, conjugated bilirubin, hemoglobin A1c. Abnormal laboratory parameters inconsistent with clinical presentation of MS or suspicious of underlying medical condition should be repeated for accuracy. If an increase of amylase above the clinically notable value ($\geq$ 300 U/L) is observed at any post randomization visit, lipase should be tested to determine the origin of elevated amylase (pancreatic versus extra pancreatic)
  - Urinalysis: leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, and urobilinogen
  - Urine beta-hCG (females of childbearing potential only). If the urine pregnancy test is positive, do not dose and confirm with a serum pregnancy test.
- Vital signs: blood pressure and heart rate
- Dispense study drug and patient diary
- Review study drug accountability and compliance
- EDSS and neurological examination
- Suicidality assessment using the C-SSRS
- Record concomitant therapy
- Record AEs/SAEs

10.3.8. Visit 8 (Month 18/Week 78 ± 5 days)

The following assessments will be performed at Visit 8 (Month 18):

- Blood/urine sampling for the following laboratory tests:
  - Hematology: RBC count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, MCV, MCH, and MCHC
    Note: All total WBC and differential WBC counts will be blinded during the study.
  - Blood chemistry: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, random glucose, albumin, alkaline phosphatase, creatinine, SGPT/ALT, SGOT/AST, GGT, amylase, total bilirubin, conjugated bilirubin, hemoglobin A1c, and total cholesterol, triglycerides, HDL and LDL. Abnormal laboratory parameters inconsistent with clinical presentation of MS or suspicious of underlying medical condition should be repeated for accuracy. If an increase of

amylase above the clinically notable value (≥ 300 U/L) is observed at any post randomization visit, lipase should be tested to determine the origin of elevated amylase (pancreatic versus extra pancreatic)

- Urinalysis: leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, and urobilinogen
- Urine beta-hCG (females of childbearing potential only). If the urine pregnancy test is positive, do not dose and confirm with a serum pregnancy test.
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- Vital signs: blood pressure and heart rate
- Dispense study drug and patient diary
- Review study drug accountability and compliance
- EDSS and neurological examination
- MSFC AND LCLA
- MSQOL-54
- Suicidality assessment using the C-SSRS
- Record concomitant therapy
- Record AEs/SAEs

10.3.9. Visit 9 (Month 21/Week 91 ± 5 days)

The following assessments will be performed at Visit 9 (Month 21):

- Blood/urine sampling for the following laboratory tests:
  - Hematology: RBC count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, MCV, MCH, and MCHC
    Note: All total WBC and differential WBC counts will be blinded during the study.
  - Blood chemistry: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, random glucose, albumin, alkaline phosphatase, creatinine, SGPT/ALT, SGOT/AST, GGT, amylase, total bilirubin, conjugated bilirubin, hemoglobin A1c. Abnormal laboratory parameters inconsistent with clinical presentation of MS or suspicious of underlying medical condition should be repeated for accuracy. If an increase of amylase above the clinically notable value (≥ 300 U/L) is observed at any post randomization visit, lipase should be tested to determine the origin of elevated amylase (pancreatic versus extra pancreatic)
  - Urinalysis: leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, and urobilinogen

  - Urine beta-hCG (females of childbearing potential only). If the urine pregnancy test is positive, do not dose and confirm with a serum pregnancy test.
- Vital signs: blood pressure and heart rate
- Dispense study drug and patient diary
- Review study drug accountability and compliance
- EDSS and neurological examination
- Suicidality assessment using the C-SSRS
- Record concomitant therapy
- Record AEs/SAEs

10.3.10. Visit 10 (Month 24/Week 104 ± 5 days)

Patients are expected to remain in Part B for 24 months.

The following assessments will be performed at Visit 10 (Month 24):

- Blood/urine sampling for the following laboratory tests:
  - Hematology: RBC count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, MCV, MCH, and MCHC
    Note: All total WBC and differential WBC counts will be blinded during the study.
  - Blood chemistry: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, random glucose, albumin, alkaline phosphatase, creatinine, SGPT/ALT, SGOT/AST, GGT, amylase, total bilirubin, conjugated bilirubin, hemoglobin A1c, and total cholesterol, triglycerides, HDL and LDL. Abnormal laboratory parameters inconsistent with clinical presentation of MS or suspicious of underlying medical condition should be repeated for accuracy. If an increase of amylase above the clinically notable value (≥ 300 U/L) is observed at any post randomization visit, lipase should be tested to determine the origin of elevated amylase (pancreatic versus extra pancreatic)
  - Urinalysis: leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, and urobilinogen
  - Urine beta-hCG (females of childbearing potential only). If the urine pregnancy test is positive, do not dose and confirm with a serum pregnancy test.
  - Coagulation panel: PT and PTT
  - sTSH
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  - Standard PK sampling: PK samples are to be taken 2 to 6 hours following administration

- Complete physical examination: including evaluation of heart, lung, head and neck, abdominal, neurological, skin, and extremities
- Weight
- Vital signs: body temperature, blood pressure and heart rate
- 12-lead ECG
- If patients will continue on treatment, dispense study drug and patient diary
- Review study drug accountability and compliance
- Brain MRI
- EDSS and neurological examination
- MSFC AND LCLA
- MSQOL-54
- Pulmonary function tests including FEV_1 and FVC measurements, and DLCO
- OCT evaluation
- Dermatological examination
- Suicidality assessment using the C-SSRS
- Record concomitant therapy
- Record AEs/SAEs

10.4. Unscheduled Relapse Assessment Visit (Part A and Part B)

Patients should be evaluated by following the onset of any new or recurrent neurological symptoms as detailed in Section 9.1.2.3.

During an unscheduled relapse assessment visit the following assessments will be performed:

- Blood/urine sampling for the following laboratory tests:
  - Hematology: RBC count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, MCV, MCH, and MCHC
    Note: All total WBC and differential WBC counts will be blinded during the study.
  - Blood chemistry: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, random glucose, albumin, alkaline phosphatase, creatinine, SGPT/ALT, SGOT/AST, GGT, amylase, total bilirubin, conjugated bilirubin, hemoglobin A1c

  - Urinalysis: leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, and urobilinogen
- Vital signs: body temperature, blood pressure and heart rate
- EDSS and neurological examination
- MSFC and LCLA
- Suicidality assessment using the C-SSRS
- Record concomitant therapy
- Record AEs/SAEs

After the Unscheduled Relapse Assessment Visit, patients should return to their usual visit schedule.

10.5. Early Termination Visit

Patients who prematurely discontinue study treatment will be asked to complete an early termination visit. The following assessments will be performed:

- Blood/urine sampling for the following laboratory tests:
  - Hematology: RBC count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, MCV, MCH, and MCHC
    Note: All total WBC and differential WBC counts will be blinded during the study.
  - Blood chemistry: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, random glucose, albumin, alkaline phosphatase, creatinine, SGPT/ALT, SGOT/AST, GGT, amylase, total bilirubin, conjugated bilirubin, hemoglobin A1c. Abnormal laboratory parameters inconsistent with clinical presentation of MS or suspicious of underlying medical condition should be repeated for accuracy. If an increase of amylase above the clinically notable value (≥ 300 U/L) is observed at any post randomization visit, lipase should be tested to determine the origin of elevated amylase (pancreatic versus extra pancreatic)
  - Urinalysis: leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, and urobilinogen
  - Urine beta-hCG (females of childbearing potential only). If the urine pregnancy test is positive, do not dose and confirm with a serum pregnancy test.
  - Coagulation panel: PT and partial thromboplastin time PTT
  - sTSH
  -
  -

  - PK sampling
- Complete physical examination: including evaluation of heart, lung, head and neck, abdominal, neurological, skin, and extremities
- Weight
- Vital signs: body temperature, blood pressure and heart rate
- 12-lead ECG
- Review study drug accountability and compliance
- Brain MRI
- EDSS and neurological examination
- MSFC and LCLA
- MSQOL-54
- Pulmonary function tests including FEV_1, FVC, and DLCO measurements
- OCT evaluation
- Dermatological examination
- Suicidality assessment using the C-SSRS
- Record concomitant therapy
- Record AEs/SAEs

10.6. Follow-Up

Patients will be asked to return for a follow-up visits 4 weeks after their last dose of study treatment of either Part A or Part B.

During the follow-up visit the following assessments will be performed:

- Blood/urine sampling for the following laboratory tests:
  - Hematology: RBC count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, MCV, MCH, and MCHC
    Note: All total WBC and differential WBC counts will be blinded during the study.
  - Blood chemistry: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, random glucose, albumin, alkaline phosphatase, creatinine, SGPT/ALT, SGOT/AST, GGT, amylase, total bilirubin, conjugated bilirubin, hemoglobin A1c. Abnormal laboratory parameters inconsistent with clinical presentation of MS or suspicious of underlying medical condition should be repeated for accuracy. If an increase of amylase above the clinically notable value (≥ 300 U/L) is observed at any post randomization visit, lipase should be tested to determine the origin of elevated amylase (pancreatic versus extra pancreatic)

  - Urine beta-hCG (females of childbearing potential only). If the urine pregnancy test is positive, do not dose and confirm with a serum pregnancy test.
- Vital signs: body temperature, blood pressure and heart rate
- 12-lead ECG
- Suicidality assessment using the C-SSRS
- Record previously ongoing AEs/SAEs

10.7. Study Stopping Rules

The Sponsor has the right to terminate the study prematurely for safety reasons. In addition, the Sponsor may terminate the study prematurely for administrative reasons at any time. In all cases all necessary measures have to be taken to guarantee appropriate safety follow-up of all patients already included in the study.

The IEC or IRB and the Regulatory Authorities will be informed in writing about any premature termination of the study.

11. METHODS OF ASSESSMENT

Tests and assessments are common to Parts A and B of the study unless otherwise indicated.

The study design is shown in Figure 1. Tests and Assessments are outlined Table 1 and Table 2 (Part A), Table 3 and Table 4 (Part B), and Table 5 (cardiac monitoring during dose titration), and additional detail regarding procedure is included in Section 10.

11.1. Efficacy Assessments

11.1.1. Magnetic Resonance Imaging (MRI)

Brain MRIs will be acquired with and without Gadolinium. The same MRI protocol will be used across all sites. To ensure quality data and standardization the same machine and software should be used throughout the study. MRIs for MS lesions will be read blinded to treatment allocation at a centralized reading facility.

In Part B and in the Blinded Extension to Part A, MRI scans should not be performed until 30 days after the last dose of methylprednisolone treatment for relapse. Previously scheduled MRIs should be rescheduled as necessary if a relapse occurs.

Total number of GdE lesions, number of new or enlarging hyperintense T2-weighted lesions, lesion volume (T2-weighted images), volume of unenhancing T1-weighted lesions and brain volume (i.e., brain atrophy) will be collected and reported.

The MRI scans will be read locally for non-MS pathology.

11.1.2. Expanded Disability Status Scale (EDSS) and Neurological Examination

The EDSS is a standardized method, widely accepted, numerical scale used to evaluate disability in people with MS (Kurtzke, 1983).

The EDSS is evaluated according to signs and symptoms observed during a standard neurological examination. These clinical observations are classified in 7 FS scales, each of them grading signs and symptoms for different neurological functions: pyramidal, cerebellar, brainstem, sensory, bowel or bladder, visual, and cerebral.

The study will require the same blinded evaluator (refer to Section 9.1.2.2) should perform all EDSS assessments for an individual patient when possible. In addition, EDSS raters will be certified using the Neurostatus Standardized Examination and Assessment prior to study initiation and examiners will be re-certified every two years throughout the conduct of the study.

11.1.3. Relapse Assessment

A relapse is defined as the occurrence of new or worsening neurological symptoms attributable to MS and immediately preceded by a relatively stable or improving neurological state of at least 30 days. The new or worsening neurological symptoms must be accompanied by objective neurological worsening consistent with an increase of at least half a point on the EDSS, or 2 points on one of the appropriate FS scores, or 1 point on two or more of the appropriate FS scores. The change must be documented by the blinded evaluator at either scheduled or unscheduled visits and must affect the FS scales that correspond to the patient's symptoms (e.g.,

pyramidal, gait, cerebellar, brainstem, sensory, or visual). Symptoms must persist for > 24 hours and should not be attributable to confounding clinical factors (e.g. fever, infection, injury, adverse reactions to concomitant medications). When a patient experiences new or worsening symptoms that may indicate a possible relapse, he/she should telephone the treating investigator within 48 hours of symptoms onset. The treating investigator, study nurse, or other medically qualified individual will conduct a telephone questionnaire and, as necessary, will arrange an unscheduled relapse assessment visit.

11.1.4. Multiple Sclerosis Functional Composite (MSFC)

The MSFC (Cutter, 1999) is a battery of the following 3 individual scales:

- The Timed 25-Foot Walk is a quantitative measure of lower extremity function
- The 9-Hole Peg Test is a quantitative measure of upper extremity (arm and hand) function
- The PASAT-3 is a measure of executive function cognition that specifically assesses auditory information, processing speed, and flexibility, as well as calculation ability

The same person, either the blinded evaluator or another independent designated team member trained in conducting MSFC assessments should administer the 3 scales that make up the MSFC with each participating patient throughout the study.

The MSFC z-score is calculated by creating z-scores for each component of the MSFC, as explained below, and averaging them to create an overall composite score, i.e.,

MSFC z-score = (Z25-foot-walk + Z9HPT + ZPASAT3)/3, where Zxxx refers to Z-scores

Details on the calculations of the z-score for each component will be described in the statistical analysis plan (SAP).

11.1.5. Low-Contrast Letter Acuity Test (LCLA)

The LCLA, which is performed with the MSFC assessments, is performed with a standardized set of charts (e.g. Sloan letter charts or Tumbling E charts) to assess low contrast visual acuity. Each chart corresponds to a different contrast level, and charts are scored according to the number of letters that are identified correctly. The LCLA captures aspects of neurological dysfunction that is not assessed by the EDSS or MSFC, and has been proposed as an additional component to the MSFC (Balcer, 2003).

11.1.6. Multiple Sclerosis Quality of Life-54 (MSQOL-54)

The MSQOL-54 is a multidimensional health-related quality of life measure that combines both generic and MS-specific items into a single instrument (Vickrey, 1995). This 54-item instrument generates 12 subscales along with two summary scores, and two additional single-item measures. The subscales are: physical function, role limitations-physical, role limitations-emotional, pain, emotional well-being, energy, health perceptions, social function, cognitive function, health distress, overall quality of life, and sexual function. The summary scores are the physical health composite summary and the mental health composite summary. The single item measures are satisfaction with sexual function and change in health.

The MSQOL-54 is a structured, self-report questionnaire that the patient can generally complete with little or no assistance. It may also be administered by an interviewer. However, patients with visual or upper extremity impairments may need to have the MSQOL-54 administered as an interview by the study nurse (or study coordinator). Interviewers should be trained in basic interviewing skills and in the use of this instrument.

11.2. Safety Assessments

11.2.1. Clinical Safety Assessments

Physical Examination

A complete physical examination will include evaluation of heart, lung, head and neck, abdominal, skin, and extremities. The EDSS, performed by the blinded evaluator, serves as the neurological examination. An interim (or brief) physical examination will include areas with previously noted abnormalities and/or that are associated with any new complaints from the patient.

Initial neurological examination will be a part of the physical examination at screening and if warranted by an unscheduled visit. All significant findings that are present at screening must be reported on the relevant medical history/current medical conditions eCRF. Significant findings made after randomization that meet the definition of an AE must be recorded on the AEs eCRF.

Height and Weight

Height will be measured at screening in Part A and Part B and at the end of the study.

Weight will be measured at screening, Baseline (Day 1), Week 24 and end of study or early termination in Part A and screening, Baseline (Day 1), Month 12, and Month 24 or early termination in Part B.

Vital Signs

Blood pressure, heart rate and body temperature will be assessed.

For the Baseline (Day 1) visit and during dose titration (Day 5 and Day 8, as applicable), vital signs should be recorded after the patient has been supine for 10-15 minutes, systolic and diastolic blood pressure and heart rate will be measured 3 times using an automated validated device. The repeat measurements will be made at 2-minute intervals and the lowest of the 3 measurements will be recorded on the eCRF, based on systolic BP. For all other visits, vital signs will be assessed once and recorded on the eCRF.

In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. Orthostatic blood pressure will then be measured once with the patient in the standing position (after standing for 2 minutes). A sudden, significant fall in blood pressure (>20 mmHg) between 2 and 5 minutes after standing from the supine position will be interpreted as an orthostatic hypotension and will be documented in the patient chart and eCRF.

Patients will be carefully monitored after the first dose of study medication with a 6 hour post-dose monitoring period of hourly recording of orthostatic blood pressure.

Chest X-ray

To be performed only at screening of Part A and Part B. It is not required if performed within 60 days prior to randomization and if documentation is on file.

ECG

12-lead ECG to be performed after the patient has been resting quietly for at least 10-15 minutes.

Digital ECG devices will be provided to each clinical site by the central ECG laboratory for the duration of the study. The screening ECG report from the central reader must be available to confirm patient eligibility before randomization. A 12-lead ECG will be performed before and 6 hours after the first dose of study drug administration, while the patient is at the clinic.

Detailed instructions describing the process for recording and transmission of the digital ECGs will be outlined in the study-specific manual and provided to the site before the start of the study. Stand-alone ECGs will be obtained, printed, photocopied to preserve the ink if necessary, and kept at the site as source documentation.

ECG & Holter Monitoring

Dual function Digital ECG devices that are capable of capturing both stand-alone ECGs and Holter data will be provided to each clinical site by the central ECG laboratory for the duration of the study. Detailed instructions describing the process for recording and transmission of the digital ECGs and Holter data will be outlined in the study-specific manual and provided to the site before the start of the study.

Stand Alone/Static ECGs

Static ECGs will be captured at intervals as defined in the schedule of assessments (Section 9.1.1). The 12-lead ECG will be performed after the patient has been resting quietly in a supine position for at least 10-15 minutes. The screening 12-lead ECG report from a central reader must be available to confirm patient eligibility before randomization. 12-lead ECGs will be performed before and 6 hours after the first dose of study drug administration for all patients on Day 1 and for the first 75 patients at Day 5, while the patient is in the clinic. Six hour post dose ECG will be evaluated by treating neurologist, with input if needed from a local cardiologist or a central reader to confirm if extended monitoring is required. Simultaneously the ECGs will be printed out locally, photocopied to preserve the ink if necessary, and kept at the site as source documentation.

Each ECG tracing should be labeled with the study number, patient initials, patient number, date, and kept in the source documents at the study site. Only clinically significant abnormalities should be reported in the medical history/current medical conditions or adverse event CRF. Clinically significant findings must be discussed with the Medical Monitor before enrolling the patient in the study.

Continuous 12-lead Holter Monitoring

24 hour continuous cardiac monitoring (12 lead digital Holter monitoring) will be captured for all Part A patients at Day 1 and the first 75 patients at Day 5 and Day 8. Holter monitoring will start at least 15 minutes prior to dose and complete at least 24 hours post dose administration. Patient should be in the supine position prior to Holter application through the capture of the static pre-dose 12-lead ECG as well as for the acquisition of the 6 hour post dose 12-lead ECG. Holter analysis parameters will be described in the operations document.

Pulmonary Function Tests

Pulmonary function tests including FEV_1 and FVC measurements will be performed as scheduled Table 1 and Table 2 (Part A), and Table 3 and Table 4 (Part B). In addition, DLCO will be performed at screening and at the Week 24 visit of Part A and at Month 12 and Month 24 for Part B. With prior approval from the sponsor, DLCO will not be required at sites where there is no local DLCO testing facility available. In addition to scheduled assessments, the pulmonary function tests should also be performed as clinically indicated in the event of clinically significant pulmonary signs or symptoms. These tests will be performed at a high quality pulmonary function testing center with the appropriate certification (as locally required), and will be overseen by a pulmonologist who does not need to see the patients. If any PFT abnormalities occur, they will be followed until such time as resolution is confirmed or no further improvement is expected by the investigator (based on a follow-up period of not less than 3 months). Patients who discontinue due to respiratory AEs should be evaluated by a pulmonary specialist and further investigations (pulmonary function test, chest radiography, high resolution chest tomography or biopsy) should be performed as needed.

The technician should demonstrate the appropriate spirometry technique to the patient and follow the standard procedure. The quality of the tests must be accounted for including the technicians' comments (especially when, despite proper coaching of the patient, full collaboration cannot be achieved). A central trial statistician will calculate the FEV_1/FVC ratio.

A minimum of 3 acceptable maneuvers will be performed at each visit. The acceptability criteria are a satisfactory start of test and a satisfactory end of test. In addition, the technician should observe that the patient understood the instructions and performed the maneuver with a maximum inspiration, a good start, a smooth continuous exhalation, and maximal effort. The largest FVC and the largest FEV_1 will be recorded, after examining the data from all of the acceptable curves, even if the 2 values do not come from the same curve. Please refer to the American Thoracic Society/European Respiratory Society guidelines for standardization of spirometry and single breath determination of carbon monoxide uptake in the lung (MacIntyre, 2005; Miller, 2005a; Miller, 2005b).

If for any reason a patient is permanently discontinued from study medication the patient will have the pulmonary function tests performed at his last visit or within 30 days of the study drug discontinuation.

Two acceptable DLCO tests should be performed at each scheduled timepoint. A DLCO test is acceptable if it fulfills all the following criteria:

- Use of proper quality-controlled equipment
- Inspired volume of greater than 85% of largest vital capacity in less than 4 seconds

- A stable calculated breath hold for 10 (±2) seconds. There should be no evidence of leaks or Valsalva or Mueller maneuvers
- Expiration in less than 4 seconds (and sample collection time less than 3 seconds), with appropriate clearance of dead space and proper sampling/analysis of alveolar gas.
- All values must be corrected for hemoglobin concentration in the study, using the central laboratory haemoglobin value for the respective visit.

Ophthalmological Examination

OCT will be performed as scheduled in Table 1 and Table 2 (Part A), and Table 3 and Table 4 (Part B). If there is a suspicion of macular edema, then general retinal exams including eye history, visual acuity, and dilated ophthalmoscopy will be obtained. A general ophthalmologist can do the examination, although a retinal specialist would be preferred to do the exams wherever possible.

Dermatological (Skin) Examination

Dermatological (skin) evaluations will be performed as part of the physical exam at screening, and then every 6 months in Part A and yearly in Part B, as scheduled in Table 1 and Table 2 (Part A), and Table 3 and Table 4 (Part B). Dermatological (skin) evaluations will be performed by the treating investigator or medically qualified designee. Patients with any suspicious finding noted during the examination will be referred to an appropriately qualified dermatologist for evaluation and treatment, if warranted.

Suicidality Assessment

Suicidality will be assessed using the C-SSRS (Posner, 2011) at all study visits during Part A and Part B. It will be self-administered through a validated IVRS.

Monitoring of AEs and SAEs

Throughout the course of the study, Part A (both periods) and Part B, every effort must be made to remain alert to possible AEs or SAEs. Refer to Section 12 for definitions of AEs/SAEs, monitoring and reporting. Refer to Section 12.4 for AEs of special interest.

Monitoring of Concomitant Therapy

The use of concomitant medication and procedures will be monitored throughout the study in Part A (both periods) and Part B. Refer to Sections 9.5.7 and 9.5.8 for prohibited concomitant therapies.

11.2.2. Laboratory Safety Assessments

will analyze the samples. Further details of the procedures to be followed for sample collection, storage, and shipment will be documented in a laboratory manual.

Additional and repeat laboratory safety testing may be performed at the discretion of the Investigator.

The following laboratory tests will be performed to assess the safety profile of RPC1063:

- Routine safety laboratory tests:
  - Hematology - RBC count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, MCV, MCH, and MCHC. Total WBC and all differential WBC counts will be blinded information for the treating investigator after the onset of study treatment.
  - Chemistry - sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, random glucose, hemoglobin A1c, albumin, alkaline phosphatase, creatinine, SGPT/ALT, SGOT/AST, GGT, amylase, total bilirubin, conjugated bilirubin as scheduled in Table 1 and Table 2 (Part A), and Table 3 and Table 4 (Part B). In addition, the following parameters will be assessed at baseline and every 6 months of Part B: total cholesterol, triglycerides, HDL and LDL. Abnormal laboratory parameters inconsistent with clinical presentation of MS or suspicious of underlying medical condition should be repeated for accuracy. If an increase of amylase above the clinically notable value (≥ 300 U/L) is observed at any post randomization visit, lipase should be tested to determine the origin of elevated amylase (pancreatic versus extra pancreatic)
  - Urinalysis - leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, and urobilinogen
- The central laboratory will analyze routine blood samples. Blood samples taken at the screening visit are to be in the fasting state. Blood samples taken at subsequent visits are recommended to be in the fasting state. Details regarding collection of samples, shipment of samples, reporting of results, laboratory reference ranges, and alerting abnormal values will be supplied to the site before site initiation in a study laboratory manual. The results of the analysis will be made available to each site by the central laboratory, at the earliest, 48 hours after receipt of the samples by the central laboratory.
- Investigators will be asked to comment on those abnormalities on the respective laboratory result page, including a notation of the clinical significance of each abnormal finding in the patient's source documents. The laboratory sheets will be filed with the patient's source documents. Abnormal laboratory values should not be recorded on the AE eCRF; however, any diagnoses (or signs or symptoms if a diagnosis is not possible) associated with the abnormal findings should be recorded on the AE eCRF.
- Pregnancy test: serum beta-hCG must be performed at screening (Part A and Part B) in women of childbearing potential; urine beta-hCG will be performed in women of childbearing potential at each visit (Part A and Part B), and if positive, do not dose, and confirm with a serum pregnancy test.
- Coagulation panel: PT and PTT. To be performed at screening, at Week 24/end of study of Part A and Month 24/end of study of Part B, and at follow-up visits.
- sTSH: To be performed at screening, at Week 24/end of study of Part A, and yearly during Part B.

- Serology testing will be performed at screening of Part A and Part B to determine the patient's immune status with respect to the following viruses:
  - VZV
  - HIV antibodies
  - anti-hepatitis A virus IgM
  - HBsAg and HBcAg IgM
  - anti-HCV IgG or IgM.

Patients who are negative for VZV IgG antibodies at screening can undergo appropriate varicella zoster vaccination and be enrolled 30 days after vaccination has been completed. Patients testing positive for HIV or for serological markers of acute or chronic hepatitis A, B, or C will be excluded from the study unless they are indicative of prior hepatitis B vaccination or cured hepatitis A or B and accompanied by normal liver transaminase values.

- Syphilis RPR: Patients must have a negative RPR result to be enrolled or, in the event of a false positive result on RPR, a negative treponeme-specific test performed at the central laboratory.
- TB test: to be assessed using the purified protein derivative test, QuantiFERON Gold, or other interferon gamma release assay (as locally available), and CXR at screening of Part A and Part B. All testing must be completed prior to administration of study drug on Day 1.

11.2.3. PK and PD Assessments

PK samples will be shipped to . Details of the procedures to be followed for sample collection, storage, and shipment will be documented in a separate PK Laboratory Manual.

The following PK and PD assessments will be performed:

- Standard PK sampling: PK samples are to be taken predose or at 2 to 6 hours postdose following administration, as indicated in the Schedule of Events
- Plasma protein biomarker analysis (cytokines, chemokines, other inflammatory proteins)
- Total Igs: IgA, IgG, IgM

The bioanalytical assay for the determination of RPC1063 and its metabolites RP101075, RP101442, and RP101988 in K_2 EDTA human plasma utilizes a liquid/liquid extraction with ultra performance liquid chromatography (UPLC) separation and Tandem Mass Spectrometry (MS/MS) detection. Quantification is achieved using analyte peak area to internal standard peak area. For each analyte, a stable labeled version (tri-deuterium) was used as the internal standard. The method was validated for the concentration range of (RPC1063 and RP101075), (RP101442), and (RP101988). The method was demonstrated to be selective, precise and accurate for analysis of RPC1063 and its metabolites in human plasma. The assay performance is not affected by hemolysis or lipemia.

RPC1063 and its metabolites were shown to be stable for at least 31 days at -70°C in human plasma and a long term stability program (-20°C and -70°C) is in progress.

12. SAFETY DEFINITIONS, MONITORING, AND REPORTING

Throughout the study, the Investigator will remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the patient and appropriate medical intervention should be provided if necessary.

At the signing for the informed consent form, patients should be given names and telephone numbers of site staff for reporting AEs and medical emergencies.

12.1. Adverse Events (AEs)

The AE definitions and reporting procedures provided in this protocol comply with current CFR 21 Part 312. An AE is any untoward medical occurrence that does not necessarily have a causal relationship with the investigational medicinal product. An AE can therefore be any unfavorable or unintended sign, including an abnormal laboratory finding, symptom or disease temporally associated with the use of an investigational medicinal product whether or not considered related to the investigational medicinal product.

Relapses and MS disease progression will be monitored as study endpoints, but will not be recorded as AEs.

AEs will be monitored throughout the entire study. Investigators will ask the patient at each visit if they have experienced any untoward occurrence since the last study visit. All AEs will be recorded on the eCRFs provided: a description of the event, severity, time of occurrence, duration, any action (e.g. treatment and follow up tests) and the outcome should be provided along with the Investigator's assessment of the relationship to the study treatment.

AEs will be recorded from the start of study drug treatment until 28 days following the last dose of treatment with the study drug.

If known, the event diagnosis should be recorded rather than listing individual signs or symptoms. AEs must be graded as being mild, moderate or severe and their approximate duration given. Definitions of severity are as follows:

Mild: an AE usually transient in nature and generally not interfering with normal activities;

Moderate: an AE that is sufficiently discomforting to interfere with normal activities;

Severe: an AE that is incapacitating and prevents normal activities.

Even if the Investigator feels there is no relationship to the study drug, all AEs MUST be recorded in the eCRF. The Investigator is requested to assess the relationship of any AEs to treatment using the following definitions:

Unrelated: those AEs which are clearly and incontrovertibly due to extraneous causes (concurrent drugs, environment etc.) and do not meet the criteria for drug relationship listed under Unlikely, Possible, Probable or Related.

Unlikely: an AE may be considered unlikely if it includes at least the first two features:

- It does not follow a reasonable temporal sequence from administration of the drug.

- It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- It does not follow a known pattern to the suspected drug.
- It does not reappear or worsen when the drug is re-administered.

Possible: an AE may be considered possible if it includes at least the first two features:

- It follows a reasonable temporal sequence from administration of the drug.
- It could readily have been produced by the patient's clinical state, environment or toxic factors, or other modes of therapy administered to the patient.
- It follows a known response pattern to the suspected drug.

Probable: an AE may be considered probable if it includes at least the first three features:

- It follows a reasonable temporal sequence from administration of the drug.
- It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient.
- It disappears or decreased on cessation or reduction in dose. There are exceptions when an AE does not disappear upon discontinuation of the drug (e.g. bone marrow depression, fixed drug eruptions, tardive dyskinesia, etc).
- It follows a known pattern of response to the suspected drug.

Related: an AE may be considered related if it includes all of the following features:

- It follows a reasonable temporal sequence from administration of the drug.
- It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient.
- It disappears or decreased on cessation or reduction in dose. There are exceptions when an AE does not disappear upon discontinuation of the drug. For example: bone marrow depression, fixed drug eruptions, tardive dyskinesia, etc.
- It follows a known pattern of response to the suspected drug.
- It reappears or worsens if the drug is re-administered.

12.2. Serious Adverse Events (SAEs)

An SAE is any untoward medical occurrence or effect that fulfills the following criteria:

- Results in death
- Is life-threatening (NOTE: the term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
    - Requires hospitalization or prolongation of existing inpatient hospitalization

- Results in persistent or significant disability or incapacity
- Is a congenital abnormality/birth defect
- Important medical events not captured by the above but which may, for example, require medical intervention to prevent one of the outcomes above.

Medical and scientific judgment 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 hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Uncomplicated cases of relapse and MS disease progression requiring hospitalization or otherwise meeting the above serious criteria do not need to be reported as SAEs, unless there are other diagnoses or complications which meet serious criteria.

12.3. Reporting of Serious Adverse Events

Full details of the procedures to be adopted will be documented in a safety management plan approved by responsible parties, in brief:

The Investigator will report any SAE that occurs to any patient from the time written informed consent is signed through the last visit. All SAEs that occur within 28 days of the last dose of treatment with the study drug, whether or not considered related to the investigational product, must also be reported. Any SAE that is ongoing when the patient completes the study or discontinues from the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

Any AE considered serious by the Investigator or Sub-investigator or that meets serious criteria should be reported to using the remote data capture (RDC) system. Data entry must be completed within 24 hours from the time the study site personnel first learned of the event.

In the event that RDC entry is not possible (e.g. system failure or access problems), the study site should complete the paper SAE report form and fax the form to within 24 hours of awareness of the event. The RDC system should be updated as soon as it is available.

Contact information for the

Refer to Study Operations Manual for local phone numbers.

The initial report should be promptly followed by detailed, written reports, which will include copies of hospital case records, discharge summaries, autopsy reports and other documents when

requested and applicable. For unrelated cases, a full detailed case description may negate the need for additional hospital case records, discharge summaries etc.

12.4. Monitoring of Patients with Adverse Events

Investigators must carefully monitor each patient for AEs. This includes clinical laboratory variables. Assessments must be made of the seriousness, severity and relationship to the administration of the study treatment. After the initial AE/SAE report the Investigator is required to follow up proactively each patient and provide further information to on the patient's condition. During the study all AE/SAEs should be followed up to resolution unless the event is considered by the Investigator to be unlikely to resolve due to the patient's underlying disease, or the patient is lost to follow up.

Monitoring of Patients with Adverse Events of Special Interest

Several of the AEs noted in fingolimod clinical studies may be a consequence of S1P1R stimulation and will therefore be closely monitored in the RPC01-201 study. These AEs include:

a. Bradycardia and heart conduction abnormalities. Dose-related transient, reversible bradycardia, symptomatic bradycardia, and first, second, or higher degree atrioventricular block were reported primarily as first dose effects in fingolimod studies. The heart rate reduction observed with sphingosine-1-receptor agonists is an expected effect of S1PR modulation and appears to be conducted through the same pathway as vagus nerve stimulation. In addition, these negative chronotropic effects of S1P1R agonists appear to attenuate over time secondary to S1PR desensitization and internalization on cardiac myocytes (Kovarik 2008). This effect appears to occur with increasing exposures of study drug, thus gradual titration of the dose of RPC1063 over several days may mitigate against larger reductions in HR.

b. Pulmonary toxicity. An initial sharp decrease followed by a slow progressive decline over time in FEV_1 was observed in fingolimod clinical studies. Nonclinical toxicity studies with RPC1063 have revealed the potential for pulmonary toxicity at doses considerably higher than the pharmacologically active dose. FEV_1, FVC, and DLCO will be measured in all patients. Every patient whose PFTs are abnormal will be followed until such time as resolution is confirmed or no further improvement is expected by the investigator (based on a follow-up period of not less than 3 months).

c. Hepatotoxicity. Fingolimod caused frequent, reversible liver enzyme elevations greater than 3-fold above the upper limit of normal in up to 12% of patients; this was a significant cause of cessation of therapy. In this study, clinical chemistry analyses to assess LFTs will be performed. Every patient whose LFTs are abnormal will be followed until values return to baseline.

d. Macular edema. Instances of serious macular edema were reported in fingolimod renal transplant studies, and a 0.8% incidence was reported as an SAE in fingolimod (1.25 mg dose) MS clinical studies. Nonclinical studies with RPC1063 have not revealed eye-related toxicities. In this study, measurement of central foveal thickness by OCT will be performed in all patients. For patients

with abnormal OCT findings or with visual signs or symptoms of macular edema, a general ophthalmologic examination including eye history, visual acuity, and dilated ophthalmoscopy will also be performed. Every patient whose ophthalmic evaluations reveal abnormalities will be followed until values return to baseline or no further improvement is expected by the investigator (based on a follow-up period of not less than 3 months).

Overall, the following procedures should be followed:

- Vital signs will be assessed in supine and standing position at every visit. A sudden, significant fall in blood pressure (> 20 mmHg) between 2 and 5 minutes after standing from the supine position will be interpreted as an orthostatic hypotension and will be documented in the patient chart and eCRF.
- Patients will be closely monitored in the clinic after their first dose of the initial dose titration regimen for a period of 6 hours after treatment. ECGs will occur predose and at Hour 6 following dosing, with more frequent assessments as clinically indicated; vital signs, including orthostatic blood pressure assessment, will be assessed predose and then hourly for 6 hours following dosing. See the monitoring guidelines in Section 10.2.1.1 for further details.
- Clinicians should be particularly mindful of patients who have a low pulse at baseline (spontaneously or through drug induced ß-receptor blockade), prior to administration of the study drug. Atropine IV is recommended as the first line treatment of bradycardia, up to a maximum daily dose of 3 mg. Furthermore, the common guidelines for treatment of bradycardia (e.g. Advanced Cardiac Life Support-ACLS guidelines) should be followed as appropriate:
  - In case of clinical symptoms or hypotension, administration of atropine 1 mg, repeated administration in 3-5 minutes.
  - If heart rate and/or blood pressure remains unresponsive, consider administration of dopamine drip 5-20 µg/kg/min or epinephrine drip 2-10 µg/min.
  - Performance of transcutaneous pacing may also be considered
  - In the setting of decreased blood pressure, isoproterenol should be avoided or used with caution.
- Any condition that might affect the outcome of pulmonary function testing (FEV_1 and FVC) including infection, respiratory symptoms, occupational exposures (including asbestos) and cigarette smoking, needs to be collected before every PFT testing and transcribed to the pulmonary function tests eCRF page. If patients have decline in PFT values (FEV_1 and/or FVC) below 50% of the predicted values, treatment should be discontinued. If a patient discontinues due to respiratory AE, the Investigator should ensure that the patient has adequate evaluations as clinically indicated by a pulmonologist (consider pulmonary function tests, chest X-ray or high resolution computed tomography, based on findings of the other exams) at the time of the AE. For patients with pulmonary nodules, lung biopsy should be considered (Cryptococcus pneumonia and pulmonary TB have been reported with fingolimod). Further evaluations will be conducted until such time as resolution is confirmed or no

further improvement is expected by the investigator (based on a follow-up period of not less than 3 months).

- If patients have elevations in the LFTs (SGPT/ALT or/and SGOT/AST) greater than 3 times the ULN, a retest must be performed within 14 days. Upon confirmation of the abnormality, retests should be performed weekly until the elevated LFT decreases to below 3 times the ULN. If the LFT increase is confirmed to be above 5 times the ULN the study medication must be permanently discontinued.
- Study drug must be discontinued in any patient who has a diagnosis of macular edema that is of new onset or worsened since baseline. Patients with a diagnosis of macular edema must be followed up monthly and more frequently if needed based on the ophthalmologist's judgment. Further ophthalmological evaluations will be conducted until such time as resolution is confirmed or no further improvement is expected by the ophthalmologist (based on a follow-up period of not less than 3 months). If the patient does not show definite signs of improvement on examination 6 to 8 weeks after discontinuation of study drug, then therapy for macular edema in conjunction with an ophthalmologist experienced in the management of this condition should be initiated.
- The treating investigator will complete a dermatological (skin) examination for monitoring of the potential development of new cutaneous malignancies during the study. Patients with any suspicious finding noted during the examination will be referred to an appropriately qualified dermatologist for evaluation and treatment, if warranted. Dermatology examinations will be performed at screening, at 6 months for Part A, at 12 months and 24 months for Part B. For patients who discontinue treatment early, a dermatological (skin) examination will be performed at end of treatment.

12.5. Procedures to be Followed in the Event of Abnormal Laboratory Test Values

In the event of unexplained abnormal laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy. For abnormal laboratory test values related to AEs of special interest refer to Section 12.4.

12.6. Clinical Laboratory Parameters and Abnormal Laboratory Test Results

Clinically significant changes, in the judgment of the Investigator, in laboratory parameters (abnormalities) will be recorded as AEs.

During the treatment period, all Total WBC and WBC differential results will be blinded. If any of the following results are observed, the Investigator will be notified and asked to repeat the laboratory tests:

- Absolute lymphocyte count [ALC] < 200 cells/µL
- Absolute neutrophil count [ANC] < 1000 cells/µL
- Total WBC > 20,000 cells/µL

If the repeat values also exceed these limits, the Investigator will be informed that the patient's results for the abnormal parameter have fallen outside the acceptable thresholds.

If ANC or total WBC counts are confirmed outside the acceptable limits, the Medical Monitor will contact the treating investigator to request close monitoring for risk of infection and appropriate follow-up, at the discretion of the investigator.

If ALC results are confirmed as below 200 cells/µL, the investigator will be instructed that study drug is to be temporarily discontinued. Laboratory testing will be repeated weekly until the results have returned to within the following acceptable ranges:

- ALC > 500 cells/µL

When values have returned to acceptable values, the Investigator will be informed that the values are no longer outside of the acceptable range and that study drug may be restarted. (See Section 9.5.1 instructions on resuming treatment after dose interruptions.)

12.7. Abnormal Clinical Safety Findings

Clinically significant changes, in the judgment of the Investigator will be recorded as AEs.

12.8. Treatment of Overdose of Study Medication

An overdose is any dose of study treatment given to a patient or taken by a patient that exceeds the dose described in the protocol. There is no information regarding overdose with RPC1063. Any overdose, with or without associated AEs, must be promptly reported to Drug Safety Center. Overdoses do not need to be recorded as AEs in the eCRF; only in case of any AEs associated with the overdose, these should be reported on relevant AE/SAE sections in the eCRF.

12.9. Procedures in Case of Pregnancy

Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

Male patients should also be instructed to notify the treating investigator in the event that their female partner becomes pregnant. Attempts should be made to follow female partners of study patients, if they should become pregnant. The treating investigator must obtain informed consent from the pregnant partner of a study patient prior to collecting data on her pregnancy and its outcome.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to .

13. PLANNED STATISTICAL METHODS

13.1. General Considerations

All patients will be randomized to either placebo (Part A) or IFN β-1a (Part B), RPC1063 0.5 mg, or RPC1063 1 mg in a 1:1:1 ratio, stratified by the following factors:

- EDSS at Baseline (≤ 3.5, >3.5)
- Country

All efficacy and safety data will be listed by patient. Baseline is defined as the last observed measurement prior to the Day 1 receipt of randomized study medication.

Descriptive statistics will consist of the number of patients (n), mean, standard deviation (SD), median, minimum, and maximum for continuous variables and counts and percentages for categorical variables.

All analyses using or higher.

13.2. Sample Size Estimation

Part A

The primary analyses will compare the cumulative number of new GdE lesions at the end of Week 24 in each of the RPC1063 groups to the placebo group using a 2-sided Wilcoxon-Mann-Whitney test. For this type of nonparametric analysis, the parameter of interest for sample size/power considerations is the probability that a randomly selected patient in an active treatment arm will have fewer lesions than a randomly selected patient in the placebo arm. Limited data are available from which to estimate this parameter. However, based on the use of patient-level data from Tubridy et al. (1999) and Miller et al. (2003), estimates of this probability range from 0.634 to 0.754. Using the approach of Noether (1987), a sample size of 59 patients per group will provide 80% power to detect a difference if the true value of this probability is equal to 0.65 (Noether, 1987). Assuming a dropout rate of 15%, the planned enrollment is 210 patients (70 patients per arm).

Part B

Approximately 1200 patients with RMS will be randomized in this part of the study (approximately 400 per treatment group). The primary analyses will compare the ARRs in each of the RPC1063 groups to the IFN β-1a group using a Poisson regression model at the alpha = 0.025 level. The control ARR is assumed to be equal to 0.3 (Mikol, 2008). Assuming extra-Poisson variation (σ^2=1.3) (Polman, 2011) and 24 months of follow-up per patient, a total sample size of 999 patients (333 per arm) is estimated to provide 90% power to detect a 37% reduction in the ARR (i.e., an ARR of 0.19 for RPC1063) (Nicholas, 2011). In order to account for an assumed dropout rate of 17%, approximately 1200 patients (400 per arm) will be enrolled.

13.3. Statistical Analysis Plan

A Statistical Analysis Plan (SAP) will be written and finalized prior to any lock of the study database. The SAP will provide a detailed description of the statistical methods and expand on the details provided in the protocol. Additional analyses may be added. Tables, listing and figures shells will also be provided.

13.4. Randomization

Patients will be randomized into the study on Day 1 using an IVRS provided by .

Part A

- Patients will be randomized 1:1:1 to receive placebo, 0.5 mg RPC1063, or 1 mg RPC1063. The randomization will be stratified by country.

Part B

- Patients will be randomized 1:1:1 to receive IFN β-1a 30 μg, 0.5 mg RPC1063, or 1 mg RPC1063. The randomization will be stratified by baseline EDSS (≤ 3.5, > 3.5) and country.

Treatment groups are described in Section 9.5.1.

13.5. Analysis Populations

The following analysis populations will be used in the statistical analysis:

Intent-to-Treat (ITT): The ITT population will consist of all randomized patients who received at least 1 dose of study medication, with treatment assignment designated according to randomized treatment.

In Parts A and B, the primary efficacy analysis will be carried out in the intent-to-treat population.

Per Protocol (PP): The PP population will consist of the subset of the ITT population that excludes those patients who have had a major protocol violation. These will be defined prospectively, in advance of data lock and primary analyses, in the final SAP, by the (aggregate results blinded) project statistician. Membership in the PP population will be determined prior to unblinding.

Safety: The Safety population will consist of all patients receiving any study treatment and safety analyses will be carried out on this population according to highest dose of RPC1063 (up to 1 mg) actually received.

13.6. Statistical Methods

13.6.1. Missing Data

Part A

Last observation carried forward (LOCF) and mean imputation will be used for patients with missing post-baseline lesions. If a patient is missing at most 2 post-baseline scans, then the last non-missing, post-baseline observation will be carried forward to impute the missing value.

However, if there are no values to be carried forward or if the patient is missing more than 2 scans, then the mean number of lesions from patients in the same treatment group at the same visit will be used as the imputed value. Sensitivity analyses will be specified in the SAP.

Part B

Sensitivity analyses will be specified in the SAP.

13.6.2. Demographic and Baseline Data

Demographic and baseline data will be summarized by treatment group and frequency distributions and summary statistics presented.

13.6.3. Patient Disposition

Patient disposition will be summarized and summary statistics presented.

13.6.4. Efficacy

Part A

For the primary analysis, the cumulative number of GdE lesions from Week 12 to Week 24 will be compared between the 1 mg RPC1063 group and the placebo group using the stratified Wilcoxon-Mann-Whitney test, stratified by presence of GdE lesions at baseline (absent or present). This comparison will be assessed using a 2-sided test at the alpha=0.04944 level of significance (to keep the overall Part A level of significant at alpha=0.05, accounting for the O'Brien-Fleming adjustment and interim analysis) (Reboussin, 2000). If the comparison between the 1 mg RPC1063 group and placebo is statistically significant, then a second primary analysis will similarly compare the 0.5 mg RPC1063 group and the placebo group, also based on a 2-sided test at the alpha=0.04944 level of significance. Sensitivity and descriptive analyses will also be presented.

The secondary endpoint of the proportion of patients free of GdE lesions at Week 24 will be analyzed using a logistic regression model with treatment group (three levels) and presence of baseline GdE lesions (absent, present) as factors. Pairwise comparisons between the 1 mg RPC1063 group and placebo, and between the 0.5 mg RPC1063 group and placebo, will be tested.

Quantitative endpoints such as the percent brain volume change over 24 weeks will be analyzed using analysis of covariance models with treatment group as a factor and the baseline value of the corresponding parameter as a covariate.

Endpoints that are defined in terms of lesion counts will be analyzed using the Wilcoxon-Mann-Whitney test. These analyses will include only the two groups being compared.

All secondary endpoints will be analyzed using 2-sided tests at the 5% level of significance.

Part B

The primary analysis for the ARR will be carried out using a Poisson regression model. The model will compare treatment groups, adjusted for region, age, and the number of GdE lesions at baseline. To account for multiple comparisons, each of the 2 treatment comparisons with IFN β-1a will be tested at the alpha = 0.025 level. Results will be summarized by randomized treatment group and expressed as unadjusted and adjusted relapse rates, odds ratios, corresponding 95% confidence intervals, and p-values.

The relapse rate will be based on only those relapses that were determined by the treating investigator to meet the protocol-defined definition of relapse, based on the EDSS scores obtained by the blinded evaluator (Section 9.1.2.3). New or recurrent neurological symptoms that occur less than 30 days following the onset of a protocol-defined relapse will be considered part of the same relapse, i.e., if 2 relapses have onset days that are ≤30 days of one another, they will be counted as 1 relapse (see Section 9.1.2.3).

The relapse rate for each treatment group will be calculated as:

(total relapses in the arm) / (total days in the study for the arm) * 365.25

The 3 key secondary endpoints will be tested in order in ranking the RPC1063 1 mg dose above the RPC1063 0.5 mg dose. If both doses are significant on the primary endpoint, then the first comparison on the key secondary endpoints will be between the RPC1063 1 mg group and the IFN β-1a group at the 5% level of significance. If that comparison is successful, then the same endpoint will be tested for the RPC1063 0.5 mg group vs. the IFN β-1a group comparison at the 5% level of significance. This procedure will continue down the key secondary endpoint list until a comparison fails to reach statistical significance, . If only 1 RPC1063 dose is significant on the primary endpoint, then the will be employed on the surviving dose only, at the 2.5% level of significance for each key secondary endpoint.

The key secondary endpoints of cumulative number of new or enlarging T2 lesions between baseline and Month 12 and the number of GdE lesions at Month 12 will be analyzed using a negative binomial regression model with factors for treatment, region, age, and baseline number of GdE lesions. The key secondary endpoint of time to onset of disability progression will be compared between treatment groups using Kaplan-Meier estimation and a Cox proportional-hazards model adjusted for region, age, and baseline EDSS score. Results will be summarized by randomized treatment group and expressed as proportions, corresponding 95% confidence intervals, and p-values. Disability progressions confirmed at 3 months and at 6 months will be analyzed separately.

Other secondary endpoints that are defined as continuous variables will be analyzed using analysis of covariance models adjusted for region, age, and baseline measurements of the response parameter of interest. Other secondary endpoints defined as response proportions will be analyzed using a Cochran-Mantel-Haenszel test stratified by region and baseline EDSS category.

13.6.5. Pharmacokinetics

Population PK analyses will use the RPC1063 dose-concentration-time data from this study combined with data from other Phase 2 and Phase 3 studies to assess the influence of study patient covariates on the exposure of RPC1063.

13.6.6. Safety

The incidence of treatment-emergent AEs will be summarized for each treatment group overall, by severity, and by relationship to study drug. SAEs will be presented by treatment group and by relationship to study drug. Summary tables will present incidence estimates and individual event rates by system organ class as well as within each system organ class. Patients experiencing an event more than once with varying severity will be counted only once with the maximum severity within each system organ class/preferred term. For incidence of relationship to study drug, patients will be counted only once, in the category of the strongest relationship to study drug within each system organ class/preferred term.

13.6.7. Interim Analysis

An interim analysis of Part A will be completed approximately 1 month prior to completion of Part A enrollment. At this time point, it is estimated that approximately 80-90% of patients will have received treatment and approximately 45% of patients will have completed 12 weeks of treatment. The primary purpose of the interim analysis is to summarize safety endpoints and to provide a preliminary assessment of the primary efficacy endpoint. The efficacy endpoint for the interim analysis will be the number of GdE lesions using all data from patients who provide data through at least Week 12 (appropriately scaled). Based on the Lan-DeMets method for group sequential trials using O'Brien-Fleming boundaries (Reboussin, 2000), the significance levels at the interim and final analyses will be 0.00167 and 0.04944, respectively.

13.6.8. Data Monitoring Committee (DMC)

An independent DMC will be charged with monitoring accumulating data from the trial, as well as general aspects of trial conduct.

The committee will meet periodically during the study to review aggregate analyses by treatment group concerning enrollment, treatment compliance, adherence to follow-up schedule, and safety data from the trial. The DMC may recommend modifying or stopping the trial early due to safety concerns based on data reviews, including the interim analysis of Part A.

The blinding plan to assure that all personnel at Receptos and all personnel involved in the conduct of the study remain blinded to the results of interim reviews will be specified in the DMC Charter.

14. MONITORING PROCEDURES (QUALITY ASSURANCE)

The Sponsor has ethical, legal, and scientific obligations to conduct this study in accordance with established research principles and ICH GCP guidelines. As such, in order to fulfill these obligations and to maintain current of study progress, the Sponsor's monitors or representatives will visit the investigative sites during study conduct, in addition to maintaining telephone and written communication. On-site visits, telephone calls, and regular inspection of the eCRFs will be conducted in order to assess patient enrolment, compliance with protocol procedures, completeness and accuracy of data entered on the eCRFs, verification of eCRF data against original source documents, and occurrence of AEs. The Investigator must provide the monitor with full access to all source and study documents.

14.1. Routine Monitoring

Sponsor assigned monitors will conduct regular site visits to the investigational facilities for the purpose of monitoring various aspects of the study. The Investigator must agree to Sponsor-authorized personnel having direct access to the clinical (or associated) files and clinical study supplies (dispensing and storage areas) for all study patients considered for study entry for the purpose of verifying entries made in the eCRF, and assist with their activities, if requested. The Investigator will make available adequate time and space for monitoring visits.

The site must complete the eCRFs in a timely manner and on an ongoing basis to allow regular review by the Study Monitor.

Whenever a patient name is revealed on a document that is to be collected for the Sponsor the name must be blacked out permanently by the site personnel, leaving the initials visible, and annotated with the patient number as identification.

14.2. Inspections and Auditing Procedures

The Sponsor or its representative may conduct audits at the investigative sites including, but not limited to, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. All medical records (progress notes) must be available for audit. The Investigator agrees to participate with audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also inspect the Investigator during or after the study. The Investigator or designee should contact the Sponsor/CRO immediately if this occurs. He/she must cooperate fully with regulatory authorities or other audits conducted at a convenient time in a reasonable manner.

The purpose of an audit is to assess whether ethics, regulatory and quality requirements are fulfilled.

15. STUDY MANAGEMENT AND MATERIALS

15.1. Electronic Case Report Forms

An eCRF will be used to store and transmit patient information. The file structure and format for the eCRF will be provided by the Sponsor or their representative and should be handled in accordance with the instructions provided.

The eCRF must be reviewed and electronically signed, and dated by the Investigator.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by treating personnel or the study coordinator. The eCRF must be completed as soon as possible after any patient evaluation or communication. If data is to be changed due to erroneous input or other reason, an electronic audit trail will track these changes. The eCRFs and computers that store them must be accessible to Study Monitors and other regulatory auditors.

15.2. Data Collection

During each study visit, a physician participating in the study will maintain progress notes in the patient's medical records to document all significant observations. At a minimum, these notes will contain: the date of the visit and the corresponding day or visit in the study schedule (e.g., screening, Day 1, Day 28, etc.); general condition and status remarks by the patient, including any *significant* medical findings; the severity, frequency, duration, and resolution of any reported AE, and the Investigator's assessment as to whether or not the reported AE is study drug-related; changes in concomitant medications or dosages; and a general reference to the procedures completed; and the signature or initials of all physicians making an entry in the medical record (progress notes).

In addition, any contact with the patient via telephone or other means that provides significant clinical information will also be documented in the medical record (progress notes), as described above.

Information from the medical records (progress notes) and other source documents will be promptly transcribed to the appropriate section of the eCRF.

Changes to information in the medical record (progress notes), eCRF, and other source documents will be initialed and dated on the day the change is made by the Investigator or designee. If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change.

15.3. Source Documents Maintenance

Source documents contain the results of original observations and activities of a clinical investigation. Source documents include, but are not limited to, medical records (progress notes), computer printouts, screening logs and recorded data from automated instruments.

All source documents from this study will be maintained by the Investigator and made available for inspection by authorized persons. The original signed informed consent for each patient shall be filed with records kept by the Investigator and a copy shall be given to the patient.

15.4. Record Maintenance

All data derived from the study will remain the property of Receptos.

Records must be retained in accordance with the current ICH Guidelines on GCP. All essential study documents including records of patients, source documents, eCRFs and study drug inventory must be kept on file.

US FDA regulations (21 CFR 312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including eCRFs, consent forms, laboratory test results, and medical inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the US FDA and the applicable national and local health authorities are notified. The Sponsor or their representative will notify the Principal Investigator of these events.

Essential documents should be retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least two years have elapsed since the formal discontinuation of clinical development of the investigational products. However, essential documents may be retained for a longer period if required by the applicable regulatory requirements or by agreement with the Sponsor. The Sponsor is responsible for informing the Investigator when these documents need no longer be retained.

The Investigator will not dispose of any records relevant to this study without written permission from the Sponsor, and will provide the Sponsor the opportunity to collect such records. The Investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the Sponsor, its representatives and regulatory authorities.

If an Investigator moves, withdraws from an investigation or retires the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor.

15.5. Confidentiality

All information obtained during the conduct of the study with respect to the patient's state of health will be regarded as confidential. For disclosure of any such information, an agreement will be obtained in writing.

The Investigator must ensure that each patient's anonymity is maintained. On eCRFs and other documents submitted to the Sponsor or the CRO, patients must not be identified by name. Instead, patients will only be known by their initials and by the unique patient number allocated to them in order to ensure confidentiality on all study documentation. Patients will retain this unique number throughout the study. The Investigator will keep a separate log of these codes.

In order to comply with government regulatory guidelines and to ensure patient safety, it may be necessary for the Sponsor and its representative, the CRO personnel, the local research review board, or the US FDA to review patients' medical records as they relate to this study. Only the patient's unique number on the eCRFs will identify him/her, but their full names may be made known to a drug regulatory authority or other authorized government or health care officials, if necessary, and to personnel designated by the Sponsor.

Documents that are not for submission to the Sponsor or the CRO (e.g., consent forms) will be maintained by the Investigator in strict confidence, except to the extent necessary to allow monitoring by the Sponsor and the CRO, and auditing by regulatory authorities. No documents identifying patients by name will leave the investigative site and patient identity will remain confidential in all publications related to the study.

16. ADMINISTRATION PROCEDURES

16.1. Regulatory Approval

Receptos or their appointed agents will be responsible for ensuring that appropriate regulatory authority approvals are obtained, according to local country requirements.

No patient may enter the study until this approval has been obtained. A copy of the approval (where one is provided, according to local country requirements) will be provided to the Investigator and to the IRB(s)/IEC(s).

16.2. Protocol Amendments

In accordance with ICH Topic E 6 (R1) Guideline for GCP the Investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and documented approval from the IRB/IECs of a protocol amendment, except where necessary to eliminate an immediate hazard(s) to study patients, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone number(s)).

Any change to the protocol must be handled as a protocol amendment. Any potential amendment must be approved by the Sponsor. A written amendment must be submitted to the appropriate regulatory authorities and to the IRB/IECs assuming this responsibility. The Investigator must await IRB/IEC approval of protocol amendments before implementing the changes, except where necessary to eliminate apparent immediate hazard to patients. In these cases, the IRB/IEC must be notified within 5 days of the change.

All amendments to the protocol must be approved in writing by both the appropriate regulatory authorities and the IRB/IEC, except for administrative amendments, which require notification but not written approval. Once approved, the protocol amendment will be distributed to all recipients of the original protocol, with instructions to append the amendment to the protocol.

If, in the judgment of the local IRB/IEC, the Investigator and/or Sponsor, the protocol amendment alters the study design, procedures and/or increases the potential risk to the patient, the currently approved written informed consent form will require modification. The modified informed consent form must also be reviewed and approved by the Sponsor, appropriate regulatory authorities, and the IRB/IEC. In such cases, repeat informed consent must be obtained from patients enrolled in the study before participation continues.

16.3. Protocol Adherence and Deviations

The protocol must be read thoroughly and the instructions must be followed. However, exceptions will be made in emergency situations when the protection, safety, and well-being of the patient requires immediate intervention based on the judgment of the Investigator or a responsible, appropriately trained, and credentialed professional(s) designated by the Investigator as a sub-investigator.

In the event of a significant protocol deviation due to an emergency, accident, or error, the Investigator or designee must contact the Medical Monitor at the earliest possible time by

telephone. This allows for an early joint decision to be made as to whether or not the patient should continue in the study. The Investigator, the Sponsor, and the Medical Monitor will document this decision.

16.4. Publication Policy

After completion of the study, the Investigator(s) may prepare a joint publication with the Sponsor. The Investigator(s) must undertake not to submit any part of the data from this protocol for publication without the prior consent of Receptos.

16.5. Clinical Study Report

A final clinical study report will be prepared according to the ICH guideline on Structure and Contents of Clinical Study Reports. A final clinical study report will be prepared regardless of whether the study is completed or prematurely terminated. The Sponsor will provide each Investigator with a copy of the final report for retention.

16.6. Contractual and Financial Details

The Investigator (and/or, as appropriate, the hospital administrative representative) and the Sponsor will sign a clinical study agreement prior to the start of the study, outlining overall Sponsor and Investigator responsibilities in relation to the study. The contract should describe whether costs for pharmacy, laboratory and other protocol-required services are being paid directly or indirectly. Financial Disclosure Statements will need to be completed, as requested by FDA CFR 21 part 54.

16.7. Insurance, Indemnity and Compensation

Receptos undertakes to maintain an appropriate clinical study insurance policy.

Deviations from the study protocol - especially the prescription of a dose other than that scheduled in the study protocol, other modes of administration, other indications, and longer treatment periods - are not permitted and shall not be covered by the statutory patient insurance scheme.

16.8. Discontinuation of the Study

This study may be terminated by the Sponsor. The study may also be terminated prematurely at any time when agreed to by both the Investigators and the Sponsor as being in the best interests of patients, and justified on either medical or ethical grounds. In terminating the study, Receptos, the CRO and the Investigator will ensure that adequate consideration is given to the protection of the patients' interests.

16.9. Study Center File Management

The Investigator is responsible for assuring that the Study Center File is maintained. The Study Center File will contain, but will not be limited to, the information listed below:

1. Investigator's Brochure;
2. Current, signed version of the protocol and any previous versions of the protocol;

3. Protocol amendments (if applicable);
4. Operations Manual (if applicable);
5. Current informed consent form (blank) and any previous versions of the informed consent form;
6. Curricula Vitae of Investigator(s) and sub-investigator(s) and photocopy of their respective license(s) where required by law; Original US FDA Form 1572 (for all studies conducted under US Investigational New Drug [IND] regulations), signed by all Principal Investigators. The names of any sub-investigators must appear on this form. Investigators must also complete all regulatory documentation as required the ICH GCP and by local or national regulations;
7. Documentation of IRB/IEC approval of the protocol, the informed consent form, any protocol amendments, and any informed consent form revisions;
8. All correspondence between the Investigator, IRB/IEC, and the Sponsor/CRO relating to study conduct;
9. Lab certification(s);
10. Monitoring log;
11. Study drug invoices;
12. Signature list of all staff completing eCRFs; and
13. Signature list of all staff completing drug accountability summaries.

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18. APPENDICES

18.1. Appendix 1: Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic

interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee

must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific

information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the

publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

18.2. Appendix 2: Elements of Informed Consent

ELEMENTS OF INFORMED CONSENT

Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

- That the study involves research.
- The purpose of the study.
- The study treatment(s) and the probability for random assignment to each treatment.
- The study procedures to be followed including all invasive procedures.
- The subject's responsibilities.
- Those aspects of the study that are experimental.
- The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
- The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
- The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
- The compensation and/or treatment available to the subject in the event of study-related injury.
- The anticipated prorated payment, if any, to the subject for participating in the study.
- The anticipated expenses, if any, to the subject for participating in the study.
- That the subject's participation in the study is voluntary and that the subject may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
- That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
- That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the study are published, the subject's identity will remain confidential.

- That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
- The person(s) to contact for further information regarding the study and the rights of study subjects, and whom to contact in the event of study-related injury.
- The foreseeable circumstances and/or reasons under which the subject's participation in the study may be terminated.
- The expected duration of the subject's participation in the study.
- The approximate number of subjects involved in the study.