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

Statistical Analysis Plan 2.0 Part B Date: 05 June 2015

DISCLOSURE

REDACTED STATYSTICAL ANALYSIS PLAN PART B VERSION 2.0

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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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

June 5, 2015

Statistical Analysis Plan – Part B

Version 2.0

Prepared by:

Receptos, Inc.

Upon review of this document, the undersigned approves the statistical analysis plan. The analysis methods are acceptable, and the table, listing, and figure shell production can begin.

Approved by: _____ Date: _____

Receptos, Inc.

Approved by: _____ Date: _____

Receptos, Inc.

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AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARR	annualized relapse rate
AST	aspartate aminotransferase
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	diastolic blood pressure
DLCO	diffusing capacity of the lung for carbon monoxide
ECG	Electrocardiogram
eCRF	electronic case report form
EDSS	Expanded Disability Status Scale
FEV_1	forced expiratory volume at 1 second
FS	Functional System
FVC	forced vital capacity
GdE	gadolinium enhancing
GGT	gamma glutamyltransferase
HDL	high-density lipoprotein
IFN	interferon
IFN β-1a	interferon beta-1a
IM	intramuscular(ly)
ITT	intent-to-treat
IVRS	Interactive Voice Response System
LCLA	low-contrast letter acuity
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
NRI	non-responder imputation
OCT	optical coherence tomography
PD	pharmacodynamic(s)
PFT	pulmonary function test
PK	pharmacokinetic(s)
PP	per protocol
QD	once daily
QW	once weekly
RBC	red blood cell

RMS	relapsing multiple sclerosis
S1P1R	sphingosine 1-phosphate 1 receptors
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SDMT	Symbol Digit Modalities Test
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
ULN	upper limit of normal
WBC	white blood cell

1. ADMINISTRATIVE STRUCTURE

This study is being conducted under the sponsorship of Receptos, Inc. The clinical monitoring, data management and statistical analysis are being performed under contract with , in collaboration with Receptos, Inc.

1.1. Data Quality Assurance

The Clinical, Data Management, and Biostatistics departments at will work diligently and collaboratively, internally and with the sponsor, to ensure that the data collected and analyzed for this study are of the highest quality possible. This will be accomplished in part by having thorough edit checks written, programmed, and updated as needed to guarantee high quality data. Edit checks will be reviewed by the statistician, programmer and other team members on an ongoing basis to evaluate whether any checks need to be added or any existing checks need to be modified.

All analyses will be conducted using SAS® Version 9.1 or higher.

2. INTRODUCTION

RPC01-201 is a phase 2/3 clinical trial consisting of a 24-week placebo-controlled (Part A, phase 2) trial and a 24-month active-controlled (Part B, phase 3) trial of RPC1063 versus interferon (IFN) β-1a in patients with relapsing multiple sclerosis (RMS). The Part A, phase 2 portion of the study characterizes the short-term efficacy and safety profile of RPC1063 on improving disease activity as measured by magnetic resonance imaging (MRI) parameters over 24-weeks of treatment. The Part B, phase 3 portion of the study characterizes the efficacy and safety profile of RPC1063 on clinical outcomes (e.g., relapse rate and disability progression) in RMS patients treated for 24 months.

The analysis of the Part A portion of the study is covered under a separate statistical analysis plan (SAP). This SAP describes the statistical methods to be used during the reporting and analysis of clinical data collected in Part B of the study. All objectives, endpoints, and analysis methods described below apply to the Part B portion of the study only. This plan should be read in conjunction with the study protocol and the case report forms (CRFs).

3. OBJECTIVES

The primary objective is:

- 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

The secondary objectives of are:

- 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

The exploratory objectives are:

-

4. INVESTIGATIONAL PLAN

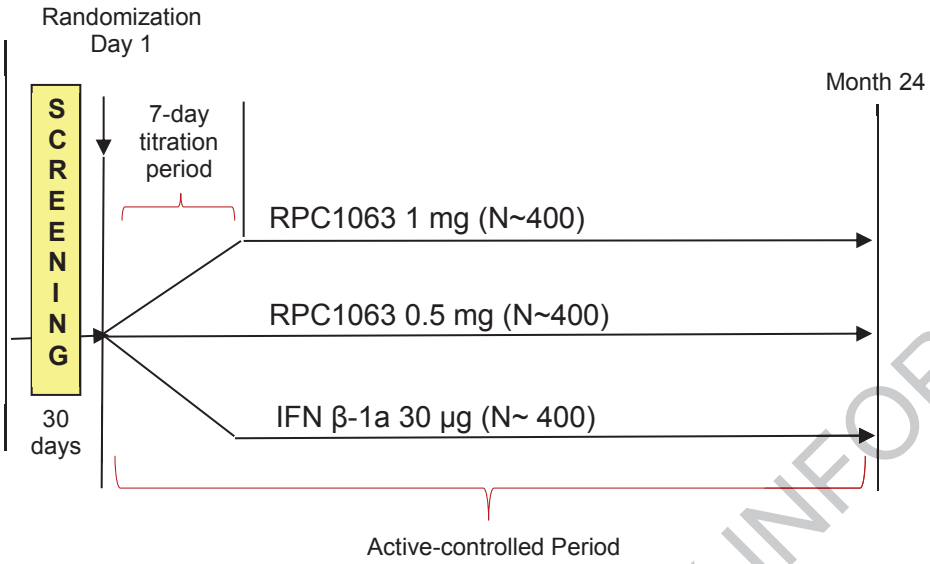
4.1. Overall Study Design and Plan

RPC01-201 Part B is a multi-center, randomized, double-blind, double-dummy, active-controlled parallel group study (Figure 1) of oral RPC1063 in adult patients with RMS. Approximately 1200 patients who meet eligibility criteria 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
- RPC1063 0.5 mg oral capsule daily
- RPC1063 1 mg oral capsule daily

The randomization will be stratified by Baseline EDSS category (≤ 3.5, > 3.5) and country. It is anticipated that the study will be performed at approximately 200 sites in North America and Eastern and Western Europe.

Figure 1. Study Schematic



4.2. Study Endpoints

The primary efficacy endpoint is:

- Annualized relapse rate (ARR) at the end of Month 24

The key secondary efficacy endpoints (rank ordered) are:

1. The number of new or enlarging hyperintense T2-weighted brain MRI lesions over 24 months
2. The number of GdE brain MRI lesions at Month 24
3. 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

The other secondary endpoints are:

- 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
- Percent change in normalized brain volume (atrophy) on 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

The exploratory endpoints are:

-

5. GENERAL STATISTICAL CONSIDERATIONS

Statistical testing for the primary efficacy endpoint will be made between each RPC1063 group and the IFN β-1a group (2 treatment contrasts). To account for multiple comparisons, each of the 2 treatment comparisons will be tested at the alpha = 0.025 level.

To control for type 1 error, the 3 key secondary endpoints will be tested in order in a sequential, that ranks the RPC1063 1 mg dose above the RPC1063 0.5 mg dose and the key secondary endpoints in the order shown in section 4.2. 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 (Figure 2A) will continue down the rank ordered key secondary endpoint list until a comparison fails to reach statistical significance, .

For the 3rd key secondary endpoint of time to onset of sustained disability progression, the data from this study will also be pooled with the data from another phase 3 study, RPC01-301, for hypothesis testing. This pooling will be described in a separate pooling plan.

If only 1 RPC1063 dose is significant on the primary endpoint, then on the rank ordered key secondary endpoint list for the surviving dose only, at the 2.5% level of significance for each key secondary endpoint (Figure 2B).

Figure 2.

Other secondary endpoint analyses will not include adjustments made for multiple comparisons and multiple endpoints.

Unless specified otherwise, all statistical analyses will be performed using a two-sided hypothesis test at the overall 5% level of significance. All p-values will be rounded to four decimal places. If a p-value is less than 0.0001, it will be reported as "<0.0001". If a p-value is greater than 0.9999, it will be reported as ">0.9999".

Continuous data will be presented using descriptive statistics: n, mean, standard deviation (SD), median, minimum and maximum. Categorical data will be summarized by the number and percent. Confidence intervals (CIs) will be 95% and two-sided, unless otherwise stated. Data will be displayed in all listings sorted by treatment group and subject number. When count data are presented, the percent will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where necessary to account for dropouts and missing values. The denominator for all percentages will be the number of patients in that treatment within the population of interest, unless otherwise stated. Non-zero percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places. Additional rounding rules are as follows:

- If the original value has 0 decimal places: mean, median, and CIs will have one decimal place and SD will have 2 decimal places
- If the original value has 1 decimal place: mean, median, and CIs will have 2 decimal places and SD will have 3 decimal places
- If the original value has 2 or more decimal places: mean, median, CIs, and SD will all have 3 decimal places

Minimum and maximum will always have the same decimal places as the original measure, up to a maximum of 3 decimal places.

Subgroup analysis will be performed for the primary and secondary efficacy endpoints where applicable. The following are the pre-defined subgroups:

- Baseline EDSS score (EDSS ≤ 3.5 vs. EDSS > 3.5)
- Baseline presence of Gd-enhancing lesions (present vs. absent)
- Prior treatment status (treatment naïve vs. previously treated)
- age at Baseline (age ≤ 40 vs. age > 40)
- sex (female vs. male)
- race (white vs. non-white)
- weight (< median vs. ≥ median)

- number of relapses in the past 12 months ($< 2, \geq 2$) for ARR endpoint only
- regions (North America, Western Europe, Eastern Europe)

Any subgroup that does not have at least 5% of the overall sample size (approximately 60 patients) will not be included in subgroup analyses.

5.1. Sample Size

Approximately 1200 patients with RMS will be randomized in this 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 at least 12 months of follow-up per patient, the method of Nicholas (Nicholas, 2011) results in a total sample size of 1059 patients (353 per arm) in order to provide 80% power to detect a 43% reduction in the ARR (i.e., an ARR of 0.17 for RPC1063). To account for an assumed dropout rate of approximately 12%, approximately 1200 patients (400 per treatment group) will be enrolled.

5.2. Randomization, Stratification, and Blinding

Patients will be randomized 1:1:1 to receive IFN β-1a 30 µg QW, RPC1063 0.5 mg QD, or RPC1063 1 mg QD. The randomization will be stratified by Baseline EDSS category ($\leq 3.5, > 3.5$) and country.

The randomization will be based on a stratified blocked algorithm and will be done centrally by using an Interactive Voice Response System (IVRS).

A "dual assessor" approach will be used to evaluate efficacy and safety to prevent potential unblinding as result of observed efficacy, adverse events (AEs), or laboratory changes. Separate treating and examining investigators will be designated at each center prior to randomization. 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.

In the event that the blinding needs to be broken because of a medical emergency, the Medical Monitor should be contacted immediately. The treatment assignment will be unblinded through the 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.

5.3. Analysis Populations

5.3.1. Intent-to-Treat (ITT) Population

The ITT population will include all randomized patients who are confirmed to have received at least one dose of study drug. This will be the primary population for the analysis of all efficacy endpoints. All patients in the ITT sample will be analyzed

according to the treatment they were randomized to receive and not according to what they actually received, if different.

5.3.2. Per-Protocol (PP) Population

The PP population will be a subset from the ITT population with high treatment compliance and without any major protocol deviations. Major protocol deviations will include one or more of the following categories: major inclusion/exclusion criteria violations, poor study drug compliance, and other. The criteria for exclusion from the PP population will include, but are not limited to, those listed below:

- Violation of any of the following three inclusion criteria related to MS specific disease activity:
  - Must have a confirmed diagnosis of MS by the revised 2010 McDonald criteria
  - Must have a Baseline EDSS score between 0 and 5.0
  - Must have at least 1 documented relapse within the last 12 months prior to screening, OR, if at least 1 documented relapse occurred within the last 24 months prior to screening, evidence of at least 1 GdE lesion on brain MRI within the last 12 months prior to randomization
- Poor study drug compliance: compliance up to last dose of study drug <80%

The PP population will be fully identified and documented prior to database lock.

5.3.3. Safety Population

The Safety population will include all patients who have received at least one dose of study drug. All patients in the Safety population will be analyzed according to the highest dose of RPC1063 treatment actually received (up to 1 mg) and not according to the treatment they are randomized to receive, in the event there is a discrepancy.

5.4. Other Important Considerations

5.4.1. Definition of Baseline

Baseline data are defined as data collected which are prior to and/or on the date of first dose, usually also the same day as the Day 1 visit. If there is more than one value on or before Day 1, the value closest to and prior to (including on) the date of first dose will be used as the Baseline value.

5.4.2. Study Day Calculation for Reporting Purposes

The following conventions will be used to calculate study day for reporting purposes:

- Study Day = date of measurement – first dose date +1, if date of measurement is on or after the first dose date.
- Study Day = date of measurement – first dose date, if date of measurement is prior to the first dose date.

- Day 1 is the first dose date, no Day 0 is defined for this study.

5.4.3. Visit Windows

A visit window method will be applied to determine visits across the study for MRI efficacy parameters and for the minimum times to confirmation of disability progressions. For MRI parameters, if a patient has multiple assessments within a visit window the value closest to the target day for that visit will be selected. If there are two values which are equidistant in terms of time then the later value will be selected. For disability progressions, a minimum length of time since the start of the progression is defined, based on the low end of the MRI visit window specifications.

The following visit windows are defined for MRI parameters:

Visit	Target Day	Window
Month 6	180	166 – 194
Month 12	360	346 – 374
Month 18	540	526 – 554
Month 24	720	706 – 734

The following minimum times are defined for disability progression confirmations:

- 3 month confirmation: ≥ 76 days after start of progression
- 6 month confirmation: ≥ 166 days after start of progression

For all efficacy and safety parameters, the last available assessment will be derived as the last value on treatment, whether scheduled or unscheduled.

5.4.4. Missing and Partial Data

Missing data may be imputed for some efficacy endpoints as described in the following sections. For partial dates, the algorithms for imputation will vary depending upon the parameter; the details can be found in Appendix A Imputation Algorithm for Partial and Missing Dates.

6. PATIENT DISPOSITION

A summary of disposition of patients will include the number and percentage of patients for the following categories: patients screened, patients randomized, patients treated (safety population), patients in the ITT population, patients in the PP population, patients completing the study, and patients discontinued from the study. All percentages will be based on the number of patients randomized.

The reasons for study discontinuation will also be summarized in this table. The reason for discontinuation may include any of the following: adverse event, death, lost to follow-up, withdrawal of consent, or other. Only one reason for study discontinuation will be recorded. For patients lost to follow-up, the number of days until lost to follow-up will also be presented using descriptive statistics. The number of days until lost to follow-up

on study is defined as the number of days from randomization until the date of last contact.

A listing will present data concerning patient disposition.

7. DEMOGRAPHICS, MEDICAL HISTORY AND BASELINE CHARACTERISTICS

7.1. Demographics

The demographics and baseline characteristics will be presented in tables. The demographic characteristics consist of age, age category, sex, race, ethnicity, weight, weight category, height, body mass index, and region. A patient's age in years is calculated using the date of the informed consent and date of birth, or recorded directly on the eCRF. Age will be summarized using the descriptive statistics. The number and percentage of patients in each age category (18-19, 20-29, 30-39, 40-49, 50-55, and >55, as well as <40, ≥40), and in each race category (White, Black, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other) will be reported. The demographics and baseline characteristics summaries will be presented for both ITT and PP populations.

Demographics and baseline characteristics data will be listed.

7.2. Medical History

7.2.1. General Medical History

Medical history data other than for MS will be presented in a table. The table summary will show the number and percentage of patients with a significant history for each body system. Percentages will be calculated out of the number of patients in the Safety population. Significant medical history including specific details will be listed.

7.2.2. Multiple Sclerosis Disease History

Multiple sclerosis disease history will be summarized for the ITT population using the descriptive statistics for the following parameters:

- EDSS score at Baseline
- EDSS category at Baseline
- Age at MS symptoms onset
- Age at MS diagnosis
- Years since MS symptoms onset
- Years category since MS symptoms onset
- Years since MS diagnosis
- Years category since MS diagnosis

- Number of relapses within the last 12 months prior to screening
- Number of relapses within the last 24 months prior to screening
- Number of GdE lesions at Baseline
- T2 lesion volume at Baseline

In addition to reporting the summary statistics, the following duration categories will be used for selected continuous parameters: For the years since MS symptom onset and years since MS diagnosis: 0 - <1, 1 - <2, 2 - <5, 5 - <10, 10 - <15, ≥15. EDSS score at Baseline: 0 - 2, 2.5 - 3.5, 4 - 5, >5. Number of relapses within the past 12 and 24 months: 0, 1, 2-3, ≥4. Number of GdE lesions at Baseline: 0, 1, 2, 3, ≥4.

MS history data will be presented in a listing. Incomplete diagnosis dates will be imputed as detailed in Appendix A.

7.3. Inclusion and Exclusion Criteria

The details of Inclusion and Exclusion criteria are listed in Section 9.4.1 and 9.4.2 of the protocol.

The protocol deviations/violations will be summarized and presented in a listing.

8. TREATMENTS AND MEDICATIONS

8.1. Prior and Concomitant Medications

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 will be documented to at least 4 weeks prior to study participation, and a history of previous treatments for MS will be documented for the prior 2 years. All medications will be coded with the WHO Drug dictionary.

Prior and concomitant medications will be summarized by drug class and preferred term. At each level of summarization, a patient is counted once if he/she reports one or more medications at that level. Prior and concomitant medications will be sorted by descending incidence within each drug class in the total RPC1063 group.

Prior medications are defined as medications with a stop date occurring before the first dose date. Concomitant medications are defined as medications that are ongoing at the first dose date or with a start date occurring on or after the first dose date. Medications with start and stop dates which bracket the first dose date will be summarized as concomitant medications. Medications will be defined as prior or concomitant, but not both. If based on start and stop dates it cannot be determined whether a medication is prior or concomitant, then it will be considered concomitant.

Prior medications used to treat MS will also be summarized separately.

All prior and concomitant medications will be presented in a listing.

8.2. Study Treatments

For all patients in the study, initial study treatment will consist of a 7-day dose titration regimen. For patients randomized to receive active treatment with RPC1063, this regimen will consist of RPC1063 0.25 mg starting on Day 1 for 4 days, then RPC1063 0.5 mg starting on Day 5 for 3 days, followed by the assigned treatment level beginning on Day 8.

8.2.1. Extent of Exposure

Extent of exposure is defined as the total number of days a patient is exposed to any study drug. Because there is no medication diary, the extent of exposure is defined as the total number of days from the first dose date (Day 1) to the last dose date as recorded on the End of Study/Early Withdrawal page on the CRF. If the last dose date on the End of Study/Early Withdrawal page is missing or a patient is lost to follow-up, but the drug accountability log confirms that the patient has taken study drug, the visit date following the last completed drug accountability log will be used.

The extent of exposure and study drug exposure will be summarized in a table by summary statistics for the Safety Population.

The listing will present patient data for the first dose date, last dose date, extent of exposure, and study drug exposure.

8.2.2. Treatment Compliance

Study drug compliance will be calculated for each patient by taking into account whether a patient takes all doses of study drug as instructed. The study drug compliance rate will be summarized by treatment group using the descriptive statistics for the Safety Population. The overall study drug compliance rate will be calculated by dividing the total number of capsules taken at all visits by the total number of capsules expected for all visits based upon the duration in the study and then multiplying by 100. The number and percentage of patients in each compliance rate category (≤50%, 51-60%, 61-70%, 71-80%, and 81-100%, >100%, <80%, and >120%) will be reported.

9. EFFICACY ANALYSIS

9.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the ARR at the end of Month 24.

9.1.1. Primary Analysis

Definition of relapses

The relapse rate will be based on only relapses that were confirmed 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 in the protocol). 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 with onset date as the earlier of the 2 relapses.

Definition of relapse rate

The relapse rate for each treatment group will be calculated as the total number of relapses experienced in the group divided by the total number of days in the study for the group, and multiplied by 365.25. This is called the unadjusted relapse rate and it will be reported for each treatment group.

The relapse rate for each patient will be calculated as the number of relapses for an individual patient divided by the number of days that patient participated in the study, and multiplied by 365.25. Summary statistics of the individual relapse rate for each treatment group will be reported.

Primary Analysis method – annualized relapse rate

All relapses will be identified as confirmed or unconfirmed prior to database lock. The primary analysis of ARR will be performed using a Poisson regression model. The model will compare treatment groups, adjusted for region, age at Baseline, and the Baseline number of GdE lesions, and will include the natural log transformation of time on study as an offset term. The adjusted relapse rates and their associated 95% CIs, the rate ratios and their associated 95% CIs, and p-values will be reported.

The primary analysis will be repeated in each of the pre-specified subgroups shown in section 5. Forest plots showing the rate ratios and 95% CI for the overall result and the results in each subgroup will be constructed.

Relapse results will be listed.

9.1.2. Sensitivity Analysis

Two sensitivity analyses will be performed. The first sensitivity analysis will repeat the primary analysis counting both confirmed and unconfirmed relapses.

The second sensitivity analysis will use a negative binomial regression model, instead of the Poisson regression model, to compare relapse rates. The same covariates and offset term will be used as specified in the primary analysis. This model will be run twice: once repeating the primary analysis (confirmed relapses only) and once repeating the first sensitivity analysis (confirmed + unconfirmed relapses).

In addition to the specified sensitivity analyses, a Kaplan-Meier analysis on the difference in time to first confirmed relapse curves will also be performed. The estimated median time to first confirmed relapse will be reported, along with the associated 95% CI and log-rank p-values. A Kaplan-Meier plot will also be produced.

9.2. Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints (rank ordered) are:

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

9.2.1. Analysis

Key Secondary Endpoint: The number of new or enlarging hyperintense T2-weighted brain MRI lesions over 24 months

The primary analysis of the number of new or enlarging T2 hyperintense lesions over 24 months will be performed using a negative binomial regression model adjusted for region, age at Baseline, and Baseline number of GdE lesions, and will include the natural log transformation of the number of available MRI scans as an offset term. The odds ratios and their associated 95% CIs, relative reductions, and p-values will be reported.

The analysis will be repeated in each of the pre-specified subgroups shown in section 5. Forest plots showing the odds ratios and 95% CIs for the overall result and the results in each subgroup will be constructed.

Three sensitivity analyses will be performed: the first will repeat the primary T2 analysis using the mean number of T2 lesions from patients from the same treatment group to impute missing T2 values. The second will repeat the primary T2 analysis using last observation carried forward (LOCF) method for imputing missing T2 data values. Only data from post-Baseline MRI scans can be carried forward to subsequent timepoints for this analysis. The third will repeat the primary T2 analysis using only patients with complete T2 data at the relevant MRI visits (observed cases analysis). All three sensitivity analyses will include the natural log transformation of exposure time on study (instead of the number of available MRI scans) as the offset term.

All T2 lesion results will be listed.

Key Secondary Endpoint: The number of GdE brain MRI lesions at Month 24

The number of GdE brain MRI lesions at Month 24 will be analyzed using a negative binomial regression model adjusted for region, age at Baseline, and Baseline number of GdE lesions, and will include the natural log transformation of the number of available MRI scans as an offset term. The odds ratios and their associated 95% CIs, relative reductions, and p-values will be reported.

The analysis will be repeated in each of the pre-specified subgroups shown in section 5. Forest plots showing the odds ratios and 95% CIs for the overall result and the results in each subgroup will be constructed.

Three sensitivity analyses will be performed: the first will repeat the primary GdE analysis using the mean number of GdE lesions from patients from the same treatment group to impute missing GdE values. The second will repeat the primary GdE analysis using last observation carried forward (LOCF) method for imputing missing GdE data

values. Only data from post-Baseline MRI scans can be carried forward to the Month 24 timepoint for this analysis. The third will repeat the primary GdE analysis using only patients with complete GdE data at Month 24 (observed cases analysis). All three sensitivity analyses will include the natural log transformation of exposure time on study (instead of the number of available MRI scans) as the offset term.

All GdE lesion results will be listed.

Key Secondary Endpoint: 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

Sustained Disability Progression

Sustained disability progression is defined as at least a 1.0 point increase on the EDSS score from Baseline, confirmed after a 3 month and a 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 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 at an unscheduled visit conducted after the relapse has resolved. The date of the initial visit at which the minimum increase in the EDSS is met will be the date of onset of the progression (tentative progression).

Disability progression can be confirmed at the early withdrawal visit, according to the rules above, as long as the early withdrawal visit is not also a relapse assessment visit.

Death due to MS will be counted as a confirmed progression. If the patient was in the midst of a tentative progression at the time of death, the progression date will be the date of the start of the progression. Otherwise, the progression date will be the date of death.

Time to Censor

A patient will be censored if follow-up ends before a sustained progression occurs, whether due to the patient completing study, withdrawing from the study, or due to the cutoff of data collection for the analysis. The censor date will be the date of the last EDSS assessment or date of last dose of study drug, whichever is later. This will apply to both 3-month confirmations and 6-month confirmations of progression. As such, a patient who is confirmed as having a progression after 3 months but does not have a 6-month confirmation will be considered as having an event in the 3-month analysis but will be censored in the 6-month analysis.

Patients in the ITT population who withdraw from the study after the Baseline visit but prior to the first clinical evaluation scheduled visit will be censored at Baseline.

Analysis Method

All disability progressions will be identified as confirmed after 3 months, confirmed after 6 months, or unconfirmed prior to database lock. The primary analysis of time to disability progression will be analyzed by a Cox proportional hazards model with factors

for treatment group, adjusted for region, age at Baseline and Baseline EDSS score. Handling of ties will be according to Efron. The hazard ratio, associated 95% CI, and p-values will be reported.

A Kaplan-Meier analysis on the difference in time to disability progression curves will also be performed. The estimated median time to disability progression will be reported, along with the associated 95% CI and log-rank p-values. A Kaplan-Meier plot will also be produced.

Each of these analyses will be performed on disability progressions confirmed after 3 months and again on disability progressions confirmed after 6 months.

Sensitivity analyses will be performed and include the following:

- Counting patients with a Baseline EDSS = 0 as a progression only if the EDSS score increases by at least 1.5 points
- Including unconfirmed progressions in each analysis
- Counting premature study discontinuations as confirmed progressions in each analysis
- Including unconfirmed progressions and counting premature discontinuations as progressions in each analysis

All disability progressions will be listed.

9.3. Other Secondary Efficacy Endpoints

The other secondary endpoints are:

- 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
- Percent change in normalized brain volume (atrophy) on 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

9.3.1. Analysis

Secondary Endpoints: The proportion of patients who are GdE lesion-free at Month 24, and the proportion of patients who are T2 lesion-free at Month 24

Each of these endpoints will be analyzed using a Cochran-Mantel-Haenszel (CMH) test

stratified by region and EDSS category at Baseline. The numbers and percentages of patients with 0, 1-2, 3-4, and ≥ 5 lesions will be reported. The proportion of patients who are lesion-free will be reported along with the associated 95% CI. The difference in proportions between each RPC1063 group and the IFN β-1a group will also be reported with the associated 95% CI and CMH p-value. Patients who are missing the Month 24 MRI data will be considered non-responders, i.e., as not being lesion-free.

Sensitivity analyses will be conducted using the LOCF method for replacing missing Month 24 MRI data and on the subset of patients with non-missing Month 24 MRI data (observed cases analysis).

Secondary Endpoint: Change in normalized brain volume (atrophy) on MRI scans from Baseline to Month 24

Brain volumes will be reported in cm^3. If the data are collected in mm^3, then a transformation will be applied by dividing the result in mm^3 by 1000 to convert to cm^3 prior to analysis.

Actual brain volumes, change from Baseline to each visit, and percent change from Baseline to each visit will be summarized. Comparisons of the change and percent changes between the treatment groups will be analyzed using an analysis of covariance (ANCOVA) model adjusted for region, EDSS category at Baseline, and brain volume at Baseline. The mean difference between each RPC1063 treatment group and IFN β-1a will be reported with the associated 95% CI and p-value. Patients with missing data will have their results imputed via LOCF.

Secondary Endpoint: Change in MSFC score from Baseline to Month 24 (including the low-contrast letter acuity test [LCLA] measurement of visual function as a component)

The MSFC score 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 Symbol Digit Modalities Test (SDMT) is a measure of cognitive impairment that assesses attention, visuoperceptual processing, working memory, and psychomotor speed

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 = $(Z_{25\text{-foot-walk}} + Z_{9HPT} + Z_{SDMT})/3$, and

MSFC z-score (LCLA) = $(Z_{25\text{-foot-walk}} + Z_{9HPT} + Z_{SDMT} + Z_{LCLA})/4$, where Z_{xxx} refers to Z-scores

A z-score represents the number of standard deviations a patient's test result is higher (z >0) or lower (z <0) than the average test result (z = 0) of the reference population.

The following describes the scoring, and rules for missing value imputation for each component.

Timed 25-Foot Walk Z-score Calculation

The Z-score is calculated as in the following formula:

$$Z_{25\text{-foot-walk}} = (-1) * \frac{((t_1 + t_2)/2) - MEAN(reference)}{SD(reference)}$$

where t_1 and t_2 are the time (in seconds) from the two trials, and the mean (reference) and SD (reference) are the mean and standard deviation respectively, of baseline values for the reference population. The reference population will be the study population.

For missing post-Baseline values, if a patient is missing only one trial for any post-Baseline visit, then the score from the non-missing trial will be used to calculate the Z-score. The steps outlined above will remain the same except the actual times will not be averaged.

The missing data algorithm suggested by the MSFC manual will be used to impute missing values. If both scores from the two trials are missing for any post-Baseline visit, due to MS related physical limitation or other physical limitations, then the patient will be given a Z-score of -13.7 for the Timed 25-Foot walk. If the reasons for missing scores on both trials are due to other reasons (non-compliance, missed visits), then LOCF from post-Baseline values will also be used as to impute the z-score for that visit. If a value is not available to carry forward, the mean of the available z-scores using all available data from the same treatment group, will be calculated at the specified visit and used as the imputed value. Values imputed using the mean will not be carried forward to other visits.

If a patient has missing data at Baseline for either trial, then the mean of the available z-scores will be evaluated by treatment group and used as the imputed value.

9HPT Z-score Calculation

Z-score for the 9HPT is calculated as in the following formula:

$$Z_{9HPT} = \frac{\left(\left(\frac{1}{(t_{11} + t_{12})/2} + \frac{1}{(t_{21} + t_{22})/2}\right)/2\right) - MEAN(reference)}{SD(reference)}$$

where t_{11}, t_{12}, t_{21}, t_{22} are the time (in seconds) taken to complete for dominant hand trial 1, dominant hand trial 2, non-dominant hand trial 1, and non-dominant hand trial 2, respectively. The mean (reference) and SD (reference) are the mean and standard deviation, respectively, of reference population's baseline score. The reference

population will be the study population.

For missing post-Baseline values, if any of the times from the two trials of the same hand is missing, then the score from the non-missing time will be used to calculate the Z-score. The steps outlined above will remain the same except the actual times will not be averaged.

The missing data algorithm suggested by the MSFC manual will be used to impute missing values. If both scores from either hands are missing for any post-Baseline visit, due to MS related physical limitation or other physical limitations, then the patient will be given a Z-score will be calculated using a value of 777 seconds. If the reasons for missing scores on both trials are due to other reasons (non-compliance, missed visits), then LOCF from post-Baseline values will also be used as to impute the z-score for that visit. If a value is not available to carry forward, the mean of the available z-scores using all available data from the same treatment group, will be calculated at the specified visit and used as the imputed value. Values imputed using the mean will not be carried forward to other visits.

SDMT Z-score Calculation

For the SDMT, the z-score for each patient at each time-point will be created by subtracting the reference population's baseline mean score on the SDMT from the patient's SDMT score and dividing by the baseline SD on the SDMT of the reference population, i.e.

$$Z_{SDMT} = \frac{\text{SDMT raw score} - MEAN(reference)}{SD(reference)}$$

and SDMT raw score = # of correct items within the timeframe of the test. The reference population will be the study population.

For missing post-Baseline values, if a patient is missing the SDMT score due to MS related physical limitation or other physical limitations, then a score of 0 will be assigned. If the reasons for missing score is due to other reasons (non-compliance, missed visits), then LOCF from post-Baseline values will also be used as to impute the z-score for that visit. If a value is not available to carry forward, the mean of the available z-scores using all available data from the same treatment group, will be calculated at the specified visit and used as the imputed value. Values imputed using the mean will not be carried forward to other visits.

The change from Baseline in the MSFC scores and the actual values at each visit will be summarized in each treatment group. The changes in MSFC scores at Month 24 will be analyzed and compared between treatment groups using an ANCOVA model adjusting for region, EDSS category at Baseline, and the Baseline MSFC score.

LCLA is performed with standardized set of charts (Sloan 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.

Change from Baseline in visual function test scores as assessed by LCLA will be summarized by treatment group and time point, and will be compared at Month 24 between treatment groups using ANCOVA adjusted for region, EDSS category at Baseline, and the Baseline visual function test score.

Secondary Endpoint: Change in MSQOL-54 score from Baseline to Month 24

Actual scores and change from Baseline by visit will be summarized for each of the 12 subscales, the 2 summary scores, and the 2 single-item measures shown below:

- Subscales
    1. Physical function
    2. Role limitations – physical
    3. Role limitations – emotional
    4. Pain
    5. Emotional well-being
    6. Energy
    7. Health perceptions
    8. Social function
    9. Cognitive function
    10. Health distress
    11. Overall quality of life
    12. Sexual function
- Summary scores
    1. Physical health composite summary
    2. Mental health composite summary
- Single item measures
    1. Satisfaction with sexual function
    2. Change in health

Comparisons of the change from Baseline to Month 24 <u>for the 2 summary scores only</u> between treatment groups will be analyzed by an ANCOVA model adjusted for region, EDSS category at Baseline, and Baseline summary score of interest. Missing data will be imputed using a mixed-effects regression model (random slope and intercept).

9.4. Exploratory Efficacy Endpoints

The exploratory endpoints are:

-

9.4.1. Analysis

10. SAFETY ANALYSIS

All analysis of safety will be conducted using the Safety population. Statistical hypothesis testing will not be performed on any safety results. No imputation of missing safety data will be performed.

10.1. Adverse Events

A treatment emergent AE is any reaction, side effect, or other untoward event, regardless of relationship to study drug, which occurs any time after the first dosing of study drug, until 28 days following the last dose of study drug. During the study, clinically significant adverse changes in clinical status, ECGs, and physical examinations are considered AEs. Any patient complaints associated with such an abnormal finding will also be reported as an AE.

Adverse events include, but are not limited to: (1) a worsening or change in nature, severity, or frequency of conditions present at the start of the study; (2) patient deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction.

An abnormal laboratory value will only be reported as an AE if it involves therapeutic medical intervention, if the Investigator considers it to be an AE, or if it leads to study discontinuation.

A treatment-emergent AE is defined as an AE that meets any of the following conditions:

- Begins on or after Study Day 1
- Begins before Study Day 1 and worsens in severity on or after Study Day 1.

Adverse events with unknown onset dates or unknown end dates will be counted as having occurred during the study treatment period unless the event resolves before Study Day 1. Adverse events with unknown severity will be counted as severe. Adverse events with unknown relationship to study drug will be counted as probably related to study drug.

Only treatment-emergent AEs will be presented, according to the Medical Dictionary for Regulatory Activities (MedDRA®), system organ class (SOC), and preferred term (PT).

10.1.1. Incidence of Adverse Events

The incidence of AE table will include only one occurrence of a PT per patient. If a patient reports the same PT multiple times, then that PT will only be incremented by one since patient counts will be presented. As with the PT, if a patient reports multiple AEs within the same SOC, then that SOC will only be incremented by one since patient counts will be presented. For tables showing incidence by SOC and PT, PTs will be sorted within SOC in descending order of incidence in the total RPC1063 group. For tables showing incidence by PT only, the PTs will be sorted in descending incidence in the total RPC1063 group.

The incidence of all treatment-emergent AEs will be presented by SOC and PT and separately by PT only. In addition, the incidence of all treatment-emergent AEs that occur in ≥ 2% of the total RPC1063 group will be presented by PT.

All AEs will be presented in a listing.

10.1.2. Relationship of Adverse Events to Investigational Product

A summary of AEs by relationship to study drug will be presented in a table by incidence of occurrence. The relationships will be collected as the possibility that study drug caused the event. The possible relationships are "Unrelated", "Unlikely", "Possible", "Probable" and "Related". A treatment-related AE is an AE with any relation to study drug other than "Unrelated" or "Unlikely". In the AE relationship table, if a patient reports multiple occurrences of the same AE, only the most closely related occurrence will be presented. Adverse events (AE) that are missing relationship will be presented in the summary table as "Probable" but will be presented in the data listing with a missing relationship.

10.1.3. Severity of Adverse Event

A summary of AEs by severity will be presented in a table. Adverse events will be classified by severity (mild, moderate and severe). In the AE severity table, if a patient reported multiple occurrences of the same AE, only the most severe will be presented. Adverse events that are missing severity will be presented on tables as "Severe" but will be presented in the data listing with a missing severity.

10.1.4. Serious Adverse Events

The seriousness of an AE should be assessed by the Investigator independently from the severity of the AE. A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing inpatient hospitalization, or results in significant disability/incapacity.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

The incidence of SAEs will be presented in a table. The incidence of treatment-related SAEs will also be presented in a table. A treatment-related SAE is a SAE with any relation to study drug other than "Unrelated" or "Unlikely". The table of SAEs will include only one occurrence of a PT per patient. If a patient reports the same SAE multiple times, then that PT will only be incremented by one since patient counts will be presented. As with the PT, if a patient reports multiple SAEs within the same SOC, then that SOC will only be incremented by one since patient counts will be presented. SAEs will also be listed separately.

10.1.5. Adverse Events Leading to Treatment Discontinuation

All AEs collected with an investigational product action taken as "Permanently discontinued" will be summarized in a table and presented in a listing.

10.1.6. Death

All patient deaths during this study will be collected and presented in a listing. The information that is presented includes date of death, days on study, cause of death, and relationship of death to study drug.

10.1.7. Adverse Events of Special Interest

Target AEs of special interest will be closely monitored in the study. These AEs include infections, malignancies, cardiac (bradycardia and heart conduction abnormalities), pulmonary function (decline in FEV1, FVC, and DLCO measurements), ophthalmic (macular edema), hepatic (LFT elevations), and dermatological (cutaneous malignancy) abnormalities. These AEs will be summarized in tables and presented in a listing.

10.2. Clinical Laboratory Evaluations

Laboratory assessments will be performed by a central laboratory. All summaries will be based on the SI units provided by the central lab.

Summary tables including actual values and change from Baseline values will be presented for clinical laboratory tests with numeric values by treatment group.

Laboratory data will be summarized using shift tables where appropriate. Each patient's hematology and blood chemistry values will be flagged as "low", "normal", or "high" relative to the normal ranges of the central laboratory or as "unknown" if no result is available. Each patient's urinalysis values will be flagged as "positive", "negative", or if no value is available, "unknown".

10.2.1. Hematology

The following laboratory tests will be included in hematology summary tables of actual value and change from Baseline: 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). Total and differential WBC counts will be blinded after the onset of study treatment. A listing will present abnormal hematology values (except for lymphocytes between 200 cells/uL and the lower limit of normal) for all patients.

Patients with abnormalities in hematology assessments, defined as absolute lymphocyte count (ALC) < 200 cells/uL, absolute neutrophil count (ANC) < 500 cells/uL, ANC < 1000 cells/uL, and total WBC > 20,000 cells/uL will be summarized by treatment group.

Actual value, change, and percent change in ALC will plotted in line graphs over time showing the means and standard errors (SE).

10.2.2. Blood Chemistry

The following laboratory tests will be included for blood chemistry summary tables at the screening visit: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, random glucose, hemoglobin A1c, albumin, alkaline phosphatase, creatinine, SGPT/ALT, SGOT/AST, gamma glutamyltransferase (GGT), amylase, total bilirubin, conjugated bilirubin, total cholesterol, triglycerides, HDL and LDL. For all other visits, which will be subject to change from Baseline reporting, the tests will include blood urea nitrogen, hemoglobin A1c, albumin, alkaline phosphatase, creatinine, SGPT/ALT, SGOT/AST, GGT, amylase, total bilirubin, and conjugated bilirubin.

A listing will present abnormal chemistry values for all patients.

The incidence of patients with abnormalities in Liver Function Tests (SGPT/ALT, SGOT/AST, and GGT) will be summarized overall and at each visit for each treatment group for the following categories:

- > 1 x upper limit of normal (ULN)
- ≥ 2 x ULN
- ≥ 3 x ULN
- ≥ 4 x ULN
- ≥ 5 x ULN

10.2.3. Urinalysis

Summary statistics for each visit and change from Baseline will be presented for specific gravity and pH. Shift table will be presented for leukocytes, bilirubin, blood, glucose, ketones, protein, and urobilinogen.

10.3. Vital Sign Measurements

Vital signs including sitting systolic blood pressure (SBP), sitting diastolic blood pressure (DBP), body temperature, and heart rate (HR) will be recorded on the eCRF once per visit. In addition, pre-dose and hourly cardiac monitoring (blood pressures and heart rates) for hours 1-6 will be recorded for all patients at the Baseline visit. Sitting blood pressures will be recorded at each hour and in addition, standing blood pressures will be recorded at Hour 0 and Hour 6 for orthostatic changes.

Summary tables including actual values and change from Baseline (defined as pre-dose on Day 1) values will be presented for vital signs including SBP (sitting and standing), DBP (sitting and standing), temperature, and HR by treatment group for the Safety population. On Day 1, hourly changes from pre-dose in blood pressures and heart rates will be shown for all patients. For all other visits only a single timepoint will be collected and shown.

For patients requiring extended cardiac monitoring due to cardiac safety issues observed in the first 6 hours on Day 1, a listing will be provided that shows the hourly change from

pre-dose assessment through the last hour of cardiac monitoring by patient for heart rate and blood pressure.

Box plots will be provided to display the distribution of vital signs. In addition, line plots will be created to display the change from Baseline over the entire study period (not including Day 1) and separately for change from pre-dose in vital signs for the Day 1 visit.

The number and percentage of patients with SBP > 180 mmHG or < 90 mmHG and HR < 40 beats per minute will be summarized by visit for each treatment group. The number and percentage of patients with clinically relevant abnormalities will be presented by treatment group. The criteria for clinically relevant abnormalities are shown in the following table. Vital signs will be presented by patient in listings.

Vital Sign	**Criteria for Abnormalities**
Temperature	>38.5°C and an increase from pre-dosing of at least 1°C
Heart Rate	>120 beats per minute post-Baseline, or an increase from pre-dosing of more than 20 beats per minute, or <45 beats per minute post-Baseline, or a decrease from pre-dosing of more than 20 beats per minute
Systolic Blood Pressure	>180 mmHg post-Baseline, or an increase from pre-dosing of more than 40 mmHg, or <90 mmHg post-Baseline, or a decrease from pre-dosing of more than 30 mmHg
Diastolic Blood Pressure	>105 mmHg post-Baseline, or an increase from pre-dosing of more than 30 mmHg, or <50 mmHg post-Baseline, or a decrease from pre-dosing of more than 30 mmHg

The lowest HR observed during cardiac monitoring between hours 1-6 on Day 1 will be identified and the incidence of patients by minimum HR observed during this time period will be summarized for the following categories for each state (sitting and standing):

- ≥ 65 bpm
- 60-64 bpm
- 55-59 bpm
- 50-54 bpm
- 45-49 bpm
- 40-44 bpm
- < 40 bpm

10.4. Electrocardiogram

Summary tables including actual values and change from Baseline values will be presented for ECG results. The overall interpretation of the ECG results (Normal; Abnormal; not Clinically Significant; and Abnormal, Clinically Significant) will be summarized for each treatment group. ECG results will also be listed.

10.5. Pulmonary Function Testing

The following laboratory tests will be included for pulmonary function testing (PFT) summary tables: forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and diffusing capacity of the lung for carbon monoxide (DLCO). For FEV_1 and FVC, summary tables for actual value, change, percent change, percent predicted, change in percent predicted, and percent change in percent predicted will be produced. For DLCO summary tables for actual value, change, and percent change will be produced. DLCO is collected at the local lab for each site, so results may be collected in domestic or SI units. DLCO results in domestic units (mL/min/mmHg) will be converted to SI units (mmol/min/kPa) prior to analysis using the following conversion factor:

DLCO in SI units = (DLCO in domestic units) / 2.986

Line plots of FEV_1, FVC, and DLCO results over time will be presented. All PFT results will be listed.

10.6. Physical Examination

Physical examination results will be listed.

10.7. Chest X-ray

Chest x-ray will be performed at screening for patients with a positive inconclusive result of QuantiFERON Gold test or other interferon gamma release assay. The results will be listed.

10.8. Suicidality

Suicidality assessment from a self-administered C-SSRS (Posner, 2011) system will be summarized for each treatment group.

10.9. Other Assessments

A summary table of dermatological abnormalities by visit will be presented. Listings of dermatological abnormalities and abnormalities in optical coherence tomography (OCT) assessment will be provided.

11. INTERIM ANALYSIS

No interim analyses are planned for this study

12. REFERENCES

Mikol DD, Barkhof F, Chang P, et. al. *Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the Rebif vs. Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicenter, randomized, parallel, open-label trial.* Lancet Neurol. 2008; 7: 864-866.

Nicholas R, Straube S, Schmidli H, et. al. *Trends in annualized relapse rates in relapsing-remitting multiple sclerosis and consequences for clinical trial design.* Mult Scler. 2011; 17: 1211-1217.

Polman CH, O'Connor PW, Havrdova E, et al. *A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis*. N Engl J Med. 2006; 354:899-910.

APPENDIX A IMPUTATION ALGORITHM FOR PARTIAL AND MISSING DATES

Incomplete Dates of MS Symptom and MS Diagnosis

If day is missing, day will be set to 15th of the month.

If month is missing, month and day will be set to July 1st.

If either imputation above results in a date ≥ informed consent, then impute it as the date of informed consent -1.

Adverse Event

If AE resolution date is present and after first dose date:

Year of onset	Month of onset	Day of onset	Onset date to be imputed as
Missing	Missing	Missing	Date of first dose
year = year of first dose	Missing	Non-missing	Set month to month of first dose
year = year of first dose	Missing	Missing	Set month and day to those of first dose
year < year of first dose	Missing	Non-missing	set month to December
year < year of first dose	Missing	Missing	set month and day to December 31
year > year of first dose	Missing	Non-missing	set month to January
year > year of first dose	Missing	Missing	set month and day to January 1
year = year of first dose	Month = month of first dose	Missing	Set day as day of 1st dose
year = year of first dose	Month < month of first dose	Missing	Set day as last day of onset month
year = year of first dose	Month > month of first dose	Missing	Set day as first day of onset month
year < year of first dose	Non-missing	Missing	Set day as last day of onset month
year > year of first dose	Non-missing	Missing	Set day as first day of onset month

If AE resolution date is present and prior to first dose date, no need to impute incomplete AE start date. The AE is not treatment emergent.

Concomitant Medications

- If year and month are present and day is missing then set day to first day of month for start date, and set day to last day of month for end date

- If year and day are present and month is missing then set month to January for start date, and set month to December for end date
- If year is present and month and day are missing then set month and day to January 1 for start date, and set month and day to December 31 for end date
- Completely missing date will not be imputed

If start date is completely missing and end date is not prior to the first dose, then the medication will be classified as concomitant; If the end date is missing, then the medication will be classified as ongoing. Medications for which the start and end dates are missing will be classified as concomitant.

Medication Start Date	Ongoing?	Medication Stop Date					
		Missing	< FD	= FD	(FD, LD)	= LD	> LD
Missing	YES	1, 2					
	NO/Missing	1, 2	1	1, 2	1, 2	1, 2	1, 2
< FD	YES	1, 2					
	NO/Missing		1	1, 2	1, 2	1, 2	1, 2
= FD	YES	2					
	NO/Missing			2	2	2	2
(FD, LD)	YES	2					
	NO/Missing				2	2	2
= LD	YES	2					
	NO/Missing					2	2
> LD	YES	3					
	NO/Missing						3

1 = Previous, 2 = Concomitant, 3 = Post-treatment
FD = first dose date, LD = last dose date.