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: NCT01628393

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DISCLOSURE

REDACTED STATYSTICAL ANALYSIS PLAN PART A VERSION 1.2

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

May 20, 2014

Statistical Analysis Plan – Part A

Version 1.2

Prepared by:

Issued by: Date:

Reviewed by: Date:

Upon review of this document, including table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable, and the table, listing, and figure duction can begin.

Approved by: Date:

Receptos, Inc

Approved by: Date:

Receptos, Inc

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS IV

1 ADMINISTRATIVE STRUCTURE 6

1.1 Data Quality Assurance 6

2 INTRODUCTION 6

3 OBJECTIVES 6

4 INVESTIGATIONAL PLAN 7

4.1 Overall Study Design and Plan 7
4.2 Study Endpoints 8

5 GENERAL STATISTICAL CONSIDERATIONS 9

5.1 Sample Size 11
5.2 Randomization, Stratification, and Blinding 11
5.3 Analysis Populations 12
5.3.1 Intent-to-Treat (ITT) Population 12
5.3.2 Per Protocol (PP) Population 12
5.3.3 Safety Population 12
5.4 Other Important Considerations 13
5.4.1 Analysis of Baseline Data and Exposure to Study Drug 13
5.4.2 Study Day Calculation for Reporting Purposes 13
5.4.3 Visit Windows 13
5.4.4 Missing and Partial Data 13

6 SUBJECT DISPOSITION 13

7 DEMOGRAPHICS, MEDICAL HISTORY AND BASELINE CHARACTERISTICS 14

7.1 Demographics 14
7.2 Medical History 14
7.2.1 General Medical History 14
7.2.2 Multiple Sclerosis Disease History 14
7.3 Inclusion and Exclusion Criteria 15

8 TREATMENTS AND MEDICATIONS 15

8.1 Prior and Concomitant Medications 15
8.2 Study Treatments 15
8.2.1 Extent of Exposure 15
8.2.2 Treatment Compliance 16

9 EFFICACY ANALYSIS 16

9.1 Primary Efficacy Endpoint 16
9.1.1 Primary Analysis 16
9.1.2 Sensitivity Analysis 17

9.2 KEY SECONDARY EFFICACY ENDPOINTS 17
9.2.1 Analyses 17
9.3 EXPLORATORY EFFICACY ENDPOINT 19
9.3.1 Analysis 19

10 SAFETY ANALYSIS 22

10.1 ADVERSE EVENTS 22
10.1.1 Incidence of Adverse Events 23
10.1.2 Relationship of Adverse Events to Investigational Product 23
10.1.3 Severity of Adverse Event 24
10.1.4 Serious Adverse Events 24
10.1.5 Adverse Events Leading to Treatment Discontinuation 24
10.1.6 Death 24
10.1.7 Adverse Events of Special Interest 25
10.2 CLINICAL LABORATORY EVALUATIONS 25
10.2.1 Hematology 25
10.2.2 Blood Chemistry 25
10.2.3 Urinalysis 26
10.3 VITAL SIGN MEASUREMENTS 26
10.4 ELECTROCARDIOGRAM 27
10.5 PULMONARY FUNCTION TESTING 27
10.6 PHYSICAL EXAMINATION 28
10.7 CHEST X-RAY 28
10.8 SUICIDALITY 28
10.9 OTHER ASSESSMENTS 28

11 PHARMACODYNAMIC ANALYSIS 28

12 INTERIM ANALYSIS 28

APPENDIX A: IMPUTATION ALGORITHM FOR PARTIAL AND MISSING DATES 29

List of Abbreviations

Abbreviation or Specialized Term	Definition
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARR	annualized relapse rate
AST	aspartate aminotransferase
CI	confidence interval
CNS	central nervous system
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
FDA	Food and Drug Administration
FEV_1	forced expiratory volume at 1 second
FS	Functional System
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
IFN	interferon
IFN β-1a	interferon beta-1a
Ig	Immunoglobulin
IM	Intramuscular(ly)
ITT	intent-to-treat
IV	intravenous(ly)
IVIg	intravenous immune globulin
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
OCT	optical coherence tomography
PD	pharmacodynamic(s)
PFT	pulmonary function testing
PK	pharmacokinetic(s)
PP	per protocol
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
SBP	systolic blood pressure
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
TB	Tuberculosis
ULN	upper limit of normal
VZV	Varicella Zoster virus
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 placebo-controlled (Part A, Phase 2) and active comparator trial (Part B, Phase 3) versus IFN β-1a in patients with relapsing multiple sclerosis (RMS). 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.

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analysis of clinical data collected in Part A of the study. This plan should be read in conjunction with the study protocol and the case report forms (CRFs). Analyses of data collected during the optional extension of Part A, as well as analysis of data collected during Part B of the study will be described in separate SAPs. A separate analysis plan will also be developed to guide analyses of population pharmacokinetic (PK) data and a separate analysis plan will be developed to guide analyses of heart rate data collected from the Holter monitors.

3 Objectives

The primary objective of Part A is:

- 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

The secondary objectives of Part A are:

- 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

The exploratory objectives of Part A are:

4 Investigational Plan

4.1 Overall Study Design and Plan

This is a multi-center, randomized, double-blind, placebo-controlled (Part A) and double-blind, double-dummy, active-controlled (Part B) parallel group study (Figure 1) 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. 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
- RPC1063 0.5 mg oral capsule daily
- RPC1063 1 mg oral capsule daily

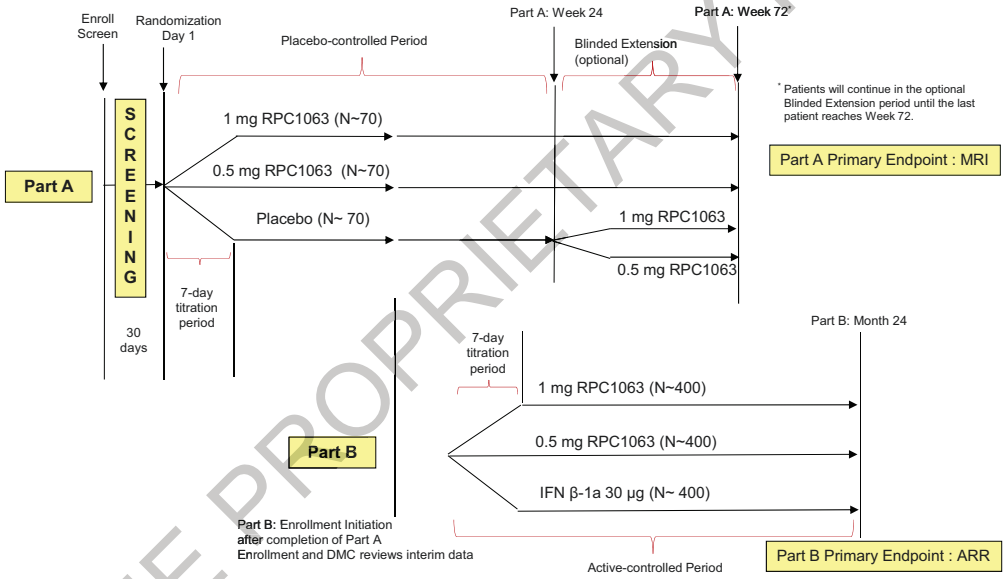
Patients who complete the 24 week placebo-controlled treatment period will have the option of entering a 24-week blinded extension period (Weeks 25 to 48). Patients assigned to either RPC1063 treatment group during the double-blind placebo-controlled period will continue in their respective treatment 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.

Part A 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. 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
- RPC1063 0.5 mg oral capsule daily
- RPC1063 1 mg oral capsule daily

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.

Figure 1. Study Schematic



4.2 Study Endpoints

The primary efficacy endpoint of Part A is:

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

The key secondary efficacy endpoints (rank ordered) of Part A are:

- 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

The secondary safety endpoints of Part A are:

- 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)

The secondary PK and PD endpoints of Part A are:

- Standard PK parameters
- CBC with differential
- Plasma protein biomarkers (e.g., cytokines, chemokines, other inflammatory proteins)
- Total immunoglobulins (Igs) - IgA, IgG, IgM

Note: PK data from this study may be integrated with PK data from other clinical trials to further enhance a population PK analysis. Population PK analyses will be described under a separate analysis plan and documented in a separate pharmacometric report.

The exploratory endpoints of Part A are:

5 General Statistical Considerations

Statistical testing for the primary efficacy endpoint will be made between each of the RPC1063 treatment groups and placebo in Part A. A sequential testing procedure will be used to control the overall Type I error rate due to multiple comparisons. If the first comparison (RPC1063 1 mg versus placebo) is statistically significant ($p \leq 0.04944$), then the second comparison (RPC1063 0.5 mg versus placebo) will be tested at the 0.04944 significance level. However, if the first comparison is not statistically significant, then the .

Provided that the primary comparisons are statistically significant, the sequential testing procedure will continue to be used for the secondary endpoints. The prespecified order includes both the order of the secondary endpoints and dose groups. Specifically, for each of the secondary endpoints, a sequential testing procedure will be used to control the overall Type I error rate due to multiple comparisons with the first comparison (RPC1063 1 mg versus placebo) and the second comparison (RPC1063 0.5 mg versus placebo). Secondary endpoints have been rank prioritized in the order shown in Section 8.2 of the protocol.

Unless specified otherwise, all statistical analyses will be performed using a two-sided hypothesis test at the overall 5% level of significance. Accordingly, p-values will be rounded to three decimal places. If a p-value is less than 0.001, it will be reported as "<0.001". If a p-value is greater than 0.999, it will be reported as ">0.999".

Continuous data will be presented using descriptive statistics: n, mean, standard deviation, 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 percents will be the number of subjects 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 versus EDSS > 3.5)
- baseline presence of GdE lesions (lesions present versus lesions absent)
- age at baseline (age ≤ 40 versus age > 40)
- sex (female versus male)
- weight (<median versus ≥median)

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

5.1 Sample Size

The primary analysis of Part A 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. 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).

5.2 Randomization, Stratification, and Blinding

In Part A, patients will be randomized 1:1:1 to receive placebo, RPC1063 0.5 mg, or RPC1063 1 mg. The randomization will be stratified by country. Patients who complete the 24 weeks placebo-controlled treatment period will have the option of entering a 24-week blinded extension period (Weeks 25 to 48). 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 randomization will be based on a stratified blocked algorithm and will be done centrally by using 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 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.

5.3 Analysis Populations

5.3.1 Intent-to-Treat (ITT) Population

The ITT population will include all randomized subjects who are confirmed to have received at least one dose of study drug. This will be the primary population for the analysis of 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 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 non-compliance, and other. The prespecified criteria for exclusion from the per protocol population are listed below, and will be finalized in a blinded review prior to the database lock.

- 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%

5.3.3 Safety Population

The Safety population will include all subjects who have received at least one dose of study drug. All enrolled subjects will be assumed to have taken study drug unless otherwise confirmed. If it is confirmed that a patient never took a dose of study drug, then the patient will be excluded from all safety analysis. All subjects in the Safety population will be analyzed according to the highest dose of RPC1063 treatment actually received 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 Analysis of Baseline Data and Exposure to Study Drug

All baseline data will be summarized for the ITT population. 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 Week 0 Day 1 visit. If there is more than one value on or before Day 1, the value (scheduled or unscheduled) 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

Visit windows will not be derived for analyses and instead the nominal visit from the eCRF will be used. A last available assessment will be derived as the last value on treatment.

5.4.4 Missing and Partial Data

Missing data may be imputed for some endpoints as seen 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.

6 Subject Disposition

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

7 Demographics, Medical History and Baseline Characteristics

7.1 Demographics

The demographics and baseline characteristics will be presented in a table. The demographic characteristics consist of age, age category, sex, race, ethnicity, weight, weight category, height, body mass index, region, and stratification factors. A subject's age in years is calculated using the date of the informed consent and date of birth. 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 summaries will be presented for both ITT and Per-Protocol populations.

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 subjects with a significant history for each body system. Percentages will be calculated out of the number of subjects in the Safety population. Significant medical history including specific details will be listed in a listing.

7.2.2 Multiple Sclerosis Disease History

The following multiple sclerosis disease history parameters will be summarized using the descriptive statistics

- EDSS score at baseline
- EDSS score 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

The following duration categories will be used 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 will be summarized at categories: 0 - 2, 2.5 - 3.5, 4 – 5, >5. Number of relapses within the past 12 and 24 months will also be summarized at categories: 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 presented in a listing.

8 Treatments and Medications

8.1 Prior and Concomitant Medications

All treatments being taken by the subjects 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 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 Name. At each level of summarization, a subject is counted once if he/she reports one or more medications at that level. Drug class will correspond to the ATC Level 2 term.

Prior medications are defined as medications with a stop date occurring before the first dose date. Concomitant medications are defined as medications with a start date or a stop 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 both prior and concomitant medications.

Prior and concomitant medications will be presented in a listing.

8.2 Study Treatments

For all subjects in both Part A and Part B of the study, initial study treatment will consist of a 7-day dose titration regimen. For subjects randomized to receive active treatment with RPC1063 in Part A or Part B, 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 subject 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 subjects is lost to follow-up, but the drug accountability log confirms that the subjects 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 subject 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 subject by taking into account whether a subject takes all doses of study drug as instructed. The study drug compliance rate will be summarized by treatment group using 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 prescribed for all visits based upon the duration in the study and then multiplying by 100. The number and percentage of subjects in each compliance rate category (<=50%, 51-60%, 61-70%, 71-80%, and 81-100%, >100%, <80%, and >120%)) will be reported. Percentages will be calculated out of the number of subjects who have been dosed in the study period.

9 Efficacy Analysis

Analysis of all efficacy endpoints will primarily be based on the ITT population. Additionally, the primary and secondary clinical efficacy endpoints will also be analyzed based on the PP population. All sensitivity analyses will only be conducted in the ITT population. The primary analysis of each efficacy endpoint will also be repeated using only the subset of observed data; i.e., without imputation for missing results. Listings will be provided for efficacy endpoints.

9.1 Primary Efficacy Endpoint

The primary efficacy endpoint of Part A is the total number of GdE lesions, assessed on brain MRIs from Week 12 to Week 24.

9.1.1 Primary Analysis

Missing data

A method of last observation carried forward (LOCF) will be used for subjects with missing post baseline lesions. If a subject is missing only 1 or 2 consecutive post-baseline scans, then the last valid non-missing, post-baseline observation will be carried forward to impute the missing value. However, if there are no post-baseline values to be carried forward or if the subject is missing more than 2 consecutive scans, then the mean

number of lesions from subjects in the same treatment group at the same visit will be used as the imputed value.

Analysis method

The total number of GdE lesions from Week 12 to Week 24 will be compared between each 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).

9.1.2 Sensitivity Analysis

The first sensitivity analysis will be using a negative binomial regression model to test the total number of GdE lesions, adjusting for the baseline number of GdE lesions and region. The results of the model are estimated as the log of the number of total GdE lesions, which will be exponentiated to present the adjusted mean number of lesions in each treatment group. The 95% confidence intervals of the mean number of total GdE lesions in each treatment group will be presented to further summarize the data.

Since corticosteroids may have a short term effect on GdE lesions, the second sensitivity analysis will be excluding MRI scans obtained with 24 days of steroid treatment. For this analysis, scans obtained within 24 days of the start date of steroid treatment will be considered missing and an imputed value, rather than the actual value, will be used in the calculation. Qualifying corticosteroids will be those with the ATC Level 2 terms of "CORTICOSTEROIDS FOR SYSTEMIC USE".

Summary statistics on the number of GdE lesions at Baseline and each visit will be reported, along with the change from Baseline and the percent change from Baseline. In addition, the proportion of subjects with 0, 1, 2, 3, 4, and >= 5 at Baseline and each visit will be reported.

9.2 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints of Part A are:

- 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

9.2.1 Analyses

Secondary Endpoint: The number of GdE lesions at Week 24

The number of GdE lesions at Week 24 will be analyzed using the stratified Wilcoxon-Mann-Whitney test, stratified by presence of GdE lesions at baseline (absent or present). A sensitivity analysis will be using a negative binomial regression model, adjusted for the baseline number of GdE lesions. Missing GdE data values will be imputed using the mean from subjects of the same treatment group at the same visit.

The proportion of subjects who are GdE lesion free at Week 24 will be analyzed using Fisher's Exact test. Missing Week 24 GdE lesion data will be handled via LOCF. A sensitivity analysis will be conducted using the non-responder imputation method. For this analysis, any subject missing their Week 24 GdE lesion data will be counted as having 1 or more lesions at Week 24 (i.e., will be considered "not GdE lesion free" for this analysis).

Secondary Endpoint: Total number of new or enlarging hyperintense T2-weighted brain MRI lesions at Week 24

The number of new or enlarging T2 hyperintense lesions at Week 24 will be analyzed using the stratified Wilcoxon-Mann-Whitney test, stratified by presence of GdE lesions at baseline (absent or present). A sensitivity analysis will be using a negative binomial regression model, adjusted for the presence of GdE lesions at baseline and region. Missing new or enlarging T2 data values will be imputed using the mean from subjects of the same treatment group at the same visit.

Secondary Endpoint: ARR at the end of Week 24

Definition of relapses

The relapse rate will be based on only 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 in 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.

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. This is called the unadjusted relapse rate.

Analysis method – annualized relapse rate

ARR at the end of Week 24 will be analyzed using a Poisson regression model. The model will compare treatment groups, adjusted for region, the number of relapses within 24 months prior to the study, and presence of GdE lesions. A sensitivity analysis will be using a negative binomial regression model to compare ARR with the same covariates as specified for the Poisson model.

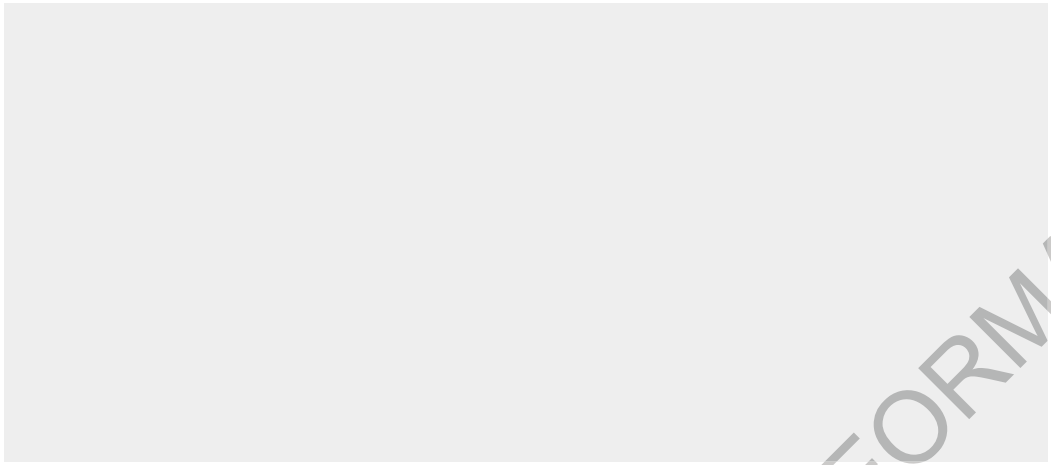
9.3 Exploratory Efficacy Endpoint

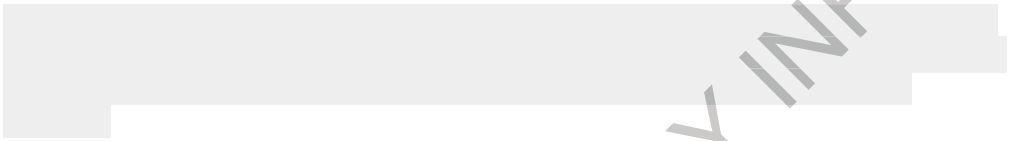
The exploratory endpoints of Part A are:

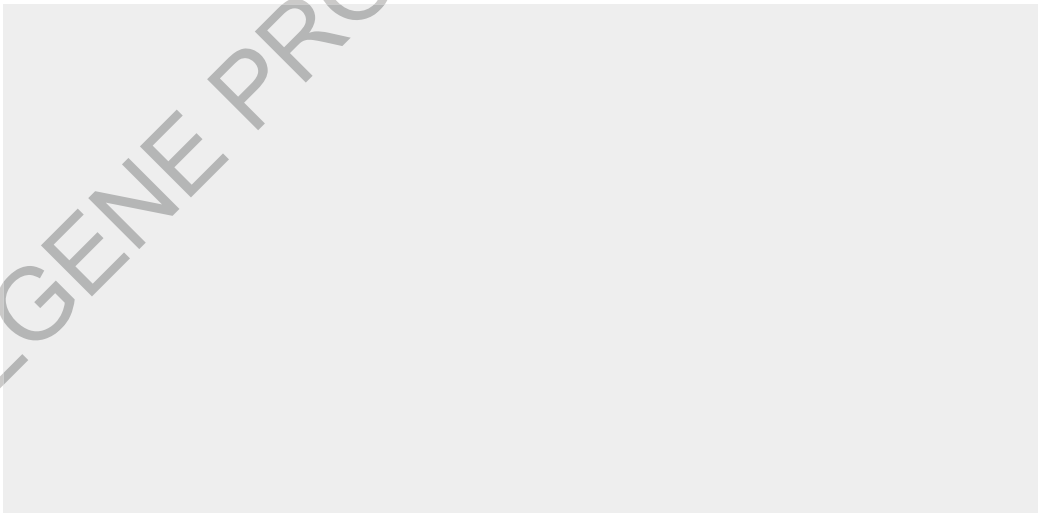
9.3.1 Analysis

Exploratory Endpoint:

Exploratory Endpoint:







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.

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 treatment with the 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 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 preferred term per patient. If a subject reports the same preferred term multiple times, then that preferred term will only be incremented by one since patient counts will be presented. As with the preferred term, if a patient reports multiple AEs within the same body system, then that body system 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 RPC1063 1 mg group. For tables showing incidence by PT only, the PTs will be sorted in descending incidence in the RPC1063 1 mg group.

The incidence of all treatment-emergent AEs will be presented by SOC and PT and separately by PT only.

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 subject 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 subject reported multiple occurrences of the same AE, only the most severe will be presented. Adverse events (AE) 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 subject 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 preferred term per patient. If a subject reports the same SAE preferred term multiple times, then that preferred term will only be incremented by one since subject counts will be presented. As with the preferred term, if a subject reports multiple SAEs within the same body system, then that body system will only be incremented by one since subject counts will be presented. Incidences of SAEs will be presented by SOC and PT. 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 subject 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 (LFTs elevation), and dermatological (cutaneous malignancy) abnormalities. These AEs will be summarized in tables.

10.2 Clinical Laboratory Evaluations

Laboratory assessments will be performed by a central laboratory. Unless otherwise specified, 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 subject'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 subject'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 for hematology summary tables: 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), mean corpuscular hemoglobin concentration (MCHC), and RBC morphology. A listing will present abnormal hematology values for all subjects.

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

In addition, the change and percent change from baseline in CBC with Differential will be summarized for each treatment group.

10.2.2 Blood Chemistry

The following laboratory tests will be included for blood chemistry summary tables: 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. A Listing will present abnormal chemistry values for all subjects.

The incidence of subjects 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 standing and supine systolic blood pressure (SBP), standing and supine diastolic blood pressure (DBP), body temperature, and heart rate (HR) will be recorded on the eCRF once per visit at Screening, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24. 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 and for the first 75 patients on Days 5 and 8.

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 (supine and standing), DBP (supine 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 starting at Week 4, only a single timepoint will be collected and shown.

For patients participating in cardiac monitoring on Days 5 and 8, a summary table will be provided that summarizes the hourly change from pre-dose assessment through hour 6 at each of the baseline, Day 5, and Day 8 visits by treatment group 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 and change from pre-dose in vital signs for the baseline, Day 5, and Day 8 visits.

The number and percentage of subjects 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 subjects 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 subject in listings.

Table 10.3.1 Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

Vital Sign	Criteria for Abnormalities
Temperature	>38°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

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.

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. 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 Pharmacodynamic Analysis

The protocol allows for the collection of samples for PD assessments including total immunoglobulins (Igs) - IgA, IgG, IgM and plasma protein biomarkers (cytokines, chemokines, other inflammatory proteins). Analysis of the PD samples, if performed, will be described in a separate analysis plan.

12 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 45% of patients will have completed 12 weeks of treatment. The endpoint for the interim analysis will be the number of new GdE lesions using all data from subjects 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.

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 both prior and 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 prior and 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.