Official Title of Study:

A Multi-Site, Open-Label Extension Trial of Oral RPC1063 in Relapsing Multiple Sclerosis

Protocol: RPC01-3001

NCT Number: NCT02576717

Document Date (Date in which document was last revised): 08-Oct-2021

1. CLINICAL TRIAL PROTOCOL

A Multi-Site, Open-Label Extension Trial of Oral RPC1063 in Relapsing Multiple Sclerosis

Investigational Drug:	RPC1063
Protocol Number:	RPC01-3001
Version and Date:	10.0, dated 08 Oct 2021
Replaces Version:	9.0, dated 26 Feb 2020
Phase:	3
IND number:	109,159
EudraCT number:	2015-002500-91

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

CONFIDENTIAL

This protocol is provided to you as an Investigator, potential Investigator, or consultant for review by you, your staff, and ethics committee/institutional review board. The information contained in this document is regarded as confidential and, except to the extent necessary to obtain informed consent, may not be disclosed to another party unless such disclosure is required by law or regulations. Persons to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them.

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SPONSOR: CELGENE INTERNATIONAL II SÀRL

2. SYNOPSIS

Sponsor/Company: Celgene International II Sàrl	
Investigational Product: RPC1063	
Name of Active Ingredient: ozanimod hydrochloride (HCl)	
Protocol Title:	A multi-site, open-label extension trial of oral RPC1063 in relapsing multiple sclerosis
Protocol No:	RPC01-3001 (EudraCT Number 2015-002500-91)
Investigators:	Approximately 275 that participated in Trial RPC01-201, Trial RPC01-301, and/or Trial RPC01-1001
Regions	North America, Europe, South Africa, and New Zealand
Trial Duration: Estimated date first patient enrolled: November 2015 Estimated date last patient completed: December 2022	**Phase:** 3

Objectives:

Primary:

- To characterize the long-term safety and tolerability of RPC1063 in patients with relapsing multiple sclerosis

Secondary:

- To characterize the long-term efficacy of RPC1063 in patients with relapsing multiple sclerosis

Methodology:

This is a multi-site, open-label extension trial of oral RPC1063 (ozanimod HCl) 1 mg (equivalent to ozanimod 0.92 mg) administered once daily to patients with relapsing multiple sclerosis (RMS) who are eligible according to the enrollment criteria and completed one of the following trials: RPC01-201, RPC01-301, or RPC01-1001 (the "parent trials"). Regardless of treatment assignment in the parent trial, patients will receive RPC1063 at a dose of 1 mg daily in RPC01-3001 after a 7-day dose escalation regimen, as applicable (0.25 mg on Days 1 to 4, 0.5 mg on Days 5 to 7, and 1 mg from Day 8 onward). Approval from the Sponsor's representative is required for enrollment more than 14 days after the patient's last dose of investigational drug in the parent trial, and the patient must undergo RPC1063 dose escalation. Patients will receive RPC1063 at 1 mg/day until the end of the trial or until the Sponsor discontinues the development program.

Scheduled trial visits include:

- Baseline (Day 1)
- Evaluations every 3 months (91 days) and every 12 months, as specified in the schedule of events. After a patient reaches their 3rd annual visit, the Every 3-Month Visit will

become the Every 6-Month Visit (one visit between annual visits instead of 3). Annual visits (Every 12 Months) are unchanged.

- Early Termination/End of Treatment Visit
- Visits at 1, 4, 7, 14, and 21 days after the last dose of investigational drug to assess dependence and withdrawal symptoms
- Absolute lymphocyte count (ALC) Follow-up Visit(s) every 14 days (± 3 days) after the last dose of investigational drug until ALC is above the lower limit of normal (LLN) (the Medical Monitor should be consulted if the ALC is not > LLN by the Day 90 Safety Follow-up Visit, and ALC visits should continue every 14 days (± 3 days) until the Investigator is notified to discontinue).
- Safety Follow-up Visit 28 days after the last dose of investigational drug
- Safety Follow-up Visit 90 days after the last dose of investigational drug
- In the event that commercial ozanimod or an access program becomes available prior to December 2022, subjects may transition to the commercial product after discussion with the Investigator at his/her discretion. Subjects who transition to commercial ozanimod are not required to attend safety follow-up visits after their end of treatment visit as long as commercial ozanimod is started within 14 days of discontinuation of study drug. Otherwise, all other subjects continuing in the study and subsequently discontinuing prior to the availability of commercial ozanimod in their country/state or by end of the study will be required to follow the schedule of assessments through the safety follow up visits.

Trial assessments include evaluation of adverse events (AEs), review of concomitant medications, clinical laboratory tests, assessment of immune response, pharmacokinetic (PK) sampling, physical and neurological examination (magnetic resonance imaging [MRI] with and without gadolinium contrast), vital sign measurements, 12-lead electrocardiogram (ECG), optical coherence tomography (OCT), pulmonary function tests, dermatological examination, and Columbia Suicide Severity Rating Scale (C-SSRS) evaluation. The Cognitive Function subscale of the Multiple Sclerosis Quality of Life 54 (MSQOL-54) will be assessed to evaluate quality of life and subjective cognitive impairment. In addition to the C-SSRS, the physician's withdrawal checklist (PWC-20), the hospital anxiety and depression scale (HADS), and the Epworth sleepiness scale (ESS) will be administered to assess dependence and withdrawal symptoms. These assessments will be administered on at least 1 visit while on study drug and in at least 80 evaluable patients after discontinuing study drug. All patients should undergo these assessments until the Sponsor decides that no further withdrawal assessments are required.

Refer to the full protocol for instructions regarding baseline assessments.

If a patient experiences a relapse after completing a parent trial, but prior to entering RPC01-3001, the patient may remain eligible for RPC01-3001. There is no minimum waiting period following the relapse; however, the Investigator should confirm that the patient is neurologically and medically stable prior to initiating investigational drug.

Patients will be evaluated for relapses throughout the trial, including during the Safety Follow-up Visit, and patients will be instructed to contact the treating Investigator for any suspected relapses during the

trial. A relapse is defined as the occurrence of new or worsening neurological symptoms attributable to MS and immediately preceded by a relatively stable or improving neurological state of at least 30 days.

The new or worsening neurological symptoms must be accompanied by objective neurological worsening, based on examination by the evaluator, consistent with an increase of at least half a point on the Expanded Disability Status Scale (EDSS), or 2 points on one of the appropriate Functional System (FS) scores, or 1 point on 2 or more of the appropriate FS scores compared to last rating (EDSS or FS scores) that did not occur during a relapse. The change in FS scale scores should correspond to the patient's symptoms (eg, patient reported change in visual acuity should correspond to a change in the vision FS score). Symptoms must persist for > 24 hours and should not be attributable to confounding clinical factors (eg, fever, infection, injury, adverse reactions to concomitant medications).

Patients who are withdrawn early from the trial will be required to visit the trial site as soon as possible so that the Early Termination assessments can be conducted. Patients who withdraw from the trial will be followed for collection of safety data, including lymphocyte recovery. In addition, PK samples will be collected at the End of Treatment/Early Termination Visit, and for Day 28 and Day 90 Safety Follow-up Visits.

Planned Number of Patients (approximately):

Based on an estimated dropout rate of 10% per year, approximately 2350 patients may be eligible for enrollment in the trial depending on completion of one of the parent trials.

Diagnosis and main eligibility criteria:

To be eligible to participate in this trial, patients must meet all of the following criteria:

1. Completed one of the parent trials
2. Does not have a condition that would require withdrawal from one of the parent trials
3. Has no conditions requiring treatment with a prohibited concomitant medication
4. Is not receiving treatment with any of the following drugs or interventions within the corresponding timeframe:
   - At Baseline (Day 1)
     - Cytochrome P450 (CYP) 2C8 inhibitors (eg, gemfibrozil or clopidogrel) or inducers (eg, rifampicin)
   - Two weeks prior to Baseline (Day 1)
     - Monoamine oxidase inhibitors (eg, selegiline, phenelzine)
5. Ability to provide written informed consent and to be compliant with the schedule of protocol assessments
6. <u>Female patients of childbearing potential</u>:

   Must agree to practice a highly effective method of contraception throughout the study until completion of the 90-Day Safety Follow-up Visit. Highly effective methods of contraception

are those that alone or in combination result in a failure rate of a Pearl index of less than 1% per year when used consistently and correctly.

Acceptable methods of birth control in this study are the following:

- combined hormonal (oestrogen and progestogen containing) contraception, which may be oral, intravaginal, or transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injectable, or implantable
- placement of an intrauterine device (IUD)
- placement of an intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence

All patients:

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

Investigational product, dosage and mode of administration:
RPC1063 will be provided as powder-filled capsules. RPC1063 drug substance is [redacted] Two RPC1063 dosage strengths (size 4 capsules) have been prepared for the clinical investigations; RPC1063 0.25 mg (equivalent to ozanimod 0.23 mg) and RPC1063 1 mg (equivalent to ozanimod 0.92 mg).

Duration of treatment: Patients will receive RPC1063 at 1 mg/day until the end of the trial or until the Sponsor discontinues the development program.

Reference therapy, dosage and mode of administration: Not applicable

Criteria for evaluation:

Safety Endpoints:

Safety and tolerability will be characterized in this trial by the incidence, relationship, and type of adverse events, serious adverse events, and adverse events leading to withdrawal from the trial; the incidence, relationship, and type of laboratory abnormalities; vital signs; ECG results; and physical examination abnormalities. Suicidality (C-SSRS) will be assessed in the trial. In addition, descriptive characterization will be provided for adverse events of special interest including bradycardia and heart conduction abnormalities (ECG and vital signs), pulmonary effects (FEV_1, FVC, and diffusing capacity of the lung for carbon monoxide measurements), macular edema (OCT), hepatic effects (liver function tests), serious or opportunistic infections, and malignancy. In addition, dependence and withdrawal symptoms will be assessed in at least 80 evaluable patients who discontinue study drug using the following assessments: PWC-20, HADS, ESS, vital signs, and the C-SSRS. Changes from

last on-study-drug assessment for each withdrawal scale (PWC-20, HADS, ESS, C-SSRS, and vital signs) to post study drug Days 1, 4, 7, 14, 21, and 90 will be summarized.

Exploratory measurements of immune response (eg, anti-SARS-CoV-2 serology) will be assessed from blood samples collected at trial visits and end of treatment, and the potential association between these measurements and selected endpoints related to safety and/or efficacy.

Efficacy Endpoints:

- Annualized relapse rate
- Time to first relapse
- The number of new or enlarging hyperintense T2-weighted brain MRI lesions at each visit
- The number of gadolinium-enhanced brain MRI lesions at each visit
- Time to onset of disability progression as defined by a sustained worsening in EDSS of 1.0 points or more from baseline, confirmed after 3 months and after 6 months
- Proportion of patients who are free of gadolinium-enhanced lesions at each visit
- Proportion of patients who are free of new or enlarging T2 lesions at each visit
- Percent change in normalized brain volume (atrophy) on brain MRI scans from Baseline at each visit
- Change in Multiple Sclerosis Functional Composite (MSFC) score from Baseline at each applicable visit (including the Low-Contrast Letter Acuity Test [LCLA] measurement of visual function as a component)
- Change in Multiple Sclerosis Quality of Life 54 score from Baseline at each applicable visit
- Changes in other MRI variables including but not limited to, number and volume of gadolinium-enhanced T1 lesions, volume of T2 lesions, number of new or enlarging T2 lesions, volume of unenhancing T1 lesions, number of new unenhancing T1 lesions

Statistical methods:

Safety

All safety data will be listed and summarized for the safety population. Adverse events will be monitored during the trial and the data analyzed with respect to incidence overall as well as severity and potential relationship of the AEs to investigational drug. Adverse events with onset on, or after the first dose of investigational drug or with onset prior to the first dose of investigational drug that increase in severity on, or after the first dose of investigational drug will be considered treatment-emergent. Treatment-emergent AEs will be summarized by system organ class and preferred term, and presented in descending order of frequency within each system organ class. Serious AEs, AEs of special interest, and AEs leading to withdrawal from the trial will be summarized similarly.

Associated laboratory parameters such as hepatic profile, renal function, and hematology values will be grouped and presented together. For each laboratory test, individual patient values outside the standard reference range will be flagged and listed. Shift tables will be produced showing the frequency of shifts from Baseline to the worst on-trial value in and out of the normal range as well as by visit. Changes from Baseline to each visit for each laboratory parameter will also be summarized.

The change from Baseline to each visit for each of the vital signs parameters will be summarized. The change from Baseline to each applicable visit for each of the ECG parameters will also be summarized.

For each dependence and withdrawal assessment (PWC-20, HADS, ESS, C-SSRS, and vital signs) changes from the last assessment on study drug to post study drug Days 1, 4, 7, 14, 21, and 90 will be summarized.

Efficacy

For the annualized relapse rate, the number of patients with relapses, the total number of relapses, the patient-years on trial, the unadjusted annualized relapse rate, and the patient relapse rate will be presented. The unadjusted annualized relapse rate will be calculated as (total number of relapses) / (total days in the trial) * 365.25. The relapse rate will be based on only those relapses that were determined by the treating Investigator to meet the protocol-defined definition of relapse, based on the EDSS scores. 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, ie, if 2 relapses have onset days that are ≤30 days of one another, they will be counted as 1 relapse.

Time to first relapse and time to onset of disability progression will be analyzed using Kaplan-Meier methods. The estimated median time to event will be reported, along with the associated 95% CI. Disability progressions confirmed after 3 months and after 6 months will be analyzed separately.

Other efficacy endpoints will be summarized by visit using descriptive statistics or counts and percentages as appropriate.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this trial protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve.
AV	Atrioventricular
BCRP	Breast cancer resistance protein
CD	Crohn's disease
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Apparent total body clearance of the drug from plasma.
CNS	Central nervous system
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
DDI	Drug-drug interaction
DLCO	Diffusing capacity of the lung for carbon monoxide
DMC	Data Monitoring Committee
DMT	Disease modifying therapy
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EDSS	Expanded Disability Status Scale
ESS	Epworth sleepiness scale
FEV_1	Forced expiratory volume at 1 second
FS	Functional System

Abbreviation or Specialist Term	Explanation
FVC	Forced vital capacity
GA	Glatiramer acetate
GCP	Good Clinical Practice
Gd	Gadolinium
GdE	Gadolinium-enhancing
GGT	Gamma-glutamyl-transferase
HADS	Hospital anxiety and depression scale
hCG	Human chorionic gonadotropin
HDL	High-density lipoprotein
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	Interferon
INR	International normalized ratio
IRB	Institutional Review Board
IRF5	Interferon regulatory factor 5 gene
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
LCLA	Low-Contrast Letter Acuity Test
LDL	Low-density lipoprotein
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
MSQOL-54	Multiple Sclerosis Quality of Life-54
OCT	Optical coherence tomography
OLE	Open-label extension
PD	Pharmacodynamic(s)
PFT	Pulmonary function test

Abbreviation or Specialist Term	Explanation
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PQC	Product Quality Complaint
PT	Prothrombin time
PTT	Partial thromboplastin time
PWC-20	Physician's withdrawal checklist
QTcF	Fridericia's corrected QT interval
RMS	Relapsing multiple sclerosis
S1P	Sphingosine 1-phosphate
$S1P_1$, $S1P_2$, $S1P_3$, $S1P_4$, or $S1P_5$	Sphingosine 1-phosphate receptor 1, 2, 3, 4, or 5
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Coronavirus 2
SDMT	Symbol Digit Modalities Test
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOP	Standard operating procedure
UC	Ulcerative colitis
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization

5. INTRODUCTION

5.1. Multiple Sclerosis

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

Currently approved first-line immune-modulating therapies include several interferon (IFN)-β products, glatiramer acetate (GA) and fingolimod. IFN-β and GA are disease-modifying therapies that have moderate efficacy, reduce the relapse rate by approximately 30% and reduce disability accumulation compared to placebo (IFNB Multiple Sclerosis Study Group 1993; Jacobs 1996; PRISMS 1998; Johnson 1995; Goodin 2002). Response to treatment with IFN-β products may be related to variation in a gene called interferon regulatory factor 5 (*IRF5*) and the interferon gene signature, and may be assessed based on data collected in this trial and the parent trials (Vosslamber 2011). Natalizumab, a humanized monoclonal antibody, is another approved immune-modulating therapy that has been shown to reduce relapse rates by 68% and reduces the risk of sustained progression of disability by 42% compared to placebo (Polman 2006). Natalizumab acts by blocking leukocyte recruitment to inflammatory sites in the CNS. Each of these drugs is characterized by a combination of limited therapeutic utility, safety concerns and/or drug compliance issues, suggesting the need for the development of effective, well tolerated orally active MS therapies.

5.2. RPC1063

RPC1063 (ozanimod hydrochloride [HCl]) is a sphingosine 1-phosphate (S1P) receptor modulator, which binds with high affinity selectively to sphingosine 1-phosphate receptor subtypes 1 and 5 ($S1P_1$ and $S1P_5$). RPC1063 causes lymphocyte retention in lymphoid tissues. The mechanism by which RPC1063 exerts therapeutic effects in MS is unknown but may involve the reduction of lymphocyte migration into the CNS.

RPC1063 is 10-fold more selective for $S1P_1$ relative to $S1P_5$ and has little activity on other S1P receptors ($S1P_2$, $S1P_3$, and $S1P_4$). RPC1063 is extensively metabolized in humans to form a number of circulating active metabolites. *In vitro*, RPC1063 and its active metabolites demonstrated similar activity and selectivity for $S1P_1$ and $S1P_5$. In humans, approximately 94% of circulating total active drug exposure is represented by RPC1063 (6%), CC112273 (73%), and CC1084037 (15%).

The $S1P_1$ target of RPC1063 is a G protein-coupled receptor whose natural ligand is S1P. Many cell types express $S1P_1$, including vascular endothelial cells, brain cells and lymphocytes (Rosen 2009). Stimulation (agonism) of this receptor results in biological activities that are likely to ameliorate pathological processes associated with MS.

5.2.1. S1P Receptor Modulation Experience in MS

Clinical experience with fingolimod strongly supports the rationale for therapeutically targeting S1P receptors in MS. Fingolimod, an oral drug approved for the treatment of MS, has demonstrated a superior efficacy profile compared to IFN-β, reducing relapse rates by 52% (Cohen 2010; Kappos 2010). Fingolimod stimulates $S1P_1$, which induces lymphocyte sequestration in peripheral lymphoid organs, resulting in temporary reduction in circulating lymphocyte counts (Sanna 2004). An inability of sequestered autoreactive lymphocytes to traffic to and exacerbate inflammation in the CNS is thought to be the primary mode of action of fingolimod (Kappos 2006). Therefore, this peripheral lymphocyte response represents a clearly defined pharmacodynamic (PD) effect of $S1P_1$ stimulation (Sanna 2006). $S1P_1$ stimulation also supports maintenance of blood-brain barrier integrity by enhancing endothelial barrier function, thereby potentially contributing to fingolimod's efficacy profile (Sanna 2006; Sanchez 2003).

Fingolimod is not specific for $S1P_1$. The compound also stimulates three other related receptors: $S1P_3$, $S1P_4$, and $S1P_5$ (Mandala 2002; Brinkmann 2002). Several toxicities associated with fingolimod treatment may be a consequence of the drug lacking specificity for $S1P_1$ and potentially having pharmaceutical liabilities related to the drug's structural class (Cohen 2010; Kappos 2006).

Siponimod, a selective $S1P_1$ and $S1P_5$ modulator with a safety profile similar to fingolimod, is another oral drug approved in the US and EU for the treatment of relapsing forms of MS. It has shown a relative risk reduction of 21% in 3-month confirmed disability progression versus placebo in patients with secondary progressive multiple sclerosis (SPMS) (Kappos 2018).

5.2.2. Clinical Trials

Completed Phase 1 trials with RPC1063 in healthy volunteers include, but are not limited to, the first-in-human trial (RPCS 001), a thorough QT trial (RPC01-102), a food-effect trial (RPC01-1901), a drug-drug interaction (DDI) trial with a potent inhibitor and potent inducer of cytochrome P450 (CYP) 3A (RPC01-1902), a DDI study with a strong inhibitor of P-glycoprotein and Breast Cancer Resistance Protein (Study RPC01-1903), a study to evaluate the PK and safety of RPC1063 in Japanese and Caucasian subjects (Study RPC01-1905), a DDI study with an oral contraceptive (Study RPC01-1907), and a DDI study with a calcium channel blocker or a beta blocker (Study RPC01-1908).

Parent trials for this protocol include RPC01-201, RPC01-301, and RPC01-1001; all have been completed. RPC01-201 consisted of 2 parts. RPC01-201 Part A was a Phase 2, randomized, double-blind, placebo-controlled, parallel group trial with a blinded extension. RPC01-201 Part B was a Phase 3, randomized, double-blind, active-controlled, parallel group trial. RPC01-301

was a Phase 3, randomized, double-blind, active-controlled, parallel group trial. RPC01-201 (Part A and Part B) and RPC01-301 were designed to evaluate the efficacy and safety of RPC1063 (0.5 mg and 1 mg) in patients with relapsing multiple sclerosis (RMS). RPC01-1001 was a Phase 1 intensive PK trial in patients with RMS.

Overall, the safety experience with RPC1063 supports its continued development in patients with RMS.

Additional information regarding company-sponsored trials in the RPC1063 clinical development program is provided in the Investigator's Brochure.

5.3. Clinical Trial Rationale

The parent trials provided opportunities for adult patients with RMS to participate in important Phase 3 clinical trials to determine if RPC1063 is effective and safe, and to participate in a clinical pharmacology study characterizing the multiple-dose PK and PD of RPC1063 in patients with RMS. This open-label extension (OLE) trial is designed to further characterize the longer-term safety and efficacy beyond that required for the Phase 3 registration trials. In addition, the trial allows all patients who are receiving clinical benefit from treatment with RPC1063 to continue to receive it until the end of the trial or until the Sponsor discontinues the development program.

6. TRIAL OBJECTIVES AND ENDPOINTS

6.1. Primary Objective

To characterize the long-term safety and tolerability of RPC1063 in patients with relapsing multiple sclerosis.

6.2. Secondary Objectives

To characterize the long-term efficacy of RPC1063 in patients with relapsing multiple sclerosis.

6.3. Endpoints

6.3.1. Safety Endpoints

Safety and tolerability will be characterized in this trial by the incidence, relationship, and type of adverse events, serious adverse events, and adverse events leading to withdrawal from the trial; the incidence, relationship, and type of laboratory abnormalities; vital signs; electrocardiogram (ECG) results; and physical examination abnormalities. Suicidality (Columbia-Suicide Severity Rating Scale [C-SSRS]) will be assessed in the trial. In addition, descriptive characterization will be provided for adverse events of special interest (AESIs) including bradycardia and heart conduction abnormalities (ECG and vital signs), pulmonary effects (forced expiratory volume at 1 second [FEV_1], forced vital capacity [FVC], and diffusing capacity of the lung for carbon monoxide measurements), macular edema (optical coherence tomography [OCT]), hepatic effects (liver function tests), serious or opportunistic infections, and malignancy (see Section 12.4.2 for the complete list of AESIs).

Exploratory measurements of immune response (eg, anti-SARS-CoV-2 serology) will be assessed from blood samples collected at trial visits and end of treatment, and the potential association between these measurements and selected endpoints related to safety and/or efficacy.

In addition, dependence and withdrawal symptoms will be assessed in at least 80 evaluable patients who discontinue study drug using the following assessments: physician's withdrawal checklist (PWC-20), hospital anxiety and depression scale (HADS), Epworth sleepiness scale (ESS), vital signs, and the C-SSRS. Changes from last on study-drug assessment for each withdrawal scale (PWC-20, HADS, ESS, C-SSRS, and vital signs) to post study drug Days 1, 4, 7, 14, 21, and 90 will be summarized.

6.3.2. Efficacy Endpoints

- Annualized relapse rate
- Time to first relapse
- The number of new or enlarging hyperintense T2-weighted brain magnetic resonance imaging (MRI) lesions at each visit
- The number of gadolinium-enhanced brain MRI lesions at each visit

- Time to onset of disability progression as defined by a sustained worsening in Expanded Disability Status Scale (EDSS) of 1.0 points or more from baseline, confirmed after 3 months and after 6 months
- Proportion of patients who are free of gadolinium-enhanced lesions at each visit
- Proportion of patients who are free of new or enlarging T2 lesions at each visit
- Percent change in normalized brain volume (atrophy) on brain MRI scans from Baseline at each visit
- Change in Multiple Sclerosis Functional Composite (MSFC) score from Baseline at each applicable visit (including the Low-Contrast Letter Acuity Test [LCLA] measurement of visual function as a component)
- Change in Multiple Sclerosis Quality of Life 54 score from Baseline at each applicable visit
- Changes in other MRI variables including number and volume of gadolinium-enhanced T1 lesions, volume of T2 lesions, number of new or enlarging T2 lesions, volume of unenhancing T1 lesions, number of new unenhancing T1 lesions

7. INVESTIGATIONAL PLAN

7.1. Overall Trial Design

This is a multi-site, open-label extension trial of oral RPC1063 (ozanimod HCl) 1 mg (equivalent to ozanimod 0.92 mg) administered once daily to patients with RMS who are eligible according to the enrollment criteria and completed one of the following trials: RPC01-201, RPC01-301, or RPC01-1001 (the "parent trials").

Based on an estimated dropout rate of 10% per year, approximately 2350 patients may be eligible for enrollment in the trial depending on completion of one of the parent trials.

Regardless of treatment assignment in the parent trial, patients will receive RPC1063 at a dose of 1 mg daily in RPC01-3001 after a 7-day dose escalation regimen, as applicable (Section 9.1). Approval from the Sponsor's representative is required for enrollment more than 14 days after the patient's last dose of investigational drug in the parent trial, and the patient must undergo RPC1063 dose escalation. Patients from either the blinded extension of the RPC01-201 Part A trial or the RPC01-1001 trial will not require initial dose escalation unless the duration between the last dose of RPC1063 in the parent trial and the first dose in RPC01-3001 is more than 14 days. Patients will receive RPC1063 at 1 mg/day until the end of the trial or until the Sponsor discontinues the development program.

It is anticipated that the trial will include approximately 275 sites in North America, Europe, South Africa, and New Zealand that participated in one or more of the parent trials.

Scheduled trial visits include:

- Baseline (Day 1)
- Evaluations every 3 months (91 days) and every 12 months, as specified in the schedule of events (Table 2). After a patient reaches their 3rd annual visit, the Every 3-Month Visit will become the Every 6 Month Visit (one visit between annual visits instead of 3). Annual visits (Every 12 Months) are unchanged.
- Early Termination/End of Treatment visit
- Visits at 1, 4, 7, 14, and 21 days after the last dose of investigational drug to assess dependence and withdrawal symptoms
- Absolute lymphocyte count (ALC) Follow-up Visit(s) every 14 days (± 3 days) after the last dose of investigational drug until ALC is above the lower limit of normal (LLN) (the Medical Monitor should be consulted if the ALC is not > LLN by the Day 90 Safety Follow-up Visit, and ALC visits should continue every 14 days (± 3 days)until the Investigator is notified to discontinue).
- Safety Follow-up Visit 28 days after the last dose of investigational drug
- Safety Follow-up Visit 90 days after the last dose of investigational drug

- In the event that commercial ozanimod or an access program becomes available prior to December 2022, subjects may transition to the commercial product after discussion with the Investigator at his/her discretion. Subjects who transition to commercial ozanimod are not required to attend safety follow-up visits after their end of treatment visit as long as commercial ozanimod is started within 14 days of discontinuation of study drug. Otherwise, all other subjects continuing in the study and subsequently discontinuing prior to the availability of commercial ozanimod in their country/state or by end of the study will be required to follow the schedule of assessments through the safety follow up visits.

Trial assessments are described in Table 2. These include evaluation of adverse events (AEs), review of concomitant medications, clinical laboratory tests, assessment of immune response, PK sampling, physical and neurological examination (MRI with and without gadolinium contrast), vital sign measurements, 12-lead ECG, OCT, pulmonary function tests, dermatological examination, and C-SSRS evaluation. The Cognitive Function subscale of the Multiple Sclerosis Quality of Life-54 (MSQOL-54) will be assessed to evaluate quality of life and subjective cognitive impairment. In addition to the C-SSRS, the PWC-20, the HADS, and the ESS will be administered to assess dependence and withdrawal symptoms. These assessments will be administered on at least 1 visit while on study drug and in at least 80 evaluable patients after discontinuing study drug (Table 3). All patients should undergo these assessments until the Sponsor decides that no further withdrawal assessments are required.

Refer to Table 2 for instructions regarding baseline assessments.

For patients from RPC01-1001, the RPC01-3001 informed consent process may begin on the last day of dosing in RPC01-1001. For the same patients, Baseline (Day 1) brain MRI, OCT, and pulmonary function tests are not required to occur on the same day; these may be performed at any time between signing informed consent and first dose of RPC1063 in RPC01-3001. The RPC01-1001 End of Study assessments and the RPC01-3001 Baseline procedures may be performed on the same day. The first dose of RPC1063 in RPC01-3001 may only be administered after completion of all RPC01-1001 End of Study assessments and all RPC01-3001 Baseline assessments.

If a patient experiences a relapse after completing a parent trial, but prior to entering RPC01-3001, the patient may remain eligible for RPC01-3001. There is no minimum waiting period following the relapse; however, the Investigator should confirm that the patient is neurologically and medically stable prior to initiating investigational drug. If the Investigator suspects the patient may require more than 14 days after the last dose of investigational drug in the parent trial to become stable, the Investigator should discuss this immediately with the Sponsor's representative to determine ongoing eligibility.

Patients will be evaluated for relapses throughout the trial, including during the Safety Follow-up Visit, and patients will be instructed to contact the treating Investigator for any new or worsening neurological symptoms during the trial that may indicate a possible relapse. If the Investigator suspects a possible relapse, an unscheduled visit is to be planned as soon as possible, ideally within 7 days of symptom onset. A relapse is defined as the occurrence of new or worsening

neurological symptoms attributable to MS and immediately preceded by a relatively stable or improving neurological state of at least 30 days.

The new or worsening neurological symptoms must be accompanied by objective neurological worsening, based on examination by the evaluator, consistent with an increase of at least half a point on the EDSS, or 2 points on one of the appropriate Functional System (FS) scores, or 1 point on two or more of the appropriate FS scores compared to last rating (EDSS or FS scores) that did not occur during a relapse. The change in FS scale scores should correspond to the patient's symptoms (eg, patient reported change in visual acuity should correspond to a change in the vision FS score). Symptoms must persist for > 24 hours and should not be attributable to confounding clinical factors (eg, fever, infection, injury, adverse reactions to concomitant medications).

A blood sample will be collected at the subject's next visit after this amendment is implemented, every 6 months thereafter, and at the end of treatment for measurements of immune response (eg, SARS-CoV-2 serology).

Patients who are withdrawn early from the trial will be required to return to the trial site as soon as possible so that the final assessments can be conducted. Patients who withdraw from the trial will be followed for collection of safety data, including lymphocyte recovery. In addition, PK samples will be collected at the End of Treatment/Early Termination Visit and for Day 28 and Day 90 Safety Follow-up Visits.

7.2. Dose Adjustment Criteria

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

7.3. Criteria for Trial Termination

The Sponsor has the right to terminate the trial for safety reasons. In addition, the Sponsor may terminate the trial for administrative reasons. In all cases, all necessary measures have to be taken to guarantee appropriate safety follow-up of all patients already included in the trial. At the time of trial termination, all patients will complete the End of Treatment/Early Termination Visit and the 28-Day and 90-Day Safety Follow-up Visits. Central laboratory testing of ALC will continue every 14 days (± 3 days) after discontinuation of RPC1063 or the End of Treatment/Early Termination Visit until ALC is above the lower limit of normal or until the Investigator is notified to discontinue (Section 12.2.1).

The Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and the Regulatory Authorities will be informed in writing about any termination of the trial.

At the End of Treatment/Early Termination Visit, patients will undergo assessments for dependency and withdrawal symptoms (Table 3). Assessments will be performed at the End of Treatment/Early Termination Visit and at scheduled follow up assessment visits after the last dose of investigational drug. Patients should schedule the End of Treatment/Early Termination Visit within 24 hours of study drug discontinuation, as appropriate.

Table 2: Schedule of Events

Procedure	Baseline (Day 1)[a]	Every 3/6 Months[p] (± 10 days)	Every 12 Months (± 10 days)	Unscheduled Relapse Visit[b]	End of Treatment/ Early Term[c]	ALC Follow-up Visit[c] (every 14 days after last dose ± 3 days)	Safety Follow-up Visit[q] (28 days after last dose ± 7 days)	Safety Follow-up Visit[m, q] (90 days after last dose ± 10 days)
Informed consent	X[a]							
Eligibility criteria	X							
Clinical laboratory tests[d]	X	X	X		X[c]	X[c]	X[c]	X[c]
Urine/serum pregnancy (women of childbearing potential only)[e]	X[a]	X	X		X		X	X
Complete physical examination	X[a]		X		X			
Vital signs	X[f]	X	X	X	X		X	X
12-lead ECG	X[g]		X		X		X	
Administer investigational drug at trial site[h]	X							
Dispense investigational drug and patient diary	X[l]	X	X					
Investigational drug accountability, compliance check, and diary collection		X	X		X			

Procedure	Baseline (Day 1)[a]	Every 3/6 Months[p] (± 10 days)	Every 12 Months (± 10 days)	Unscheduled Relapse Visit[b]	End of Treatment/ Early Term[c]	ALC Follow-up Visit[c] (every 14 days after last dose ± 3 days)	Safety Follow-up Visit[q] (28 days after last dose ± 7 days)	Safety Follow-up Visit[m, q] (90 days after last dose ± 10 days)
Brain MRI[n]	X[i]		X		X			
EDSS and neurological examination	X[a]	X	X	X	X			
MSFC and LCLA	X[a]		X	X	X			
MSQOL-54	X[a]		X		X			
Pulmonary function tests[J]	X[a]		X		X			
OCT[k]	X[a]		X		X			
Dermatological (skin) examination	X[a]		X		X			
Columbia-Suicide Severity Rating Scale (C-SSRS)	X[a]	X	X	X	X		X	X
Prior/concomitant therapy	X	X	X	X	X		X	X
AEs/SAEs	X	X	X	X	X		X	X
PK Sampling					X[o]		X[o]	X[o]
Blood Sample[r]	A blood sample will be collected at the patient's next visit after this amendment is implemented, every 6 months thereafter, and at the end of treatment for potential measurements of immune response (eg, SARS-CoV-2 serology).							

Footnotes are provided on the next page.

[a] Perform specified procedures at Baseline (Day 1) only if they were not performed at the end of treatment/study visit of the parent trial or not within the timeframe prior to the end of treatment/study visit specified by the parent trial protocol. Perform a urine pregnancy test at Baseline if more than 1 month has elapsed from the last pregnancy test in the parent trial. Approval from the Sponsor's representative is required for enrollment more than 14 days after the patient's last dose of investigational drug in the parent trial, and the patient must undergo RPC1063 dose escalation. For patients from RPC01-1001, the RPC01-3001 informed consent process may begin on the last day of dosing in RPC01-1001. For the same patients, Baseline (Day 1) brain MRI, OCT, and pulmonary function tests are not required to occur on the same day; these may be performed at any time between signing informed consent and first dose of RPC1063 in RPC01-3001. The RPC01-1001 End of Study assessments and the RPC01-3001 Baseline procedures may be performed on the same day.

[b] The Unscheduled Relapse Visit will be conducted if a possible relapse is suspected at any time prior to the 90-Day Safety Follow-up Visit. The visit is to be planned as soon as possible, ideally within 7 days of symptom onset. If the relapse is confirmed, the Unscheduled Relapse Visit and Early Term procedures may occur at the same visit. If the relapse is not confirmed, patients should return to their usual visit schedule.

[c] Central laboratory testing of ALC will continue every 14 days (± 3 days) after discontinuation of RPC1063 or the End of Treatment/Early Termination Visit until ALC is above the lower limit of normal for patients who discontinue treatment. If an ALC Follow-up Visit is needed within the window of the 90-Day Safety Follow-up Visit, the patient should only return for the 90-Day Safety Follow-up Visit and ALC should be collected at that visit. If a patient has started a lymphocyte-depleting treatment during the safety follow up period, ALC should only be determined at the 90-Day Safety Follow-up Visit. The Medical Monitor should be consulted if the ALC is not > LLN by the Day 90 Safety Follow-up Visit for subjects without lymphocyte depleting DMTs and ALC visits should continue every 14 days (± 3 days) until the Investigator is notified to discontinue.

[d] Baseline (Day 1), 28-Day Safety Follow-up Visit, End of Treatment/Early Termination clinical laboratory tests include chemistry (full panel), hematology, and urinalysis. Every 3/6 months clinical laboratory tests include: Chemistry (abbreviated panel) and hematology. Every 12 months (annually) clinical laboratory tests include: Chemistry (full panel) and hematology.

[e] Urine beta-human chorionic gonadotropin (hCG) test at each visit for women of childbearing potential only. Between scheduled visits up until the 90-Day Safety Follow-up Visit, monthly home urine pregnancy tests should be performed by the patient. If a urine pregnancy test result is positive, the Investigator will instruct the patient to suspend further RPC1063 dosing, if applicable, and schedule a follow-up appointment as soon as possible. A serum pregnancy test will be performed for confirmation, including after the 90-Day Safety Follow-up Visit, if needed.

[f] Vital signs will be collected at pre-dose and every hour (± 10 min) for 6 hours post-dose unless the patient is entering the trial from Trial RPC01-201 Part A or Trial RPC01-1001 and does not require dose escalation. For these patients, the End of Treatment vital signs from Trial RPC01-201 Part A or End of Study vital signs from Trial RPC01-1001 will be used as the baseline vital signs for the current trial.

[g] ECG will be performed at pre-dose and 6 hours post-dose unless the patient is entering the trial from Trial RPC01-201 Part A or Trial RPC01-1001 and does not require dose escalation. Baseline or pre-dose ECG should be provided by the site and be available for comparison to the post-dose ECG in order to determine if discharge criteria are met.

[h] The investigational drug regimen will begin with a 7-day dose escalation regimen: RPC1063 0.25 mg on Days 1 to 4, 0.5 mg on Days 5 to 7, and 1 mg from Day 8 onward. Patients from either the blinded extension of the RPC01-201 Part A trial or the RPC01-1001 trial will not require initial dose escalation unless the duration between the last dose of RPC1063 in the parent trial and the first dose in RPC01-3001 is more than 14 days.

[i] The brain MRI must be performed at Baseline (Day 1) if the last MRI in the parent trial was performed ≥ 6 months prior to entry into the current trial. For patients who enter RPC01-3001 from parent trial RPC01-1001, the Baseline (Day 1) brain MRI may occur at any time between signing of informed consent and the first dose of RPC1063 in RPC01-3001.

[j] Pulmonary function tests will include forced expiratory volume at 1 second (FEV_1) and forced vital capacity (FVC) measurements at all the above indicated visits. In addition, diffusing capacity of the lung for carbon monoxide (DLCO) will be assessed where locally available. DLCO will only be assessed at the End of Treatment/Early Termination Visit. If any abnormalities occur, they will be followed until such time as resolution is confirmed or no further improvement is expected by the Investigator (based on a follow-up period of not less than 3 months).

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

[l] Patients from Trial RPC01-201 Part A who do not require dose escalation or cardiac safety monitoring may have the parent trial End of Treatment visit on the same day as the Baseline visit for this trial. If the patient has already taken RPC1063 that day, a duplicate dose should not be taken. The first dose for the current trial may be dispensed at the Baseline visit to allow administration the following day.

[m] The 90-Day Safety Follow-up Visit should be conducted as a clinic visit. However, if the patient is not available for a clinic visit, a telephone call follow-up should be performed (with at least 3 attempts within the visit window) to record the pregnancy test result, concomitant medications, and AEs, including information regarding relationship of AEs to RPC1063.

[n] MRI scans should not be performed until 30 days after the last dose of methylprednisolone treatment for relapse. Previously scheduled MRIs should be rescheduled as necessary if a relapse occurs (see Section 11.1).

[o] Samples will be collected at the End of Treatment/Early Termination Visit and for Day 28 and Day 90 Safety Follow-up Visits.

[p] After a patient reaches their 3rd annual visit, the Every 3 Month Visit will become the Every 6 Month Visit (one visit between annual visits instead of 3). Annual visits (Every 12 months) are unchanged.

[q] In the event that commercial ozanimod or an access program becomes available prior to December 2022, subjects may transition to the commercial product after discussion with the Investigator at his/her discretion. Subjects who transition to commercial ozanimod are not required to attend safety follow-up visits after their end of treatment visit as long as commercial ozanimod is started within 14 days of discontinuation of study drug. Otherwise, all other subjects continuing in the study and subsequently discontinuing prior to the availability of commercial ozanimod in their country/state or by end of the study will be required to follow the schedule of assessments through the safety follow up visits.

[r] Assessment of immune response may also include analyzing stored blood collected during previous visits prior to implementation of amendment 10.

Abbreviations: AEs/SAEs = adverse events/serious AEs; ALC = absolute lymphocyte count; DMTs = disease modifying therapies; EDSS = Expanded Disability Status Scale; ECG = electrocardiogram; MRI = magnetic resonance imaging; LCLA = Low-Contrast Letter Acuity Test; LLN = lower-limit of normal; MSFC = Multiple Sclerosis Functional Composite; MSQOL-54 = Multiple sclerosis quality of life; OCT = optical coherence tomography.

Table 3: Dependence and Withdrawal-related Assessments

Visit Assessment	On Study-Drug Visit [a]	End of Treatment/ Early Termination[b]	Follow-up Visit Day 1 (+1d) [c]	Follow-up Visit Day 4 (±1d) [c]	Follow-up Visit Day 7 (±2d) [c]	Follow-up Visit Day 14 (±3d) [c]	Follow-up Visit Day 21 (±3d) [c]	Follow-up Safety Visit Day 90 (±10d) [c]
Vital signs [d]	X	X	X	X	X	X	X	X
PWC-20	X	X	X	X	X	X	X	X
HADS	X	X	X	X	X	X	X	X
ESS	X	X	X	X	X	X	X	X
C-SSRS [d]	X	X	X	X	X	X	X	X
Concomitant medications [d]	X	X	X	X	X	X	X	X
AEs/SAEs [d]	X	X	X	X	X	X	X	X

[a] The "On Study-Drug Visit" assessments should be performed at the first scheduled visit after Protocol Amendment 8 is approved at the site and the patient has been re-consented. It serves to provide a baseline assessment on study drug, particularly for patients who discontinue study drug before the End of Treatment/Early Termination Visit.

[b] Patients should schedule the End of Treatment/Early Termination Visit within 24 hours of study drug discontinuation, as appropriate.

[c] If an on-site study visit cannot be performed, the PWC-20, C-SSRS, HADS, and ESS should be assessed remotely. Patients should be encouraged to complete all follow-up visits according to the visit schedule. If a patient does not return to the site for a visit, at a minimum, the site must attempt to contact the patient (eg, by phone) for a remote assessment of the PWC-20, C-SSRS, HADS, ESS, concomitant medications, and AE/SAEs.

[d] If these assessments are performed as part of a scheduled visit procedure in Table 2, then they do not have to be repeated on the same day for dependence withdrawal assessments.

Abbreviations: AEs = adverse events; C-SSRS = Columbia-Suicide Severity Rating Scale; d = day; ESS = Epworth sleepiness scale; HADS = hospital anxiety and depression scale; PWC-20 = Physician's withdrawal checklist; SAEs = serious adverse events.

Table 4: Cardiac Monitoring During Dose Escalation

	Day 1		
Procedure[a]	**Pre-dose**	**Hours 1, 2, 3, 4, 5** (± 10 min)	**Hour 6** (± 10 min)
Vital signs[b]	X	X	X
12-lead ECG	X[c]		X
Assess Discharge Criteria[d]			X

[a] These assessments should also be conducted at the indicated times on Days 5 and 8 if issues are identified on the prior dose escalation day. These Day 1 assessments are not required if the patient is entering the trial from Trial RPC01-201 Part A or Trial RPC01-1001 and does not require dose escalation.
[b] Resting heart rate and blood pressure in the sitting position at each time point.
[c] Baseline or pre-dose ECG should be available for comparison to the post-dose ECG in order to determine if discharge criteria are met.
[d] See Section 12.1.11 for monitoring patients for discharge status. Additional observation should be instituted until resolution of the following: heart rate (per hourly vital signs measurement) 6 hours post-dose is < 45 bpm and > 10 bpm below pre-dose; heart rate (per hourly vital signs measurement) 6 hours post-dose is at the lowest value post-dose; ECG 6 hours post-dose shows new onset second degree or higher atrioventricular (AV) block; the ECG 6 hours post-dose shows a prolonged QTcF interval (> 450 msec men, > 470 msec women).

Abbreviations: ECG = electrocardiogram; QTcF = Fridericia's corrected QT interval.

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Patient Eligibility Criteria

To be eligible to participate in this trial, patients must meet all of the following criteria:

1. Completed one of the parent trials
2. Does not have a condition that would require withdrawal from one of the parent trials
3. Has no conditions requiring treatment with a prohibited concomitant medication
4. Is not receiving treatment with any of the following drugs or interventions within the corresponding timeframe:

   - At Baseline (Day 1)
     - CYP2C8 inhibitors (eg, gemfibrozil or clopidogrel) or inducers (eg, rifampicin)

   Two weeks prior to Baseline (Day 1)

     - Monoamine oxidase inhibitors (eg, selegiline, phenelzine)
5. Ability to provide written informed consent and to be compliant with the schedule of protocol assessments
6. Female patients of childbearing potential:

   Must agree to practice a highly effective method of contraception throughout the study until completion of the 90-Day Safety Follow-up Visit. Highly effective methods of contraception are those that alone or in combination result in a failure rate of a Pearl index of less than 1% per year when used consistently and correctly.

   Acceptable methods of birth control in this study are the following:

   - combined hormonal (oestrogen and progestogen containing) contraception, which may be oral, intravaginal, or transdermal
   - progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injectable, or implantable
   - placement of an intrauterine device (IUD)
   - placement of an intrauterine hormone-releasing system (IUS)
   - bilateral tubal occlusion
   - vasectomised partner
   - sexual abstinence.

   All patients:

   Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are

not acceptable methods of contraception. Female condom and male condom should not be used together.

8.2. Patient Withdrawal Criteria

Reasons for patient withdrawal from the trial include, but are not limited to the following:

- Investigator decision: The Investigator may withdraw the patient from the trial if it is determined that it is not safe or is not in the patient's best interest to receive further treatment with RPC1063. The Medical Monitor should be promptly notified of the decision.
- Noncompliance with investigational drug: After consultation between the Investigator, the Medical Monitor, and the Sponsor when appropriate, a patient may be withdrawn from the trial for failure to comply with dosing regimen as specified by the protocol.
- Intercurrent illness: A patient may be withdrawn from the trial if, in the judgment of the treating Investigator, the patient develops an intercurrent illness or complication that is not consistent with the protocol requirements or that, in any way, justifies withdrawal.
- Adverse event: A patient must be withdrawn from the trial if, in the judgment of the Investigator or if specified in the protocol, the patient develops an AE such as an intercurrent illness or complication that justifies withdrawal.
- Lack of efficacy: Decision by the patient and/or the Investigator to withdraw the patient from the trial due to a lack of expected or desired effect related to a therapy.
- Withdrawal of Consent: The patient may choose to withdraw from the trial at any time. Every effort should be made within the bounds of safety and patient choice to have each patient complete the Early Termination Visit and the 28-Day and 90-Day Safety Follow-up Visits. If a patient withdraws consent, the only additional investigational data to be collected will be the follow up of SAEs as mandated by the protocol.
- Pregnancy: If the patient becomes pregnant, the patient must be withdrawn from the trial (see also Section 12.4.5)
- Trial termination by Sponsor
- Other

All patients who withdraw from the trial should complete an Early Termination Visit. Patients should be instructed to contact the Investigator (e.g. by phone) if they plan to withdraw from the study to discuss study drug discontinuation plans, and schedule the dependence and withdrawal assessment visits. Central laboratory testing of ALC will continue every 14 days (± 3 days) after discontinuation of RPC1063 or the End of Treatment/Early Termination Visit until ALC is above the lower limit of normal or until the Investigator is notified to discontinue (Section 12.2.1). Patients should be encouraged to complete the ALC and Safety Follow-up Visits for the

collection of safety data, including lymphocyte recovery, PK sampling, and to assess their disease status. Treatment for MS can be started after the 28-Day Safety Follow-up Visit based on Section 9.5.

The reason for withdrawal from the trial will be recorded in the clinical records and the patient's electronic case report form (eCRF). For those patients whose status is unclear because they fail to appear for trial visits without stating an intention to withdraw from trial participation, the Investigator should document in the source documents the steps taken to contact the patient (eg, dates of telephone calls, registered letters) prior to withdrawing the patient from the trial.

9. TREATMENT

9.1. Treatments Administered

The Investigator must ensure that RPC1063 will be used only in accordance with the protocol.

Initial investigational drug treatment will consist of a 7-day dose escalation regimen, as applicable, of RPC1063 0.25 mg (equivalent to ozanimod 0.23 mg) on Days 1 to 4, RPC1063 0.5 mg (equivalent to ozanimod 0.46 mg) on Days 5 to 7, and RPC1063 1 mg (equivalent to ozanimod 0.92 mg) from Day 8 onward. Patients from either the blinded extension of the RPC01-201 Part A trial or the RPC01-1001 trial will not require initial dose escalation unless the duration between the last dose of RPC1063 in the parent trial and the first dose in RPC01-3001 is more than 14 days. Patients will receive RPC1063 at 1 mg/day until the end of the trial or until the Sponsor discontinues the development program.

In the event that commercial ozanimod or an access program becomes available prior to December 2022, subjects may transition to the commercial product after discussion with the Investigator at his/her discretion. Subjects who transition to commercial ozanimod are not required to attend safety follow-up visits after their end of treatment visit as long as commercial ozanimod is started within 14 days of discontinuation of study drug. Otherwise, all other subjects continuing in the study and subsequently discontinuing prior to the availability of commercial ozanimod in their country/state or by end of the study will be required to follow the schedule of assessments through the safety follow up visits.

9.2. Selection of Dose in the Trial

The dose of 1 mg RPC1063 is the higher of the two doses (0.5 and 1 mg) that demonstrated clinically meaningful and statistically significant efficacy in the Phase 2 and Phase 3 RMS trials. To date, the 2 doses have a comparable safety profile.

By assigning all patients to the 1 mg dose, this trial will collect safety data that would support marketing applications for both doses.

9.3. Selection and Timing of Dose for Each Patient

Patients will self-administer RPC1063 by mouth once per day. Patients should be instructed to take RPC1063 at approximately the same time each day with or without food.

9.3.1. Instructions for Missed Dose(s) of RPC1063 Capsules

Patients should be instructed that if they forget to take a dose, they can take the dose within 4 hours of the normal dosing time; otherwise they should take their next dose at the regular time on the following day. If the patient vomits the capsule, he/she should be instructed not to take another capsule on the same day, but to take the next dose at the regular time on the following day. Patients will record missed doses in a diary that will be reviewed at every visit by site staff and the site monitor.

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

If the patient misses more than 7 consecutive doses for any reason, Day 1 cardiac monitoring procedures will be performed on the first day that the patient resumes dosing. If the patient misses more than 14 consecutive doses for any reason, the Medical Monitor must be contacted to discuss procedures for resuming therapy, which will include an additional dose escalation schedule.

9.4. Treatment of Relapses

Patients who experience a relapse may receive treatment with intravenous (IV) corticosteroids, if judged to be clinically appropriate by the Investigator. The following standard treatment regimen should be used: as warranted, up to 1.0 g IV methylprednisolone per day for a maximum of 5 consecutive days. Any other medications or deviation from the allowed IV methylprednisolone treatment should be discussed with the Medical Monitor.

A patient who experiences a relapse after completing a parent trial, but prior to entering RPC01-3001, may receive the IV methylprednisolone treatment regimen.

9.5. Concomitant Medications

All treatments, other than RPC1063, being taken by the patients on entry to the trial or at any time during the trial, including through the 90-Day Safety Follow-up Visit, are regarded as concomitant treatments and must be documented on the appropriate section of the eCRF.

Treatment for symptoms related to MS (eg, spasticity, incontinence, pain, fatigue, and depression) is not restricted, but Investigators should attempt to keep therapies or treatments reasonably constant throughout the trial. Changes may be made if appropriate for a patient's well-being in the clinical judgment of the treating Investigator.

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

9.5.1. Concomitant Medications Prohibited Through the 28-Day Safety Follow-up Visit

The following medications cannot be used during the trial through the 28-Day Safety Follow-up Visit:

- Any approved and unapproved disease-modifying MS agents
- Treatment with Class Ia or Class III anti-arrhythmics (examples of prohibited systemic cardiac medications are provided in Table 5) or treatment with a combination of 2 or more agents known to prolong PR interval (eg, combination of a beta blocker and verapamil) are prohibited during the study unless approved by the Sponsor's representative. (Note that Table 5 does not provide a comprehensive list. The Medical Monitor should be contacted for further guidance if needed).

- Systemic corticosteroid therapy or ACTH, except for treatment of protocol-defined treatment of relapses. Corticosteroids that are by non-systemic routes (eg, topical, inhaled, intra-articular) are allowed.
- Live or live attenuated vaccines
- Intravenous immunoglobulin (IVIg) or plasmapheresis
- Immunosuppressive agents that deplete lymphocytes
- Breast cancer resistance protein (BCRP) inhibitors (eg, cyclosporine, eltrombopag)
- Monoamine oxidase inhibitors (eg, selegiline, phenelzine)
- CYP2C8 inhibitors (eg, gemfibrozil and clopidogrel) or inducers (eg, rifampicin)

For patients who are currently enrolled and are receiving BCRP inhibitors, monoamine oxidase inhibitors or CYP2C8 inhibitors or inducers, an individual safety assessment will be conducted and, if indicated, either the concomitant medication will be discontinued and the patient will continue in the study or investigational drug will be discontinued and the patient will be withdrawn from the study.

Table 5: Examples of Prohibited Cardiac Medications (Systemic Use)

Pharmaceutical Class	Example Medications
Class Ia or Class III Anti-arrhythmic drugs	amiodarone, bepridil hydrochloride, disopyramide, dofetilide, dronedarone, flecainide, sotalol, ibutilide, lidocaine, procainamide, propafenone, quinidine, tocainide

9.5.2. Concomitant Medications Between the 28-Day Safety Follow-up Visit and the 90-Day Safety Follow-up Visit

Interferon-β and glatiramer acetate may be started after the 28-Day Safety Follow-up Visit at the Investigator's discretion.

Certain disease-modifying MS agents, lymphocyte-trafficking inhibitors (eg, fingolimod, natalizumab) or immunosuppressive agents that deplete lymphocytes (eg, ocrelizumab, cladribine, alemtuzumab) may be used in consultation with the Medical Monitor between the 28-Day Safety Follow-up Visit and the 90-Day Safety Follow-up Visit.

The following medications should not be used without consultation with the Medical Monitor between the 28-Day Safety Follow-up Visit and the 90-Day Safety Follow-up Visit:

- Treatment with Class Ia or Class III anti-arrhythmics (examples of prohibited systemic cardiac medications are provided in Table 5) or treatment with a combination of 2 or more agents known to prolong PR interval (eg, combination of a beta blocker and verapamil) are prohibited during the study unless approved by the Sponsor's representative. (Note that Table 5 does not provide a comprehensive list. The Medical Monitor should be contacted for further guidance if needed).

- Live or live attenuated vaccines
- Monoamine oxidase inhibitors (eg, selegiline, phenelzine)
- CYP2C8 inhibitors (eg, gemfibrozil and clopidogrel) or inducers (eg, rifampicin)

9.6. Treatment Compliance

It is the Investigator's responsibility to ensure that patients are correctly instructed on how to take their investigational drug and that each patient is fully compliant with their assigned dosage regimen. Records of investigational drug used and intervals between visits will be kept during the trial. Drug accountability will be noted by the site monitor during site visits and at the completion of the trial. Patients will be asked to return all unused investigational drug at each visit. The investigational drug should be dispensed by the Investigator, or by a qualified individual under the Investigator's supervision. An up-to-date treatment inventory/dispensing record must be maintained as described in Section 10.3.

Overall trial non-compliance is defined as taking less than 80% or more than 120% of investigational drug during the entire treatment period. Patients will record missed doses in a diary that will be reviewed at every visit by site staff and the site monitor. Patients exhibiting poor compliance as assessed by investigational drug counts (2 or more missed investigational drug days in 1 week) should be counseled on the importance of good compliance to the trial dosing regimen. Patients who are persistently non-compliant (< 80% or > 120%) should be discussed with the Medical Monitor to determine whether they should be withdrawn from the trial.

9.7. Randomization and Blinding

This is an open-label trial; there is no randomization or blinding.

10. INVESTIGATIONAL DRUG MATERIALS AND MANAGEMENT

10.1. Investigational Drug

RPC1063 will be provided as powder-filled capsules. RPC1063 drug substance is [redacted]. Two RPC1063 dosage strengths have been prepared for the clinical investigations; 0.25 mg (size 4 capsule) and 1 mg (size 4 capsule).

RPC1063 capsules will be manufactured, quality control tested and released in accordance with good manufacturing practices.

All investigational drug must be stored in a secure location.

10.2. Packaging and Labeling

RPC1063 capsules will be packaged in 30 cc white high-density polyethylene bottles (35 capsules per treatment bottle; 12 capsules per dose escalation bottle), closed with a 28 mm child resistant screw-cap that is induction sealed.

The labeling of investigational drug will be in accordance with GMP and Good Clinical Practice (GCP) and any other local regulatory requirements.

10.3. Investigational Drug Accountability

Investigational drug should not be used for purposes other than as defined in this protocol.

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

The Investigator will provide the investigational drug only to the identified patients of this trial, according to the procedures described in this trial protocol. After the end of the trial, the Site Monitor will perform final accountability, package, seal, and prepare for shipment. Investigational drug and all investigational drug containers will be returned to the clinical supply distribution vendor and documentation will be returned to the Sponsor and/or designee. The Sponsor and/or designee will verify that a final report of drug accountability is prepared and maintained in the Investigator's Trial Master File.

11. EFFICACY ASSESSMENTS

11.1. Magnetic Resonance Imaging (MRI)

Brain MRIs will be acquired with and without gadolinium (Gd). The same MRI protocol will be used across all sites. To ensure quality data and standardization, the same machine and software should be used throughout the trial. MRIs for MS lesions will be read at a centralized reading facility.

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

The baseline MRI scans for patients from the Phase 3 parent trials (RPC01-201 and RPC01-301) will be read locally only for non-MS pathology to avoid potential unblinding of treatment assignments in the parent trials. Post-baseline MRI scans for these patients and all MRIs for patients from the RPC01-1001 parent trial will be read locally for non-MS pathology, and due to the open-label design of this trial, may be used by the Investigators to monitor MS disease activity.

MRI scans should not be performed until 30 days after the last dose of methylprednisolone treatment for relapse. Previously scheduled MRIs should be rescheduled as necessary if a relapse occurs.

11.2. Expanded Disability Status Scale and Neurological Examination

The EDSS is a standardized method, widely accepted, numerical scale used to evaluate disability in people with MS (Kurtzke 1983). The EDSS is evaluated according to signs and symptoms observed during a standard neurological examination. These clinical observations are classified in 7 FS scales, each of them grading signs and symptoms for different neurological functions: pyramidal, cerebellar, brainstem, sensory, bowel or bladder, visual, and cerebral.

The trial requires that the same evaluator performs all EDSS assessments for an individual patient when possible. In addition, EDSS raters will be a neurologist or other health care practitioner who was certified using the Neurostatus Standardized Examination and Assessment prior to trial initiation and examiners will be re-certified every 2 years throughout the conduct of the trial.

11.3. Relapse Assessment

A relapse is defined as the occurrence of new or worsening neurological symptoms attributable to MS and immediately preceded by a relatively stable or improving neurological state of at least 30 days. The new or worsening neurological symptoms must be accompanied by objective neurological worsening consistent with an increase of at least half a point on the EDSS, or 2 points on one of the appropriate FS scores, or 1 point on two or more of the appropriate FS scores compared to last rating (EDSS or FS scores) that did not occur during a relapse. The change must be documented by the evaluator at either scheduled or unscheduled visits and must affect the FS scales that correspond to the patient's symptoms (eg, pyramidal, cerebellar, brainstem, sensory, bowel or bladder, visual, or cerebral). Symptoms must persist for > 24 hours

and should not be attributable to confounding clinical factors (eg, fever, infection, injury, adverse reactions to concomitant medications). When a patient experiences new or worsening symptoms at any time prior to the 90-Day Safety Follow-up Visit that may indicate a possible relapse, he/she should telephone the treating Investigator within 48 hours of symptoms onset. The treating Investigator (or designee) will conduct a telephone questionnaire and, as necessary, will arrange an Unscheduled Relapse Visit. The visit is to be planned as soon as possible, ideally within 7 days of symptom onset.

11.4. Multiple Sclerosis Disability Progression

MS disability progression is defined as a sustained worsening in EDSS of 1.0 points or more from baseline, confirmed after a 3-month and 6-month period. Confirmation of MS disability progression must not occur at the time of a relapse. If the patient is scheduled to be evaluated to confirm their disability at the time of a relapse, the disability event must be assessed at a later visit, which may be the next scheduled visit, or an unscheduled visit conducted after the relapse has resolved. In case of MS disability progression the treating Investigator will discuss with the patient the treatment alternatives outside of the study.

11.5. Multiple Sclerosis Functional Composite

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

- The Timed 25-Foot Walk is a quantitative measure of lower extremity function
- The 9-Hole Peg Test is a quantitative measure of upper extremity (arm and hand) function
- The Symbol Digit Modalities Test (SDMT) is a measure of executive function cognition that assesses processing speed, flexibility, and calculation ability (Drake 2010).

The same person, either the evaluator or another independent designated team member trained in conducting MSFC assessments should administer the 3 scales that make up the MSFC with each participating patient throughout the trial. 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, ie, MSFC z-score = (Z25-foot-walk + Z9HPT + ZSDMT)/3, where Zxxx refers to Z-scores.

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

11.6. Low-Contrast Letter Acuity Test

The LCLA which is performed with the MSFC assessments, is performed with a standardized set of charts (Sloan letter charts or Tumbling E charts) to assess low contrast visual acuity. Each chart corresponds to a different contrast level, and charts are scored according to the number of letters that are identified correctly. The LCLA captures aspects of neurological dysfunction that

is not assessed by the EDSS or MSFC, and has been proposed as an additional component to the MSFC (Balcer 2003).

11.7. Multiple Sclerosis Quality of Life-54

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

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

12. SAFETY ASSESSMENTS

12.1. Clinical Safety Assessments

12.1.1. Physical Examination

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

Initial neurological examination will be a part of the physical examination at baseline and if warranted, will be performed at an unscheduled visit. All significant findings that are present at baseline must be reported on the relevant current medical conditions eCRF. Significant findings made after enrollment that meet the definition of an AE must be recorded on the AE eCRF.

12.1.2. Vital Signs

Blood pressure, heart rate, and body temperature will be assessed. Systolic and diastolic blood pressure and heart rate will be assessed in a sitting position using an automated validated device, if available. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

Patients who require RPC1063 dose escalation will be carefully monitored after the first dose of investigational drug with a 6-hour post-dose monitoring period of hourly recording of heart rate and blood pressure as described in Section 12.1.11.

Guidelines regarding monitoring of patients with an AE of bradycardia are also described in Section 12.1.11.

12.1.3. Electrocardiogram

A 12-lead ECG is to be performed after the patient has been resting quietly for at least 5 minutes.

The 12-lead digital ECG devices will be provided to each clinical site by the central ECG laboratory for the duration of the trial. Detailed instructions describing the process for recording and transmission of the digital ECGs will be outlined in the trial-specific manual and provided to the site before the start of the trial. A 12-lead ECG will be performed before and 6 hours after the first dose of investigational drug administration, while the patient is at the clinic. The 6-hour post-dose ECG will be evaluated by the treating physician, with input from a local cardiologist or a central reader, if needed, to confirm if extended monitoring is required. Baseline or pre-dose ECG should be available for comparison to the post-dose ECG in order to determine if discharge criteria are met. Additional ECG monitoring will be performed on Days 5 and 8 if cardiac issues are identified on the prior day of dose escalation, as described in Section 12.1.11.

Only clinically significant ECG abnormalities should be reported in the AE eCRF. Clinically significant findings on the baseline ECG must be discussed with the Medical Monitor before enrolling the patient in the trial.

12.1.4. Pulmonary Function Tests

Pulmonary function tests (PFTs) including FEV_1 and FVC measurements will be performed as scheduled in Table 2. In addition, DLCO will be assessed (where locally available). DLCO will only be assessed at the End of Treatment/Early Termination Visit. DLCO will not be required at sites where there is no local testing facility.

These tests will be performed at a high quality pulmonary function laboratory or respiratory department. Please refer to the American Thoracic Society/European Respiratory Society guidelines for standardization of spirometry and single breath determination of carbon monoxide uptake in the lung (MacIntyre 2005; Miller 2005a; Miller 2005b).

For patients with abnormal PFTs (based on predicted FVC or $FEV_1 < 70\%$), PFTs will be repeated within < 30 days. Upon confirmation of abnormal PFTs, patients will be followed until resolution or no further improvement is expected by the Investigator (based on a follow-up period of not less than 3 months). If the PFT decrease persists, consult with the Medical Monitor. If patients have a confirmed decline in PFT values (FEV_1 and/or FVC) < 50% of the predicted values, investigational drug should be discontinued and the Investigator should consult the Medical Monitor.

If a patient is temporarily or permanently discontinued from investigational drug due to a respiratory AE, the Investigator should ensure that the patient has adequate evaluations as clinically indicated.

12.1.5. Ophthalmological Examination

OCT will be performed as scheduled in Table 2.

Suspicion of Macular Edema. If abnormal OCT findings, or visual signs or symptoms of macular edema are observed, a general ophthalmologic examination including eye history, visual acuity, and dilated ophthalmoscopy will also be performed. If the ophthalmic evaluation reveals abnormalities suggestive of macular edema, investigational drug will be temporarily discontinued. Patients will be followed with repeat ophthalmology examinations until evaluations return to baseline or no further improvement is expected (based on a follow-up period of not less than 3 months).

Confirmed Macular Edema. Investigational drug must be permanently discontinued in any patient with a confirmed diagnosis of macular edema that is of new onset or worsened since baseline. Patients with a confirmed diagnosis of macular edema must be evaluated by an ophthalmologist on a monthly basis or more frequently if needed based on the ophthalmologist's judgment. Further ophthalmological evaluations will be conducted until resolution or no further improvement is expected by the ophthalmologist (based on a follow-up period of not less than 3 months). If the patient does not show definite signs of improvement on examination 6 to 8 weeks after discontinuation of investigational drug, then therapy for macular edema should be initiated in conjunction with an ophthalmologist experienced in the management of this condition.

12.1.6. Dermatological Examination

Dermatological (skin) evaluations will be performed by the treating Investigator or designee as part of the physical examination at baseline, and as scheduled in Table 2. Patients with any abnormal finding noted during the examination will be referred to an appropriately qualified dermatologist for evaluation and treatment, if warranted.

12.1.7. Suicidality Assessment

Suicidality will be assessed using the C-SSRS (Posner 2011) as indicated in Table 2. The C-SSRS is a rater-administered questionnaire. A patient indicating suicidal ideation on the C-SSRS will be assessed by the Investigator and referred for further assessment by other health care professionals as indicated. It is important that the C-SSRS be completed early in the visit to ensure the report and any associated alerts are reviewed during the visit, while the patient is at the site.

12.1.8. Dependence and Withdrawal Battery

The Dependence and Withdrawal Battery include the C-SSRS and additional assessments:

12.1.8.1. Physician's Withdrawal Checklist (PWC-20)

The PWC-20 is a rater-administered 20-item scale to assess signs and symptoms of withdrawal. Twenty items are rated on a 4-point scale as not present (0 points), mild (1 point), moderate (2 points), or severe (3 points). The points from all items are calculated as a total score. Higher scores indicate more severe withdrawal symptoms (Rickels 2008).

12.1.8.2. Hospital Anxiety and Depression Scale (HADS)

The HADS is a validated patient reported outcome for assessing anxiety and depression (Zigmond 1983; Bjelland 2002). It consists of 14 items in total, 7 items related to anxiety and 7 items related to depression. For each item patients select a statement (valued at 0 to 3 points) that closest matches their own feeling over the past week. Separate total scores for anxiety and depression are derived by adding up points. Total scores can range from 0 to 21 points. Higher scores indicate more severe anxiety and depression and scores of 8 to 10 are generally considered indicative of borderline anxiety/depression disorders and scores of 11 and higher are generally considered indicative of anxiety/depression disorders.

12.1.8.3. Epworth Sleepiness Scale (ESS)

The ESS is a validated self-administered questionnaire with 8 questions (Johns 1997). Respondents rate on a 4-point scale (0 to 3) their chances of dozing off or falling asleep while engaged in 8 different activities. The ESS score is the sum of 8 item scores and can range from 0 to 24 points. Higher scores indicate more daytime sleepiness.

12.1.9. Monitoring of Adverse Events and Serious Adverse Events

Throughout the course of the trial, every effort must be made to remain alert to possible AEs or SAEs. Refer to Section 12.3 for definitions of AEs/SAEs, monitoring, and reporting. Refer to

Section 12.4.2 for AESIs and Section 12.4.3 for monitoring of patients with AEs, SAEs, and AESIs.

Reductions in ALC levels for patients in this study is an expected primary pharmacodynamic effect. Reductions in ALC, in general, need not be reported as AEs unless there are clinical consequences. The protocol requirements in Section 12.2.1 should be followed for confirmed ALC < 200 cells/μL. The decision to report decreased ALC as an AE is at the Investigator's discretion.

12.1.10. Monitoring of Concomitant Therapy

The use of concomitant medication and procedures will be monitored throughout the trial. Refer to Section 9.5 for prohibited concomitant therapies.

12.1.11. Guidelines for Monitoring Patients Taking Their Day 1 Dose of RPC1063

On Day 1 of treatment, careful cardiac monitoring is required for patients undergoing RPC1063 dose escalation. The Investigator is responsible for monitoring the patient following the first intake of the investigational drug. The Investigator must review the pre-dose and post-dose ECG, and heart rate and blood pressure during the 6-hour monitoring period, and assess discharge status at 6 hours after dosing.

Resting heart rate and blood pressure in the sitting position will be measured before the first dose of investigational drug, then every hour (± 10 min) for at least 6 hours thereafter (by the Investigator, an assisting nurse, or other medically qualified staff member). When obtaining the heart rate and blood pressure before the first dose, the patient should be allowed to rest in a seated position at least 5 minutes before taking measurements. The heart rate and sitting blood pressure measurements should be repeated 2 additional times (only before the first dose of investigational drug) and all of these measurements should be recorded in the eCRF. The repeat measurements will be made at approximately 2-minute intervals. For the hourly measurements after investigational drug administration, heart rate and sitting blood pressure will be measured once and recorded in the eCRF. The lowest pre-dose value of sitting heart rate and blood pressure (based on systolic blood pressure) will be recorded in the case report form and serve as baseline for comparison to post-dose values.

Patients should receive the first dose of investigational drug before 12:00 pm (noon) in the clinic. The first dose of RPC1063 should be administered in a setting in which resources to appropriately manage symptomatic bradycardia are available. A member of the Investigator team should be available to monitor the patient for the 6-hour monitoring period and will need to report any abnormalities to the Investigator. Atropine and isoproterenol or epinephrine need to be readily available to the site personnel. Although atropine and isoproterenol are preferred, epinephrine may be used as a substitute if the preferred medications are not available.

If any of the following criteria are met, additional extended monitoring should be instituted until the finding has resolved. Baseline and hourly vital signs measurements (Hours 1 through 6) should be used to assess heart rate (criteria 1 and 2 below) and ECG should be used to assess for atrioventricular (AV) block and Fridericia's corrected QT (QTcF) interval (criteria 3 and 4 below).

1. The heart rate 6 hours post-dose is < 45 bpm, and > 10 bpm below predose
2. The heart rate 6 hours post-dose is at the lowest value post-dose (suggesting that the maximum PD effect on the heart may not have occurred)
3. The ECG 6 hours post-dose shows new onset second degree or higher AV block
4. The ECG 6 hours post-dose shows a prolonged QTcF interval (> 450 msec men, > 470 msec women).

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

Should a patient require pharmacologic intervention for symptomatic bradycardia, continuous overnight ECG monitoring in a medical facility should be instituted, and the first dose monitoring strategy should be repeated the following day (Day 2). The first dose monitoring strategy should also be repeated at Day 5 or at Day 8 if any cardiac safety issues were observed on the previous day of dose escalation.

Patients should have written instruction on when to return to clinic and a 24-hour contact phone number to call in the event of any new or warranted symptoms (eg, chest pain, dizziness, palpitations, syncope).

12.2. Laboratory Assessments

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

Additional and repeat laboratory safety testing, preferably using the central laboratory, may be performed at the discretion of the Investigator. The following laboratory tests will be performed to assess the safety profile of RPC1063:

- Hematology - Red blood cell count, total and differential white blood cell (WBC) count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.
- Chemistry
  - Full chemistry panel at Baseline, every 12 months (annually), at the 28-Day Safety Follow-up Visit, and at End of Treatment/Early Termination Visit: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, glucose, albumin, alkaline phosphatase, creatinine, serum glutamic pyruvic transaminase (SGPT)/alanine aminotransferase (ALT), serum glutamic oxaloacetic transaminase (SGOT)/aspartate aminotransferase (AST), gamma-glutamyl-transferase (GGT), amylase, total bilirubin, conjugated bilirubin, total cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL).

  - All other visits: blood urea nitrogen, albumin, alkaline phosphatase, creatinine, SGPT/ALT, SGOT/AST, GGT, amylase, total bilirubin, conjugated bilirubin.

- Urinalysis at Baseline, at the 28-Day Safety Follow-up Visit, and at End of Treatment/Early Termination Visit - leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, and urobilinogen.
- Exploratory measurements of immune response (eg, anti-SARS-CoV-2 serology) will be assessed from blood samples collected at trial visits and end of treatment, and the potential association between these measurements and selected endpoints related to safety and/or efficacy.
- Pregnancy test - In women of childbearing potential, urine beta-human chorionic gonadotropin (hCG) test will be performed at Baseline if more than 1 month has elapsed from the last pregnancy test in the parent trial. Urine beta-hCG test will be performed in women of childbearing potential at each scheduled visit. Between scheduled visits, up until the 90-Day Safety Follow-up Visit, monthly home urine pregnancy tests should be performed by the patient. If a urine pregnancy test result is positive, the Investigator will instruct the patient to suspend further RPC1063 dosing, if applicable, and schedule a follow up appointment as soon as possible. A serum pregnancy test will be performed for confirmation, including after the 90-Day Safety Follow-up visit, if needed.

12.2.1. Clinical Laboratory Parameters and Abnormal Laboratory Test Results

Hematology

Starting with the Month 3 visit (ie, excluding the Baseline visit), complete hematology laboratory values will be available to the Investigator. Reductions in ALC levels is a known pharmacodynamic effect of RPC1063. If any of the following results are observed, the Investigator will be notified and asked to repeat the laboratory tests within approximately 7 days:

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

If the ANC is confirmed < 1000 cells/µL, the Investigator will be requested to closely monitor for risk of serious infection and institute appropriate follow-up at his or her discretion.

If ALC is confirmed < 200 cells/µL, the Investigator will temporarily discontinue treatment and then consult the Medical Monitor. Laboratory testing will be repeated weekly until ALC is > 500 cells/µL. When ALC has returned to > 500 cells/µL, treatment may be reinitiated at the Investigator's discretion. (See Section 9.3.1 for instructions on resuming treatment after missing doses.)

For patients who permanently discontinue treatment or complete the trial, central laboratory testing of ALC will continue every 14 days (± 3 days) after discontinuation of RPC1063 or the End of Treatment/Early Termination Visit until ALC is above the lower limit of normal.

If an ALC Follow-up Visit is needed within the window of the 90-Day Safety Follow-up Visit, the patient should only return for the 90-Day Safety Follow-up Visit and ALC should be collected at that visit.

If the patient has started a lymphocyte-depleting treatment during the Safety Follow-up period, ALC should only be determined at the 90-Day Safety Follow-up Visit. The Medical Monitor should be consulted if the ALC is not > LLN by the Day 90 Safety Follow-up Visit for subjects not started on lymphocyte-depleting disease modifying therapies (DMTs), and ALC visits should continue every 14 days (± 3 days) until the Investigator is notified to discontinue.

Liver Function Tests

If patients have elevations in ALT and/or AST > 3x the upper limit of normal (ULN), a retest should be performed as soon as possible but not later than 14 days after the original test. If the abnormality is confirmed, weekly testing should continue until ALT and AST are < 3x ULN. If the ALT and/or AST stabilizes at a level > 3x ULN, the Medical Monitor may agree to less frequent testing. The Investigator should establish causality. In addition, the confirmed elevation > 3x ULN is an AESI (see Section 12.4.2) and should be reported by the Investigator.

At any time, if any of the following occur and there are no apparent alternative causes for the finding, the investigational drug must be permanently discontinued:

- ALT or AST > 8x ULN or
- ALT or AST > 5x ULN with confirmation, within 2 weeks or
- ALT or AST > 3x ULN and (total bilirubin > 2x ULN or INR > 1.5) or
- ALT or AST > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

The Investigator should establish causality.

After discontinuation due to elevation of ALT or AST > 5x ULN or concurrent elevations of ALT or AST > 3x ULN and bilirubin > 2x ULN, further liver function evaluation should be performed (for example, coagulation panel and alkaline phosphatase) in consultation with the Medical Monitor.

12.2.2 Pharmacokinetics

Since the active major metabolites of RPC1063, CC112273 and CC1084037, have long elimination half-lives, a total of 3 PK blood samples per patient will be collected at the End of Treatment/Early Termination Visit and on Day 28 and Day 90 Safety Follow-up Visits to assess if ALC recovery after study drug discontinuation is related to plasma concentrations of these metabolites (see Table 2). The sampling will continue until the Sponsor determines enough data is obtained to achieve PK recovery modeling but may require up to approximately 80 evaluable subjects. If deemed necessary, the data obtained from these subjects may be combined with those from other clinical studies for pharmacometric analysis.

Additional PK samples may be obtained for patients with prolonged ALC recovery or for appropriate safety reasons (ie, AEs resulting in discontinuation, or relevant SAEs) at the request of and in consultation with the Medical Monitor.

12.3. Adverse and Serious Adverse Events

12.3.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal product, whether or not considered related to the investigational medicinal product (ICH E2A, II.A.1).

Relapses (confirmed or unconfirmed) and MS disease progression will be monitored as trial endpoints, but will not be recorded as AEs.

AEs will be monitored for each patient from their first dose following enrollment and throughout the duration of their participation in the trial, including the 90-Day Safety Follow-up Visit. Investigators will ask the patient at each visit if they have experienced any untoward occurrence since the last trial visit. All AEs will be recorded on the eCRFs provided: a description of the event, severity, time of occurrence, duration, any action (eg, treatment and follow up tests) and the outcome should be provided along with the Investigator's assessment of the relationship to the investigational drug.

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

An Adverse Drug Reaction (ADR) is defined as all noxious and unintended responses to a medicinal product related to any dose (ICH E2A, II.A.2).

An Unexpected ADR is defined as an adverse reaction, the nature of which is not consistent with the applicable product information (ICH E2A, II.A.3).

Each AE is to be evaluated for duration, severity, seriousness and causal relationship to the investigational drug. The action taken and the outcome must also be recorded.

12.3.2 Definition of Serious Adverse Events

An SAE (experience) or reaction is any untoward medical occurrence that at any dose (ICH E2A, II.B):

- Results in death
- Is life-threatening

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity, or
- Is a congenital abnormality/birth defect

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. *These should also usually be considered serious.*

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

In case of a fatality, the cause of death is considered as the SAE, and the death is considered as its OUTCOME.

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

12.3.3 Assessment of Adverse Event Severity

The severity of the AE will be characterized as "mild, moderate, or severe" according to the following definitions:

- Mild events are usually transient and do not interfere with the patient's daily activities.
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities.
- Severe events are incapacitating and interrupt the patient's usual daily activity.

12.3.4 Assessment of Adverse Event Relationship to Investigational Drug

The causal relationship between RPC1063 and the AE has to be characterized as unrelated, unlikely, possible, probable, or related. This medical assessment should be made as soon as feasible when reporting an SAE.

The Investigator is requested to assess the relationship of any AEs to treatment using the following definitions:

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

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

- It does not follow a reasonable temporal sequence from administration of the drug
- It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient

- It does not follow a known pattern to the suspected drug
- It does not reappear or worsen when the drug is re-administered

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

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

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

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

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

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

All efforts should be made to classify the AE according to the above categories.

After initiation of investigational drug, all AEs, regardless of relationship to investigational drug, will be recorded until the patient completes his or her last trial visit.

12.4 Reporting of Serious Adverse Events

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

The Investigator will report any SAE that occurs to any patient from the time written informed consent is signed through the last visit. If an SAE occurs after informed consent and is resolved

before the first dose of investigational drug in RPC01-3001, the event will be captured in the parent trial only. If the SAE is ongoing at the time of the first dose in RPC01-3001, it will be transcribed into the eCRF for RPC01-3001. All SAEs that occur within 90 days of the last dose of treatment with the investigational drug, whether or not considered related to the investigational product, must also be reported. Any SAE that is ongoing when the patient completes the trial or withdraws from the trial will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status. The following are not generally considered valid SAEs: hospitalizations or procedures planned prior to signing the informed consent form (ICF), hospitalizations that are <24 hours, admission for elective procedures that are not a result of a worsening condition, or admissions for procedures required by protocol.

An electronic form must be completed in the eCRF or a written SAE report must be sent within 24 hours from the time the trial site personnel first learned of the event. For Safety contact information, please refer to the Celgene General Guidelines for SAE Recording and Reporting.

12.4.1 Reporting of Serious Adverse Events to Regulatory Authorities and Investigators

Investigators will be notified by the Sponsor and/or its designee of all SAEs that require prompt submission to their IRB or IEC. Investigators should provide written documentation of IRB/IEC notification for each report to the Sponsor and/or its designee. The Sponsor and/or its designee will ensure that all SAEs are reported to the appropriate regulatory authorities as required. Reporting of SAEs must comply with ICH E6, 4.11.1.

12.4.2 Adverse Events of Special Interest

Investigators should identify AEs that meet the following criteria for AESIs. AESIs fall into a number of categories based on the safety observations from the fingolimod trials and the potential pharmacologic effects of S1P modulators. These include:

- Cardiac:
  - Asymptomatic bradycardia with heart rate < 35 bpm
  - Symptomatic bradycardia with heart rate < 45 bpm, and > 10 bpm below pre-dose
  - 2nd degree AV block type II or higher
- Pulmonary:
  - Decreases in FEV_1 measurements to < 50% predicted
  - FVC measurements to < 50% predicted
- Ophthalmologic:
  - New onset or clinically significant worsening of existing macular edema by OCT
- Malignancy
- Hepatic:
  - Confirmed elevations in liver transaminases > 3x ULN

- Infections:
  - Serious and opportunistic infections

12.4.3 COVID-19 Pandemic

The global coronavirus disease 2019 (COVID-19) pandemic has been identified as a potential risk to clinical trial subjects in general and may particularly affect individuals with underlying chronic diseases on immunomodulatory therapies. It is not known whether taking ozanimod increases the risk of SARS-CoV-2 infection, or the duration or severity of COVID-19.

Evaluation and management of SARS-CoV-2 infections arising during the course of the trial are left to the discretion and expertise of the investigator. For subjects who exhibit symptoms consistent with SARS-CoV-2, testing for SARS-CoV-2 to inform decisions and clinical care during the study should follow local standard practice. The sponsor also suggests the investigator to refer to the Multiple Sclerosis International Federation (MSIF) guidelines per DMC recommendation, and to consult the Medical Monitor as needed.

Each study visit will include an assessment for AEs including SARS-CoV-2 and other infections. In order to facilitate reporting of SARS-CoV-2 events that occur during the study, all AEs and SAEs related to SARS CoV-2 should be reported from the time of consent until the final study Visit.

Procedures related to COVID-19 identification (eg, MERS-CoV test, SARS-CoV-2 antibody test, SARS-CoV-2 ELISA test), and treatment (eg, intubation, dialysis) must be reported in the appropriate eCRF.

Non-live COVID-19 vaccination is considered a simple concomitant medication within the study. However, the safety and efficacy of non-live vaccines (including non-live COVID-19 vaccines) in patients receiving ozanimod is unknown. Ozanimod treatment may cause vaccines to be less effective. If the assessment of the Investigator suggests the vaccine to be beneficial, it must be a non-live, replication incompetent vaccine, and be approved or authorized (ie, Emergency Use Authorization [FDA] or equivalent) by national health authorities.

Administration of vaccinations must be reported along with dosage information, dates of administration and vaccine name/trade name in the appropriate eCRF. A separate logline should be entered for each vaccine administered with the dose number following the vaccine name/trade name.

12.4.4 Monitoring of Patients with Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

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

resolve due to the patient's underlying disease, or the patient is lost to follow-up. Safety reporting must comply with ICH E6, 4.11.

12.4.5 Treatment of Overdose of Trial Investigational Drug

An overdose is any dose of investigational drug given to a patient or taken by a patient that exceeds the dose described in the protocol. There is no information regarding overdose with RPC1063. Any overdose, with or without associated AEs, must be promptly reported to the Sponsor and/or its designee. Overdoses do not need to be recorded as AEs in the eCRF; only in the case of any AEs associated with the overdose should these be reported on relevant AE/SAE sections in the eCRF. Overdose without an associated AE will be promptly reported to PPD.

12.4.6 Procedures in Case of Pregnancy

If a urine pregnancy test is positive, the Investigator will instruct the patient to suspend further RPC1063 dosing. If the test was performed by the patient between scheduled visits, a follow-up appointment will be scheduled as soon as possible. A serum pregnancy test will be performed for confirmation.

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

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

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to the Sponsor and/or its designee. In cases of live birth, the infant will be followed for up to a year.

12.5 Data Monitoring Committee

An independent data monitoring committee (DMC) originally convened for the blinded, Phase 3 parent trials will be charged with monitoring safety data from RPC01-3001 and general aspects of trial conduct. The DMC may recommend modifying or stopping the trial early due to safety concerns based on data reviews.

13 PLANNED STATISTICAL METHODS

13.1 General Considerations

All efficacy and safety data will be listed by patient.

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

All confidence intervals will be calculated at the 95% level and no statistical hypothesis testing will be performed. All analyses will be performed using SAS® software version 9.1 or higher.

13.2 Analysis Populations

All patient populations will be defined and documented prior to database lock. Due to the open-label, non-randomized nature of the trial design, the intent-to-treat (ITT) and safety populations will be the same: all enrolled patients who receive at least 1 dose of RPC1063. These populations will be used for the reporting of all efficacy and safety results.

Dependence and withdrawal-related assessments will be analyzed in those patients who underwent assessments specific to Table 3 at least once while on study drug and at least once at any of the following visits: Follow-up Visits on Days 1,4, 7, 14, 21, or 90.

13.3 Statistical Methods

13.3.1 Disposition, Demographics and Baseline Characteristics

The number and percentage of patients in each population will be summarized. Patient disposition, including the number of patients who enrolled, were dosed, completed the trial, and discontinued the trial with reasons for discontinuation, will be summarized for the safety population. Patient demographics will be summarized for the safety population and will include age, sex, race, ethnicity, height, weight, and body mass index.

Baseline characteristics will be summarized for the safety population and will include age at MS symptom onset, age at MS diagnosis, years since MS symptom onset, years since MS diagnosis, EDSS score, number of relapses within the last 12 months, number of relapses within the last 24 months, and number of GdE lesions.

Compliance with investigational drug will be summarized for the safety population and will include the number of patients estimated to be < 80% compliant, 80 to 100% compliant, and > 100% compliant. The total dose and average daily dose will also be summarized.

13.3.2 Safety Analyses

All safety data will be listed and summarized for the safety population. Adverse events will be monitored during the trial and the data analyzed with respect to incidence overall as well as severity and potential relationship of the AEs to investigational drug. Adverse events with onset on, or after the first dose of investigational drug or with onset prior to the first dose of

investigational drug that increase in severity on, or after the first dose of investigational drug will be considered treatment-emergent. Treatment-emergent AEs will be summarized by system organ class and preferred term and presented in descending order of frequency within each system organ class. Serious AEs, AESIs, and AEs leading to withdrawal from the trial will be summarized similarly.

Associated laboratory parameters such as hepatic profile, renal function, and hematology values will be grouped and presented together. For each laboratory test, individual patient values outside the standard reference range will be flagged and listed. Shift tables will be produced showing the frequency of shifts from Baseline to the worst on-trial value in and out of the normal range as well as by visit. Changes from Baseline to each visit for each laboratory parameter will also be summarized.

The change from Baseline to each visit for each of the vital signs parameters will be summarized. The change from Baseline to each applicable visit for each of the ECG parameters will also be summarized.

For the analyses of dependence and withdrawal assessments, the change from the last assessment while on study drug to the Follow-up Visits on Days 1, 4, 7, 14, 21, and 90 (Table 3) will be described using summary statistics.

13.3.3 Efficacy Analyses

For the annualized relapse rate, the number of patients with relapses, the total number of relapses, the patient-years on trial, the unadjusted annualized relapse rate, and the patient relapse rate will be presented. The unadjusted annualized relapse rate will be calculated as (total number of relapses) / (total days in the trial) * 365.25. The relapse rate will be based on only those relapses that were determined by the treating Investigator to meet the protocol-defined definition of relapse, based on the EDSS scores. 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, ie, if 2 relapses have onset days that are ≤ 30 days of one another, they will be counted as 1 relapse.

Time to first relapse and time to onset of disability progression will be analyzed using Kaplan-Meier methods. The estimated median time to event will be reported, along with the associated 95% confidence interval (CI). Disability progressions confirmed after 3 months and after 6 months will be analyzed separately.

Other efficacy endpoints will be summarized by visit using descriptive statistics or counts and percentages as appropriate.

13.3.4 Interim Analysis

Interim analyses will occur as appropriate.

14 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1 Monitoring

Monitors employed by the Sponsor and/or designee will work in accordance with the relevant SOPs. A Sponsor's designee will have the same rights and responsibilities as monitors from the Sponsor organization. Monitors will establish and maintain regular contact with the Investigator.

Monitoring visits will be conducted according to all applicable regulatory requirements and standards. Regular monitoring visits will be made to each site while patients are enrolled in the trial.

14.2 Data Management/Coding

Electronic Data Capture (EDC) will be used for this trial, meaning that all eCRF data will be entered in electronic forms at the site. All EDC systems used in the trial will have access-controlled security and an audit history available to document any changes made to the data throughout the course of the trial. Data collection recorded in site source documents will be entered into the eCRF by authorized site staff designated by the Investigator. Patients will record missed doses directly into a diary. The EDSS, MSFC, MSQOL-54, LCLA, OCT, and C-SSRS will be administered by site staff or completed by the patient, as applicable. Appropriate training and security measures will be completed with the Investigator, all authorized site staff, and patients prior to the trial being initiated and any data being entered into the system for and/or by any trial patients.

All data entered by the site staff must be entered in English. The eCRFs should be completed contemporaneous to the patient's visit. The Investigator may delegate data entry, but is responsible for verifying that all data entries in the eCRFs are accurate and correct at the conclusion of the trial.

Source documents are all documents used by the Investigator or hospital that relate to the patient's medical history, that verify the existence of the patient, the eligibility criteria, and all records covering the patient's participation in the trial. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, patient files, etc.

Source documents will be made available for inspection by the site monitor at each monitoring visit. The Investigator must complete eCRFs for each patient who receives investigational drug. Any copy of source document(s) that are provided to the Sponsor or its representatives for any purpose (eg, in support of an SAE report) must be redacted such that all personally-identifiable information is removed, and clearly labeled with the trial and patient number.

All AEs recorded in the eCRF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. Versions of dictionaries to be used will be specified in the data management plan for the trial.

14.3 Quality Assurance and Inspections

Sites, the trial database, and trial documentation may be subject to Quality Assurance audit during the course of the trial by the Sponsor and/or designee. In addition, inspections may be conducted by regulatory bodies at their discretion.

15 QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Study Monitoring and Source Data Verification

According to the Guidelines of Good Clinical Practice (CPMP/ICH/135/95), the Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOPs).

Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Central laboratories for clinical laboratory parameters and ECGs
- Site Initiation visit
- Early site visits post-enrollment
- Routine site monitoring
- Ongoing site communication and training
- Data management quality control checks
- Continuous data acquisition and cleaning
- Internal review of data
- Quality control check of the final clinical study report

In addition, Sponsor and/or designee Clinical Quality Assurance Department may conduct periodic audits of the trial processes, including, but not limited to site facilities, central laboratories, vendors, clinical database, and final clinical study report. When audits are conducted, access must be authorized for all trial-related documents, including medical history and concomitant medication documentation, to authorized Sponsor's representatives and regulatory authorities.

15.2 Product Quality Complaint

A Product Quality Complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, purity, or performance of any drug product manufactured by or on behalf of Celgene after it is released for distribution. PQCs may reduce the usability of the product for its intended function or affect performance of the product and therefore pose a significant risk to the patient. Examples of PQCs include (but are not limited to): mixed product, mislabeling, lack of effect, seal/packaging breach, product missing/short/overage, contamination, suspected falsified, tampered, diverted or stolen material, and general product/packaging damage. If you become aware of a suspected PQC, you are obligated to report the issue immediately. You can do so by emailing customercomplaints@celgene.com or by contacting the Celgene Customer Care Center (1-888-423-5436).

16 ETHICS

16.1 Institutional Review Board or Independent Ethics Committee

An IRB/IEC should approve the final protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The Investigator will provide the Sponsor and/or designee with documentation of IRB/IEC approval of the protocol and informed consent before the trial may begin at the site(s). The Investigator should submit the written approval to the Sponsor or representative before enrollment of any patient into the trial.

The Sponsor or representative should approve any modifications to the ICF that are needed to meet local requirements.

The Investigator will supply documentation to the Sponsor and/or designee of required IRB/IEC's annual renewal of the protocol, and any approvals of revisions to the informed consent document or amendments to the protocol.

The Investigator will report promptly to the IRB/IEC, any new information that may adversely affect the safety of patients or the conduct of the trial. Similarly, the Investigator will submit written summaries of the trial status to the IRB/IEC annually, or more frequently if requested by the IRB/IEC. Upon completion of the trial, the Investigator will provide the Ethics Committee with a brief report of the outcome of the trial, if required.

16.2 Ethical Conduct of the Trial

This trial will be conducted and the informed consent will be obtained according to the ethical principles stated in the Declaration of Helsinki (48th General Assembly, Somerset West, Republic of South Africa, October 2008 [or current version]), the applicable guidelines for Good Clinical Practice (GCP; CPMP/ICH/135/95), or the applicable drug and data protection laws and regulations of the countries where the trial will be conducted.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human patients. The trial will be conducted in compliance with GCP and the applicable national regulations so as to assure that the rights, safety and well-being of the participating trial patients are protected consistent with the ethical principles that have their origin in the Declaration of Helsinki.

16.3 Patient Information and Informed Consent

The Investigator will explain the benefits and risks of participation in the trial to each patient and obtain written informed consent. Written informed consent must be obtained prior to the patient entering the trial and before initiation of any trial related procedure. The final, version dated form must be agreed to by the IRB/IEC and must be provided in language readily understood by the patient. In case the patient is unable to read or write, an impartial witness should be present during the entire informed consent discussion. After the patient has orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. The Investigator will retain an original

consent form for each patient, signed and dated by the patient or witness, and by the person who conducted the informed consent discussion. The Investigator will supply all enrolled patients with either a copy of their signed informed consent or, depending upon local requirements, a second original informed consent, signed by both parties.

The consent form may need to be revised during the trial due to a protocol amendment or should important new information become available that may be relevant to the safety of the patient. In this instance, approval should always be given by the IRB/IEC and existing patients informed of the changes and re-consented, as directed by the IRB/IEC and in accordance with its policies and procedures; however, in some instances where an immediate change is necessary to eliminate an apparent hazard to patients, then it would not be necessary for a protocol amendment to receive IRB/IEC review and approval before being implemented. Those patients who are presently enrolled and actively participating in the trial should be informed of the change if it might relate to the patients' willingness to continue their participation in the trial.

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

16.4 Patient Data Protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

16.5 Investigator Obligations

This trial will be conducted in accordance with the ICH Harmonized Tripartite Guideline for GCP (GCP 1997); the US Code of Federal Regulations (CFR) Title 21 parts 50, 56, and 312; and European Legislation; and the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator agrees to conduct the clinical trial in compliance with this protocol after the approval of the protocol by the IRB/IEC in compliance with local regulatory requirements. The Investigator and the Sponsor will sign the protocol to confirm this agreement.

16.6 Protocol Signatures

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative. By signing the protocol, the Investigator confirms in writing that he/she has read, understands and will strictly adhere to the trial protocol and will conduct the trial in accordance with ICH Tripartite Guidelines for Good Clinical Practice and applicable regulatory requirements. The trial will not be able to start at any site where the Investigator has not signed the protocol.

17 DATA HANDLING AND RECORDKEEPING

17.1 Inspection of Records

The Investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each patient enrolled in the trial.

The Investigator will allow the Sponsor, Sponsor's designee, and authorized regulatory authorities to have direct access to all documents pertaining to the trial, including individual patient medical records, as appropriate.

17.2 Retention of Records

It is the Investigator's responsibility to maintain essential trial documents (protocol and protocol amendments, completed eCRFs, signed ICFs, relevant correspondence, and all other supporting documentation). The trial site should plan on retaining such documents for approximately 15 years after trial completion. The trial site should retain such documents until at least 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the trial is being conducted. Patient identification codes (patient names and corresponding trial numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to Sponsor. The Investigator must contact Sponsor prior to disposing of any trial records.

No records should be disposed of without the written approval of the Sponsor.

18 PUBLICATION POLICY, FINANCING, AND INSURANCE

The data generated by this trial are confidential information of the Sponsor. The Sponsor will make the results of the trial publicly available. The publication policy, financing and insurance information with respect to the Investigator and site will be set forth in the Clinical Trial Agreement.

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APPENDIX 1. INVESTIGATOR SIGNATURE

PROTOCOL TITLE: A Multi-Site, Open-Label Extension Trial of Oral RPC1063 in Relapsing Multiple Sclerosis

PROTOCOL NO.: RPC01-3001

I have read and agree to the RPC01-3001 protocol, Version 10.0, dated 08 Oct 2021. I am aware of my responsibilities as an Investigator under the guidelines of GCP, local regulations (as applicable), and the trial protocol. I agree to conduct the trial according to these responsibilities and to appropriately direct and assist the staff under my control, who will be involved in the trial. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Clinical Site: _____

Site Number: _____

Site Principal Investigator:

_____ _____

Print Name Title

_____ _____

Signature Date

Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.

[redacted]

– SUMMARY OF CHANGES –

AMENDMENT NO. 10

A Multi-Site, Open-Label Extension Trial of Oral RPC1063 in Relapsing Multiple Sclerosis

INVESTIGATIONAL PRODUCT (IP):	**RPC1063**
PROTOCOL NUMBER:	**RPC01-3001**
AMENDMENT No. 9 DATE:	**26 FEB 2020**
AMENDMENT No. 10 DATE:	**08 OCT 2021**
EudraCT NUMBER:	2015-002500-91
IND NUMBER:	109,159

Contact Information:

Name: [redacted]

Title: [redacted]

Address:

[redacted]

Phone:

[redacted]

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}	
Signature of Celgene Therapeutic Area Head	**dd mmm yyyy**
Printed Name of Celgene Therapeutic Area Head and Title By my signature, I indicate I have reviewed this summary of changes and find its content to be acceptable.	

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- Added assessment of immune response as exploratory objective, which includes additional blood samples at each visit and potential assessment of stored blood
- Added section regarding COVID-19 pandemic, including handling COVID related AEs and vaccines through the study
- Updated Celgene address
- Minor editorial changes to enhance clarity of the Details of Changes from the Prior Protocol Version

Table 1: Specific Changes to Protocol RPC01-3001 from Version 9.0 (26 Feb 2020) to Version 10.0 (08 Oct 2021)

Protocol Section(s)	Original Text	Revised Text	Rationale
Title page	[redacted]	Celgene International II Sàrl Route de Perreux 1, 2017 Boudry, Switzerland [redacted]	Change of address
Synopsis Methodology, 7.1 Overall Trial Design		Assessment of immune response	Assessment of immune response added to trial assessments
7.1 Overall Trial Design, Table 2: Schedule of Assessments		A blood sample will be collected at the subject's next visit after this amendment is implemented, every 6 months thereafter, and at the end of treatment for measurements of immune response (eg, SARS-CoV-2 serology).	Due to COVID-19 pandemic, assessment of immune response in patients taking ozanimod will be evaluated. An additional blood sample will be collected at each patient visit after amendment 10 is implemented.
Synopsis Safety Endpoints, 6.3.1 Safety Endpoints, and 12.2 Laboratory Assessments		Exploratory measurements of immune response (eg, anti-SARS-CoV-2 serology) will be assessed from blood samples collected at trial visits and end of treatment, and the potential association between these measurements and selected endpoints related to safety and/or efficacy.	Due to COVID-19 pandemic, assessment of immune response in patients taking ozanimod will be evaluated
Table 2: Schedule of Assessments, footnote [R]		Assessment of immune response may also include analyzing stored blood collected during previous visits prior to implementation of amendment 10.	To allow for stored blood to be evaluated in assessment of immune response

Protocol Section(s)	Original Text	Revised Text	Rationale
12.4.3 COVID-19 Pandemic		The global coronavirus disease 2019 (COVID-19) pandemic has been identified as a potential risk to clinical trial subjects in general and may particularly affect individuals with underlying chronic diseases on immunomodulatory therapies. It is not known whether taking ozanimod increases the risk of SARS-CoV-2 infection, or the duration or severity of COVID-19. Evaluation and management of SARS-CoV-2 infections arising during the course of the trial are left to the discretion and expertise of the investigator. For subjects who exhibit symptoms consistent with SARS-CoV-2, testing for SARS-CoV-2 to inform decisions and clinical care during the study should follow local standard practice. The sponsor also suggests the investigator to refer to the Multiple Sclerosis International Federation (MSIF) guidelines per DMC recommendation, and to consult the Medical Monitor as needed. Each study visit will include an assessment for AEs including SARS-CoV-2 and other infections. In order to facilitate reporting of SARS-CoV-2 events that occur during the study, all AEs and SAEs related to SARS CoV-2 should be reported from the time of consent until the final study Visit.	To provide background information on COVID-19 pandemic, and handling cases of COVID-19 and COVID-19 vaccinations throughout the trial

Protocol Section(s)	Original Text	Revised Text	Rationale
		Procedures related to COVID-19 identification (eg, MERS-CoV test, SARS-CoV-2 antibody test, SARS-CoV-2 ELISA test), and treatment (eg, intubation, dialysis) must be reported in the appropriate eCRF. Non-live COVID-19 vaccination is considered a simple concomitant medication within the study. However, the safety and efficacy of non-live vaccines (including non-live COVID-19 vaccines) in patients receiving ozanimod is unknown. Ozanimod treatment may cause vaccines to be less effective. If the assessment of the Investigator suggests the vaccine to be beneficial, it must be a non-live, replication incompetent vaccine, and be approved or authorized (ie, Emergency Use Authorization [FDA] or equivalent) by national health authorities. Administration of vaccinations must be reported along with dosage information, dates of administration and vaccine name/trade name in the appropriate eCRF. A separate logline should be entered for each vaccine administered with the dose number following the vaccine name/trade name.	