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STATISTICAL ANALYSIS PLAN

TITLE: **A PHASE IIIB, OPEN-LABEL STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF SHORTER INFUSIONS OF OCRELIZUMAB IN PATIENTS WITH PRIMARY PROGRESSIVE AND RELAPSING MULTIPLE SCLEROSIS**

PROTOCOL NUMBER: ML40638

STUDY DRUG: Ocrelizumab (RO4964913)

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STATISTICAL ANALYSIS PLAN APPROVAL

Approved by [redacted] *Ph.D. on June 26, 2019*

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Table 1 List of Abbreviations and Definition of Terms

BSOC	body system organ class
□C	Celsius
CI	confidence interval
CNS	Central Nervous System
CTCAE	Common Terminology Criteria For Adverse Events
eCRF	electronic Case Report Form
EDSS	Expanded Disability Status Scale
ITT	Intent-to-Treat
IRR	Infusion Related Reactions
IV	Intravenous
kg	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
mmHg	Millimeter of Mercury
MS	Multiple Sclerosis
NCI	National Cancer Institute
PPMS	Primary Progressive Multiple Sclerosis
PT	Preferred Term
RMS	Relapsing Multiple Sclerosis
SD	Standard Deviation
U.S.	United States
USPI	United States Package Insert

1. BACKGROUND

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, and degenerative disease of the central nervous system (CNS) that affects approximately 400,000 people in the United States (U.S.) and 2.3 million worldwide (National Multiple Sclerosis Society).

Ocrelizumab is a recombinant humanized monoclonal antibody that selectively targets CD20-expressing B cells (Klein et al. 2013), which are believed to play a critical role in MS. Ocrelizumab is indicated for the treatment of adult patients with relapsing or primary progressive forms of MS (United States Package Insert [USPI]). See the Ocrelizumab Investigator's Brochure for additional details on nonclinical and clinical studies.

According to the currently approved U.S. label, ocrelizumab must be administered at a 600-mg dose through slow intravenous (IV) infusion. The first dose is given as two doses, separated by 14 days, and administered as two 300-mg infusions over the course of 2.5 hours, while subsequent doses are given as a single 600-mg infusion over 3.5 hours.

The most common safety events reported with ocrelizumab are infusion related reactions (IRRs). IRRs occur more frequently during the first infusion of the first dose. The majority of IRRs (>90% of patients reporting IRRs) were of mild to moderate intensity, and the intensity of IRRs decreased with subsequent dosing. Different doses of ocrelizumab have been studied over the years in various patient populations, showing consistently that the proportion of reported IRRs is dose-dependent. However, there is no direct evidence on whether a shorter infusion time would pose an additional safety risk to patients. This study will explore, for the first time, the effect of a shorter infusion on the rate and severity of IRRs.

Refer to the study protocol regarding more details of the study background.

2. STUDY DESIGN

This study is an open-label, non-randomized study to evaluate rate and severity of IRRs of ocrelizumab infused over a shorter time period than the approved administration rate in patients with Primary Progressive MS (PPMS) or Relapsing MS (RMS) in the U.S. The study will have 2 cohorts:

- Cohort 1 will examine the effect of administering ocrelizumab per a shorter infusion protocol for Dose 2 or Dose 3 (Week 24 or 48 from the initial infusion). This cohort will consist of patients who have already received one or two doses of ocrelizumab according to the approved infusion protocol (i.e., per current U.S. label) and have reported no serious IRRs and who will then receive the next infusion of ocrelizumab at a higher rate in order to deliver 600 mg over the course of approximately 2 hours.

- Cohort 2 will examine the effect of administering ocrelizumab per a shorter infusion protocol for the second infusion of Dose 1. This cohort will consist of ocrelizumab-naïve patients who, after receiving Infusion 1/Dose 1 of ocrelizumab at the approved rate (300 mg over approximately 2.5 hours or longer) have no reported serious IRRs, will then receive the second 300-mg shorter infusion over approximately 1.5 hours.

All patients will have two safety follow-up telephone calls: the first within 24 hours of the ocrelizumab infusion and the second 30 days after their last ocrelizumab dose.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2.

2.2 OUTCOME MEASURES

2.2.1 Primary Endpoint

The primary endpoint is the rate and frequency of National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0) Grade 3 and 4 IRRs in patients who receive the 600 mg shorter infusion.

2.2.2 Secondary Endpoints

The secondary endpoints for this study are as follows:

- Rate and frequency of NCI CTCAE v4.0 Grade 1–4 IRRs in patients who receive the shorter infusion for both cohorts
- Rate and frequency of NCI CTCAE v4.0 Grade 3 and 4 IRRs in patients who receive the 300 mg shorter infusion

2.2.3 Safety Outcome Measures

In addition to IRRs collected as the primary and secondary endpoints, additional safety outcome measures of interest include the number and proportion of patients who require slowing down, interruption, or discontinuation of ocrelizumab due to IRRs following the 300-mg or 600-mg shorter infusion and the following:

- Count and proportion of patients who experienced
    - Treatment-emergent adverse events
    - CTCAE v4.0 Grade 3 to 5 adverse events
    - Serious treatment-emergent adverse events
    - Treatment-emergent adverse events of special interest as applicable
    - Adverse events leading to treatment discontinuation
    - Adverse events leading to withdrawal from study
    - Adverse events leading to infusion adjustment

- Treatment-related adverse events
- Adverse events with fatal outcome

- Summary of patients who experienced abnormalities (as appropriate), i.e., hepatic function, renal function and hematology values.
- Descriptive statistics (n, mean, standard deviation [SD], median, min, max), including change from baseline analysis, of vital signs -
  - Sitting and supine diastolic blood pressure (mmHg)
  - Sitting and supine systolic blood pressure (mmHg)
  - Pulse rate (beats/minute)
  - Temperature (□C)
  - Weight (kg)

2.3 DETERMINATION OF SAMPLE SIZE

This study will enroll approximately 150 patients, with 100 from Cohort 1 and 50 from Cohort 2.

Based on the sample size of 100 patients in Cohort 1 and 50 patients in Cohort 2, the 95% confidence intervals (CIs) for some assumed Grade 3 or 4 IRRs are provided in the table below.

Table 2 Determination of Sample Size

Sample Size	Number of Pts with Grade 3 or 4 IRRs	IRR Rate (%)	Exact LCL (%)	Exact UCL (%)
50	1	2	0.05	10.65
50	2	4	0.49	13.71
50	3	6	1.25	16.55
50	4	8	2.22	19.23
50	5	10	3.33	21.81
50	6	12	4.53	24.31
50	7	14	5.82	26.74
50	8	16	7.17	29.11
50	9	18	8.58	31.44
100	1	1	0.03	5.45
100	2	2	0.24	7.04
100	3	3	0.62	8.52
100	4	4	1.10	9.93
100	5	5	1.64	11.28
100	6	6	2.23	12.60
100	7	7	2.86	13.89
100	8	8	3.52	15.16
100	9	9	4.20	16.40
150	1	0.67	0.02	3.66
150	2	1.33	0.16	4.73
150	3	2	0.41	5.73
150	4	2.67	0.73	6.69
150	5	3.33	1.09	7.61
150	6	4	1.48	8.50
150	7	4.67	1.90	9.38
150	8	5.33	2.33	10.24
150	9	6	2.78	11.08

Pts=Patients; IRR=infusion-related reaction; LCL=lower confidence limit; UCL=upper confidence limit based on 95% confidence interval.

2.4 ANALYSIS TIMING

The first 50 patients in cohort 1 were summarized for baseline characteristics and presented at the 2019 American Academy of Neurology (AAN) and Consortium of Multiple Sclerosis Centers (CMSC) 2019 congresses.

Final analysis will be conducted when all planned 150 patients (100 patients from Cohort 1 and 50 patients from Cohort 2, respectively) have completed the 30-day follow-up after the study drug administration and the database is cleaned and locked.

Regular safety reviews will be conducted by Data Management and the sponsor.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Not applicable.

4. STATISTICAL METHODS

This study is designed to evaluate the safety (i.e. IRRs) of ocrelizumab administered over a shorter time period than the approved administration rate in patients with PPMS or RMS in the U.S. No efficacy outcome is collected in this study.

Descriptive statistics, i.e. frequency and proportion of patients, will be used to summarize the incidence of IRR events and potential incidence of modifications (i.e. slowing, interruption, or discontinuation) to the study drug following IRRs in respective study cohorts. When applicable, 95% confidence intervals (CIs) will be provided using exact Clopper-Pearson method for the proportion to quantify the uncertainty of the observed value.

4.1 ANALYSIS POPULATIONS

Based on the study design and objectives, all safety analyses and exposure summaries will be performed using the safety population. Demographic, baseline characteristics, and patient disposition will be summarized using intent-to-treat (ITT) population.

4.1.1 Intent-to-Treat Population

All enrolled patients will be included in the ITT population. Patients who prematurely withdrew from the study for any reason and who did not have any assessments for any reason will still be included in the ITT population.

4.1.2 Safety Population

The safety population is defined as all enrolled patients who received any dose of study treatment, even if the infusion was incomplete.

4.2 ANALYSIS OF STUDY CONDUCT

Enrollment, infusion experience, discontinuation, and completion of the study will be summarized. Patient disposition and the incidence of treatment discontinuation for reasons other than disease progression will be tabulated. Pre-infusion medications and concomitant medications will be summarized. Major protocol violations, including violations of inclusion/exclusion criteria, will be listed.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

All patients will be treated in this study and treatment group comparability is not applicable. Instead, analysis will be conducted by the treatment cohort.

For continuous variables, the mean, median, SD, minimum, and maximum will be calculated. For categorical variables, number and percentage in each category will be displayed. The units/categories to be used are indicated within the brackets and separated by commas.

4.3.1 Demographics and Baseline Characteristics

The following patient demographics and baseline characteristics will be summarized for the ITT population:

- Age (years)
- Age (years) group: (age categories ≤ 40, > 40, and age categories ≥18− <40, ≥ 40−≤55)
- Sex
- Self-reported race and ethnicity
- Baseline weight
- EDSS score
- EDSS category: (EDSS categories < 4, ≥ 4, and EDSS categories < 2.5, ≥ 2.5)
- Female fertility status
- MS type (RMS, PPMS)

Demographics and baseline characteristics will be summarized further by MS diagnosis categories (RMS, PPMS).

4.3.2 Multiple Sclerosis Disease History

MS medical history will be summarized by system organ classes and preferred terms for the safety population. A listing of medical history will also be provided by treatment cohort.

4.4 EFFICACY ANALYSIS

Not applicable.

4.5 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Not applicable.

4.6 SAFETY ANALYSES

4.6.1 Exposure to Study Medication

Patients will receive only one infusion in this study. Patients will be considered to have received study medication even if the infusion was incomplete.

Descriptive statistics (n, mean, SD, median, minimum, maximum, 25^{th} and 75^{th} percentiles) of infusion duration (hours) and actual dose administered (mg and mL) and count and proportion of patients by infusion duration category (hours) (≤ 1.5, >1.5 to ≤2, >2 to ≤2.5, >2.5 to ≤3, >3) will be tabulated.

Infusion start and stop date and time, total duration (hours), actual dose administered (mL), type of dose adjustment, and reason for infusion modification will be listed separately for all patients and for only those who experienced slowed, interrupted, or discontinued infusion.

4.6.2 Adverse Events

Adverse event analyses will be generated by summarizing and listing treatment-emergent adverse events only. Treatment-emergent events are defined as those adverse events with an observed or imputed onset date on or after the start date of study treatment and up to 30 days after the last dose of study drug. Only where the most extreme intensity is greater than the initial intensity will events with an onset date prior to the start of study treatment (and with an end date on or after the start of study treatment) be considered treatment-emergent. An adverse event with a completely missing non-imputed start date will be assumed to be treatment-emergent unless the adverse event has a complete non-imputed end date that is prior to start of study treatment.

For each adverse event recorded, the term entered by the investigator describing the event (the “reported term”) will be assigned a standardized term (the “preferred term” [PT]) based on the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0. All adverse events will be mapped to PTs and body system organ class (BSOC). All analyses of adverse events data will be performed using the PTs unless otherwise specified.

All adverse events will be summarized by NCI CTCAE v4.0 grade, and tabulated by body system and PT for individual adverse events within each body system. Multiple occurrences of the same event within a patient will be counted once. Adverse events will be sorted by body system (in decreasing order of overall incidence) and then by PT (in decreasing order of overall incidence).

CTCAE V4.0 Grade 3 to 5 adverse events, serious adverse events, adverse events leading to treatment discontinuation, adverse events leading to infusion adjustment, treatment-related adverse events, and adverse events with a fatal outcome will be summarized. In addition, all serious adverse events and deaths will be listed as applicable. Serious adverse events will be defined as all serious adverse events including serious IRRs.

All IRRs will be included in the adverse event analyses. An IRR and its corresponding symptoms are collected on the electronic Case Report Form (eCRF). The symptom(s) of an IRR and the IRR itself may be of different intensities. As other symptoms can be recorded as free-text on the eCRF page, symptoms will be coded using MedDRA and summarized by PT.

IRRs are categorized by the time of the event occurring during the infusion and within 24 hours of completion of the infusion. The number and percentage of patients with at least one IRR will be presented by cohort and infusion (patients with multiple events within an infusion will count only once). In addition, the total number of IRRs will be summarized (multiple events will be counted). The total and percentage (based on the total number of patients with at least one IRR) will be summarized by most extreme intensity. The number of patients who experienced an IRR that led to slowing down, interruption, or discontinuation of study drug will be summarized.

Symptoms of IRRs and serious IRRs will also be listed.

For the primary analysis, the number and proportion of patients who experience Grade 3 or 4 IRRs following the 600-mg shorter infusion will be provided with a 2-sided 95% exact Clopper-Pearson CI of the proportion.

For secondary analyses, the number and proportion of patients who experience Grade 1–4 IRRs following the 600-mg shorter infusion and the 300-mg shorter infusion, and the number and proportion of patients who experience Grade 3 or 4 IRRs following the 300-mg shorter infusion will be provided with a 2-sided 95% exact Clopper-Pearson CI of the proportion.

The number and proportion of patients who require slowing, interruption, or discontinuation of ocrelizumab due to IRRs following the 300-mg or 600-mg shorter infusion will be provided with a 2-sided 95% exact Clopper-Pearson CI of the proportion. In addition, the number and proportion patients with local and/or systemic infusion site

reactions will be summarized. Listings of infusion related reactions will be presented separately for all patients and for only those patients for whom the IRR led to infusion slowing down, interruption, and discontinuation.

4.6.3 Laboratory Data

Not applicable.

4.6.4 Vital Signs

Baseline, post-baseline, and change from baseline in vital signs will be summarized. Baseline for vital signs is defined as the last measurement prior to pre-infusion medication at Day 1 for both cohort 1 and cohort 2.

4.6.5 Subgroup Analyses

The primary and secondary endpoints will be summarized and analyzed by subgroup of RMS and PPMS patients. The number and proportion of patients and associated 95% CIs will be presented for these analyses, if applicable. Adverse events will be summarized further by RMS and PPMS patients.

4.7 MISSING DATA

Missing and partial dates for adverse events and concomitant medications will be handled according to Roche STREAM algorithm.

4.8 INTERIM ANALYSES

One planned analysis was performed for the first 50 patients in cohort 1 (see Section 2.4).

5. REFERENCES

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Appendix 1
Protocol Synopsis

TITLE:	**AN OPEN-LABEL STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF SHORTER INFUSIONS OF OCRELIZUMAB IN PATIENTS WITH PRIMARY PROGRESSIVE AND RELAPSING MULTIPLE SCLEROSIS**
PROTOCOL NUMBER:	ML40638
VERSION NUMBER:	1
EUDRACT NUMBER:	Not applicable
IND NUMBER:	100593
TEST PRODUCT:	Ocrelizumab (RO4964913)
PHASE:	Phase IIIb
INDICATION:	PPMS and RMS
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

This study will evaluate the safety of administering ocrelizumab per a shorter infusion protocol (i.e., shorter than the currently approved U.S. labeling rate) in patients with primary progressive multiple sclerosis (PPMS) and relapsing multiple sclerosis (RMS). Specific objectives and corresponding endpoints for the study are outlined below.

Primary Objective	Corresponding Endpoint
• To evaluate the occurrence of severe IRRs with ocrelizumab 600 mg IV administered over the course of 2 hours	• Rate and frequency of NCI CTCAE v4.0 Grade 3 and 4 IRRs in patients who receive the 600 mg shorter infusion
Secondary Objective	**Corresponding Endpoints**
• To evaluate the occurrence of overall IRRs with ocrelizumab administered per a shorter infusion protocol for both cohorts	• Rate and frequency of NCI CTCAE v4.0 Grade 1–4 IRRs in patients who receive the shorter infusion for both cohorts • Rate and frequency of NCI CTCAE v4.0 Grade 3 and 4 IRRs in patients who receive the 300 mg shorter infusion

IRR=infusion-related reaction; IV=intravenous; NCI CTCAE v4.0=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.

Study Design

Description of Study

This study is an open-label, non-randomized study to evaluate rate and severity of infusion-related reactions (IRRs) of ocrelizumab infused over a shorter time period than the approved administration rate in patients with PPMS or RMS in the U.S. The study will have 2 cohorts:

- Cohort 1 will examine the effect of administering ocrelizumab per a shorter infusion protocol for Dose 2 or Dose 3 (Week 24 or 48 from the initial infusion). This cohort will consist of patients who have already received one or two doses of ocrelizumab according to the approved infusion protocol (i.e., per the currently U.S. label) and have reported no serious IRRs and who will then receive the next infusion of ocrelizumab at a higher rate in order to deliver 600 mg over the course of approximately 2 hours.
- Cohort 2 will examine the effect of administering ocrelizumab per a shorter infusion protocol for the second infusion of Dose 1. This cohort will consist of ocrelizumab-naïve patients who, after receiving Infusion 1/Dose 1 of ocrelizumab at the approved rate (300 mg over approximately 2.5 hours or longer) have no reported serious IRRs, will then receive the second 300-mg shorter infusion over approximately 1.5 hours.

All patients will have two safety follow-up telephone calls: the first within 24 hours of the ocrelizumab infusion and the second 30 days after their last ocrelizumab dose.

Number of Patients

Approximately 150 patients with PPMS and RMS at approximately 5 study sites in the U.S. who fulfill the eligibility criteria listed below may participate in this study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Eligible to receive ocrelizumab per the United States Package Insert (USPI)
- Able to comply with the study protocol, in the investigator's judgment
- Age 18–55 years, inclusive
- Have a diagnosis of PPMS or RMS, confirmed per the revised 2017 McDonald criteria (Thompson et al. 2017)
- Expanded Disability Status Scale (EDSS) score of 0 to 6.5, inclusive

  EDSS does not need to be performed if results within 6 months are available.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period and for at least 6 months after the last dose of study treatment (per the USPI)

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, established hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Experienced serious IRR(s) (see Section 5.2.2 for seriousness criteria) for those who have previously received ocrelizumab
- History of life-threatening infusion reaction to ocrelizumab

- Known presence of other neurological disorders, including but not limited to, the following:

  History or known presence of infectious causes of myelopathy (e.g., syphilis, Lyme disease, human T-lymphotropic virus 1 [HTLV-1], herpes zoster myelopathy)

  History of genetically inherited progressive central nervous system degenerative disorder (e.g., hereditary paraparesis; MELAS [mitochondrial myopathy, encephalopathy, lactic acidosis, stroke] syndrome)

  Neuromyelitis optica

  History or known presence of systemic autoimmune disorders potentially causing progressive neurologic disease (e.g., lupus, anti-phospholipid antibody syndrome, Sjogren's syndrome, Behçet's disease)

  History or known presence of sarcoidosis

  History of severe, clinically significant brain or spinal cord trauma (e.g., cerebral contusion, spinal cord compression)

  History of progressive multifocal leukoencephalopathy (PML)
- Pregnancy or lactation, or intention to become pregnant during the study

  Women of childbearing potential must have a negative serum or urine pregnancy test result prior to initiation of study drug.
- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study
- Significant, uncontrolled disease, such as cardiovascular (including cardiac arrhythmia), pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine, and gastrointestinal or any other significant disease that may preclude patient from participating in the study
- Congestive heart failure (New York Heart Association [NYHA] Class III–IV functional severity)
- Known active bacterial, viral, fungal, mycobacterial infection or other infection (including tuberculosis [TB] or atypical mycobacterial disease but excluding fungal infection of nail beds) or any severe episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks prior to baseline visit or oral antibiotics within 2 weeks prior to baseline visit
- History of or currently active primary or secondary immunodeficiency
- History or known presence of recurrent or chronic infection (e.g., HIV, syphilis, tuberculosis)
- History of recurrent aspiration pneumonia requiring antibiotic therapy
- History of malignancy, including solid tumors and hematological malignancies, except basal cell, in situ squamous cell carcinoma of the skin, and in situ carcinoma of the cervix of the uterus that have been excised with clear margins
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies
- History of alcohol or drug abuse within 24 weeks prior to enrollment
- Receipt of a live vaccine within 6 weeks prior to enrollment
- Systemic corticosteroid therapy within 4 weeks prior to enrollment

  There should be 4 weeks from last dose of systemic corticosteroid therapy prior to first infusion.
- Contraindications to or intolerance of oral or IV corticosteroids, including IV methylprednisolone (or equivalent steroid) administered according to the country label, including:

  Psychosis not yet controlled by a treatment

  Hypersensitivity to any of the constituents preceding
- Treatment with alemtuzumab (Lemtrada®)

- Treatment with a B-cell targeted therapies other than ocrelizumab (e.g., rituximab, atacicept, belimumab, or ofatumumab)
- Treatment with a drug that is experimental
- Any of the following abnormal laboratory results per local laboratory standards and investigator assessment. Results should be available per medical history within 6 months prior to the study; otherwise, assessments should be repeated prior to Day 1:

  Lymphocyte count

  CD4 count

  AST or ALT

  Platelet count

  Total neutrophil count

  Positive screening tests for hepatitis B (hepatitis B surface antigen [HBsAg] positive, or positive hepatitis B core antibody [total HBcAb] confirmed by a positive viral DNA polymerase chain reaction [PCR]) or hepatitis C antibody (HepCAb)

End of Study

The end of this study is defined as the date when the last patient, last visit occurs. The last scheduled visit is 30 days after the last dose.

Length of Study

The total length of the study for both cohorts is up to approximately 8 weeks.

Investigational Medicinal Products

Test Product (Investigational Drug)

The investigational medicinal product for this study is ocrelizumab, which is approved for the treatment of PPMS and RMS.

Non-Investigational Medicinal Products

Premedicate with slow IV infusion of 100-mg methylprednisolone (or equivalent) completed approximately 30 minutes prior to each ocrelizumab infusion and with an antihistaminic drug (e.g., diphenhydramine) approximately 30–60 minutes before each infusion of ocrelizumab to reduce the frequency and severity of IRRs.

The addition of an antipyretic (e.g., acetaminophen/paracetamol) may also be considered 30–60 minutes before ocrelizumab infusion to further reduce the frequency and severity of IRRs.

Statistical Methods

Primary Analysis

For the primary analysis, the number and proportion of patients who experience Grade 3 or 4 IRRs following the 600 mg shorter infusion will be provided with a 2-sided 95% exact Clopper-Pearson confidence interval (CI) of the proportion.

Determination of Sample Size

This study will enroll approximately 150 patients.

Based on the sample size of 100 patients in Cohort 1 and 50 patients in Cohort 2, the 95% CIs for some assumed Grade 3 or 4 IRRs are provided in the Determination of Sample Size table (Table 2).

Appendix 2
Schedule of Activities: Cohort 1

	Screening (Up to 28 days prior to Day 1)	Treatment Visit (Day 1) [a]	Telephone Call (24 hours after infusion)	Safety Follow-up (Day 30) [b]
Informed consent [c]	x			
Medical history and demographic data [d]	x			
Review inclusion and exclusion criteria	x			
Physical examination [e]	x			
Vital signs [f]		x		
EDSS	(x) [g]			
Hematology	x			
Pregnancy test [h]		x		
Adverse event assessment [i]			x	x
Concomitant treatment review	x	x		x [j]
Methylprednisolone and antihistamine premedication [k]		x		
Ocrelizumab administration		x [l]		

eCRF=electronic Case Report Form; EDSS=Expanded Disability Status Scale; IRR=infusion-related reaction; IV=intravenous.

[a] Day 1 may occur at Week 24 or 48, depending on the previous treatment cycle.

[b] Patients who receive ocrelizumab in this study or who discontinue from treatment or the study early, should enter the Safety Follow-up Period and be assessed 30 days counting from the date of their last ocrelizumab infusion via telephone.

[c] Written informed consent will be obtained from all patients in order to be eligible for the study and prior to any study procedures.

[d] Medical history includes clinically significant diseases, surgeries, reproductive status, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, and nutritional supplements) used by the patient within 4 weeks prior to the visit. Demographic data will include age, sex, and self‑reported race/ethnicity.

[e] A physical examination may be conducted, per standard of care. Any abnormality identified should be recorded on the eCRF. New or worsened clinically significant abnormalities should be recorded as adverse events, if appropriate.

[f] Vital signs will include the measurements of heart rate, systolic and diastolic blood pressures, and temperature. Vital signs should be taken approximately 45 minutes prior to the premedication methylprednisolone infusion. In addition, vital signs should be obtained prior to the ocrelizumab infusion then approximately every 15 minutes for the first hour, followed by approximately every 30 minutes until 1 hour after the end of the infusion.

[g] EDSS does not need to be performed if results within 6 months are available.

[h] On infusion visits, a urine pregnancy test must be performed prior to premedication in all women of childbearing potential. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Ocrelizumab must be withheld until pregnancy status is confirmed.

[i] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported. After initiation of study drug, related serious adverse events must be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed. Unrelated serious adverse events must be collected and reported during the study and Safety Follow-up. Non-serious adverse events have to be reported until the end of Safety Follow-up.

[j] Medications used after treatment discontinuation should be recorded during Safety Follow-up.

[k] All patients must receive prophylactic treatment with 100 mg methylprednisolone (or equivalent), to be completed approximately 30 minutes before the start of each ocrelizumab infusion, and with an antihistaminic drug (e.g., diphenhydramine) approximately 30–60 minutes before each infusion of ocrelizumab. Prophylactic treatment with an analgesic/antipyretic (e.g., 1 g acetaminophen) is strongly recommended 30–60 minutes prior to the start of ocrelizumab infusion to reduce the risk of IRRs.

[l] Ocrelizumab will be administered as one 600-mg IV infusion over the course of approximately 2 hours (shorter infusion) for Infusion 2 or 3, depending on how many prior doses the patient has received.

Appendix 3
Schedule of Activities: Cohort 2

	Screening (Up to 28 days prior to Day 1)	Treatment Visit (Day 15)	Telephone Call (24 hours after infusion)	Safety Follow-up (Day 30) [a]
Informed consent [b]	x			
Medical history and demographic data [c]	x			
Review inclusion and exclusion criteria	x			
Physical examination [d]	x			
Vital signs [e]		x		
EDSS	(x) [f]			
Hematology	x			
Pregnancy test [g]		x		
Adverse event assessment [h]			x	x
Concomitant treatment review	x	x		x [i]
Methylprednisolone and antihistamine premedication [j]		x		
Ocrelizumab administration		x [k]		

eCRF=electronic Case Report Form; EDSS=Expanded Disability Status Scale; IRR=infusion-related reaction; IV=intravenous.

[a] Patients who receive ocrelizumab in this study or who discontinue from treatment or the study early, should enter the Safety Follow-up Period and be assessed 30 days counting from the date of their last ocrelizumab infusion via telephone.

[b] Written informed consent will be obtained from all patients in order to be eligible for the study and prior to any study procedures.

[c] Medical history includes clinically significant diseases, surgeries, reproductive status, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, and nutritional supplements) used by the patient within 4 weeks prior to the visit. Demographic data will include age, sex, and self‑reported race/ethnicity.

[d] A physical examination may be conducted, per standard of care. Any abnormality identified should be recorded on the eCRF. New or worsened clinically significant abnormalities should be recorded as adverse events, if appropriate.

[e] Vital signs will include the measurements of heart rate, systolic and diastolic blood pressures, and temperature. Vital signs should be taken approximately 45 minutes prior to the premedication methylprednisolone infusion. In addition, vital signs should be obtained prior to the ocrelizumab infusion then approximately every 15 minutes for the first hour, followed by approximately every 30 minutes until 1 hour after the end of the infusion.

[f] EDSS does not need to be performed if results within 6 months are available.

[g] On infusion visits, a urine pregnancy test must be performed prior to premedication in all women of childbearing potential. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Ocrelizumab must be withheld until pregnancy status is confirmed.

[h] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported. After initiation of study drug, related serious adverse events must be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed. Unrelated serious adverse events must be collected and reported during the study and Safety Follow-up. Non-serious adverse events have to be reported until the end of Safety Follow-up.

[i] Medications used after treatment discontinuation should be recorded during Safety Follow-up.

[j] All patients must receive prophylactic treatment with 100 mg methylprednisolone (or equivalent), to be completed approximately 30 minutes before the start of each ocrelizumab infusion, and with an antihistaminic drug (e.g., diphenhydramine) approximately 30–60 minutes before each infusion of ocrelizumab. Prophylactic treatment with an analgesic/antipyretic (e.g., 1 g acetaminophen) is strongly recommended 30–60 minutes prior to the start of ocrelizumab infusion to reduce the risk of IRRs.

[k] Ocrelizumab will be administered as a split infusion for Dose 1: 300-mg IV per standard of care for Infusion 1 and 300-mg IV over the course of approximately 1.5 hours (shorter infusion) for Infusion 2.