Official Title: A Phase III, Non-Inferiority, Randomized, Open-Label, Parallel Group, Multicenter Study to Investigate the Pharmacokinetics, Pharmacodynamics, Safety and Radiological and Clinical Effects of Subcutaneous Ocrelizumab Versus Intravenous Ocrelizumab in Patients with Multiple Sclerosis

NCT Number: NCT05232825

Document Date: Protocol Amendment Version 4: 07-Jul-2023

Protocol Amendment Version 3: 13-Mar-2023

PROTOCOL

PROTOCOL TITLE:	**A PHASE III, NON-INFERIORITY, RANDOMIZED, OPEN-LABEL, PARALLEL GROUP, MULTICENTER STUDY TO INVESTIGATE THE PHARMACOKINETICS, PHARMACODYNAMICS, SAFETY AND RADIOLOGICAL AND CLINICAL EFFECTS OF SUBCUTANEOUS OCRELIZUMAB VERSUS INTRAVENOUS OCRELIZUMAB IN PATIENTS WITH MULTIPLE SCLEROSIS**
PROTOCOL NUMBER:	CN42097
STUDY NAME:	OCARINA II
VERSION NUMBER:	*4 (United States)*
TEST *COMPOUND*:	Ocrelizumab (RO4964913)
STUDY PHASE	*Phase III*
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 100,593 EU CT Number: 2020-005448-48 NCT Number: NCT05232825
SPONSOR*'S NAME AND LEGAL REGISTERED ADDRESS*:	F. Hoffmann-La Roche Ltd *Grenzacherstrasse 124* *4070 Basel, Switzerland*
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol			Associated Parent Protocol	
Country	**Version**	**Date Final**	**Version**	**Date Final**
United States	4	See electronic date stamp on the final page.	3	13 March 2023
–	–	–	3	13 March 2023
–	–	–	2	24 February 2022
–	–	–	1	21 January 2021

PROTOCOL AMENDMENT, VERSION 4 (UNITED STATES): RATIONALE

Protocol CN42097 has primarily been amended the timing of premedication for subcutaneous (SC) ocrelizumab has been modified, and [redacted] following feedback from the U.S. Food and Drug Administration (FDA). In addition, the treatment period has also been extended from 48 weeks to 96 weeks. Substantive changes to the protocol, along with a rationale for each change, are summarized below:

- [redacted] almost all injection reactions in Study CN41144 were CTCAE Grade 1–2 and their incidence decreased after the first injection. The large majority of reactions were local, a minority were systemic, and all were manageable as per the guidelines from the previous versions of the protocol (Section 5.1.4 and Appendix 11) which continue to apply without any changes. [redacted] Following feedback from FDA, oral premedications (dexamethasone and antihistamine) **can be administered 30–60 minutes before ocrelizumab SC injection**. This aligns the premedication time window of SC ocrelizumab with that of ocrelizumab IV (Sections 3.3.5 and 4.3.2.1).
- In line with feedback from the FDA, [redacted] A 1-hour period of post-injection monitoring has been included (Section 4.3.2.1) as well as the requirement to measure vital signs assessment at the end of this monitoring period (Section 4.5.4.1).
- Information regarding continued access to ocrelizumab has been corrected (Section 4.3.4). Ocrelizumab IV, not SC, may be offered under the Roche Global Policy on Continued Access to Investigational Medicinal Product (IMP). It has been clarified that, should SC ocrelizumab not be commercially available or be reasonably accessible for the patient at the end of the treatment phase, the Sponsor may decide to offer access to another study using the Roche IMP.
- It has been made explicit that expedited safety reports are notified to EudraVigilance (Section 5.7).

The following key changes were made in the Global Protocol Version 3 and are listed below for clarity:

- The treatment period has been extended from 48 weeks to a maximum of 96 weeks for continued assessment of safety and tolerability, immunogenicity, home administration, radiological and clinical effects, pharmacodynamics,

biomarkers, and patient-reported outcomes after longer-term SC administration of ocrelizumab (Section 3.1.1.2, Appendix 3). Endpoints for the exploratory radiological and clinical objective, patient reported objective, pharmacodynamic objective and biomarker objective have been modified accordingly to include assessments at later visits during the extended treatment period (Section 2.2, 2.3, 2.6, 2.7).

- Home administration of ocrelizumab can occur from the third ocrelizumab dose onwards (i.e., Week 48, Week 72, Week 96; Section 3.1.1.2, Appendix 4) and there is no longer a maximum number of patients. In the mobile nursing schedule of assessments it has been clarified that EDSS assessment must occur at the site (i.e. at Week 46, Week 70 or Week 94 visits) and cannot be performed at the patient's home or other dosing location (Appendix 4).
- A new patient-reported outcome has been included at Week 96 during the extended treatment period to assess patients' global impression of overall satisfaction of SC ocrelizumab as a treatment for their MS symptoms during the study (Section 2.3, 4.5.13, Appendix 3, Appendix 14).
- Potential risks have been updated with current information about PML (Section 5.1.1.2).
- The duration of the Safety Follow–Up (SFU) period has been shortened from 48 weeks to 24 weeks after last dose of study drug (Section 3.1.1.3 and 3.2). No safety concerns post last dose (e.g., withdrawal syndrome, immune reconstitution inflammatory syndrome, rebound in MS activity/progression) have been identified from the SFU periods of the ocrelizumab intravenous (IV) studies, and differences are not expected between SC and IV with respect to safety after the last dose. An extended SFU period in the SC studies will not contribute to the further characterization of the risks of local and systemic injection reactions, which are the only risks specific to this route of administration. In addition, shortening the SFU period will avoid unnecessarily delaying patient access to post-study treatment indicated for their multiple sclerosis (MS).
- The option to collect information about the patient's planned post-study MS treatment has been added to the 24-week SFU visit (Section 3.1.1.3).
- The email address for withdrawal from the Research Biosample Repository after site closure has been corrected (Section 4.5.14.5).
- Language has been added to clarify that adverse events associated with a special situation that also qualify as adverse events of special interest should be reported within 24 hours (Section 5.3.5.12).
- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol (Section 5.4.1). Medical Monitor contact information has been replaced with a sentence indicating that this information will be provided separately to sites.

- A description of the technical and organizational security measures taken to protect personal data has been added to align with CTR requirements (Section 8.4).
- Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access in addition to redacted Clinical Study Reports (Section 9.6).
- The name of a Roche policy on data sharing has been corrected (Section 9.6).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL *AMENDMENT* ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE III, NON-INFERIORITY, RANDOMIZED, OPEN-LABEL, PARALLEL GROUP, MULTICENTER STUDY TO INVESTIGATE THE PHARMACOKINETICS, PHARMACODYNAMICS, SAFETY AND RADIOLOGICAL AND CLINICAL EFFECTS OF SUBCUTANEOUS OCRELIZUMAB VERSUS INTRAVENOUS OCRELIZUMAB IN PATIENTS WITH MULTIPLE SCLEROSIS**
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TEST *COMPOUND*:	Ocrelizumab (RO4964913)
SPONSOR *NAME*:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

PROTOCOL SYNOPSIS

PROTOCOL **TITLE:**	**A PHASE III, NON-INFERIORITY, RANDOMIZED, OPEN-LABEL, PARALLEL GROUP, MULTICENTER STUDY TO INVESTIGATE THE PHARMACOKINETICS, PHARMACODYNAMICS, SAFETY AND RADIOLOGICAL AND CLINICAL EFFECTS OF SUBCUTANEOUS OCRELIZUMAB VERSUS INTRAVENOUS OCRELIZUMAB IN PATIENTS WITH MULTIPLE SCLEROSIS**
REGULATORY AGENCY IDENTIFIER NUMBERS:	*IND Number: 100,593* *EU CT Number: 2020-005448-48* *NCT Number: NCT05232825*

OBJECTIVES AND ENDPOINTS

This study will evaluate the pharmacokinetics, pharmacodynamics, safety, immunogenicity, and radiological and clinical effects of subcutaneous (SC) administration of ocrelizumab compared with the intravenous (IV) infusion of ocrelizumab in patients with either relapsing multiple sclerosis (RMS) or primary progressive multiple sclerosis (PPMS). Specific objectives and corresponding endpoints for the study are outlined below.

PRIMARY PHARMACOKINETIC OBJECTIVE

The primary *pharmacokinetic (*PK*)* objective of this study is to demonstrate PK non-inferiority of the SC formulation of ocrelizumab in patients with multiple sclerosis (MS) on the basis of the following endpoint:

- Serum ocrelizumab area under the concentration–time curve (AUC_{W1-12}) after SC administration compared to IV infusion from Day 1 to Week 12.

SECONDARY PHARMACOKINETIC OBJECTIVE

The secondary PK objective of this study is to determine the maximum serum concentration (C_{max}) of ocrelizumab SC in patients with MS.

SECONDARY RADIOLOGICAL OBJECTIVE

The secondary radiological objective for this study is to evaluate the radiological effects of ocrelizumab SC compared with ocrelizumab IV in patients with MS on the basis of the following endpoints:

- Total number of *gadolinium-enhancing lesions on T1-weighted (*T1Gd+*)* lesions as detected by brain *magnetic resonance imaging (*MRI*)* at Weeks 8 and 24.
- Total number of new or enlarging T2 lesions as detected by brain MRI at Weeks 12 and 24 relative to the previous scan, respectively.

EXPLORATORY RADIOLOGICAL AND CLINICAL OBJECTIVE

The exploratory radiological and clinical objective for this study is to explore the radiological and clinical effects of ocrelizumab SC compared with ocrelizumab IV in patients with MS on the basis of the following endpoints:

- Total number of T1Gd+ lesions as detected by brain MRI at Week 48 *and Week 96*.
- Total number of new or enlarging T2 lesions as detected by brain MRI at Weeks 8, 48*, and 96* relative to the previous scan, respectively.
- The annualized protocol-defined relapse rate by Weeks 24, 48*, and 96* in RMS patients.
- Change from baseline in the expanded disability status scale (EDSS) at Week*s* 48*, 72, and 96*.

PATIENT-REPORTED OBJECTIVE

The exploratory patient-reported outcome (PRO) objective for this study is to evaluate patient preference and satisfaction for ocrelizumab SC and IV in relation to other disease-modifying treatments (DMTs) taken prior to the study, as well as preference for the SC or IV route of administration in a subset of patients:

- Patient satisfaction and experience receiving SC administration (at site and at home) and IV route of administration:
  - Patient administration satisfaction and experience scores using the Treatment Administration Satisfaction Questionnaires (TASQ) for IV Infusion following the first treatment administration in a subset of patients
  - Patient administration satisfaction and experience scores using the TASQ for SC injection
- Patient satisfaction and preference taking ocrelizumab administered SC compared to previous DMTs taken prior to the study:
  - Entry treatment experience questions to report overall treatment satisfaction scores from patients who received an MS treatment prior to the study
  - MS treatment preference score to report overall satisfaction taking ocrelizumab
  - MS treatment preference score to report the proportion of patients with a preference for ocrelizumab SC compared to previously taken DMTs.
- Patient preference for the SC or IV route of administration, specifically:
  - Proportion of patients who prefer the SC or IV route of administration using the Patient Preference Questionnaire (PPQ)
- *Patient global impression of overall satisfaction (PGI-SF) for SC ocrelizumab*
  - *Proportion of patients who are satisfied or dissatisfied with ocrelizumab SC as a treatment for their MS symptoms*

SAFETY OBJECTIVE

The safety objective of this study is to evaluate and compare the safety profile after administration of ocrelizumab SC versus ocrelizumab IV and to assess the safety of ocrelizumab SC at the selected dose in patients with MS on the basis of the following endpoints during the conduct of the study:

- Incidence and severity of adverse events, with severity determined according to the *National Cancer Institute Common Terminology Criteria for Adverse Events (*NCI CTCAE*)*, version 5.0.
- Change from baseline in targeted vital signs.
- Change from baseline in targeted clinical laboratory test results.

IMMUNOGENICITY OBJECTIVE

The immunogenicity objective for this study is to evaluate the immune response to ocrelizumab SC and IV, and *recombinant human hyaluronidase PH0 (*rHuPH0*)*, based on the following endpoints:

- Incidence of treatment-emergent anti-drug antibodies (ADAs; formation of ADAs) to ocrelizumab after SC or IV administration relative to the presence of ADAs at baseline.
- Relationship between ADA status to ocrelizumab and pharmacokinetics, pharmacodynamics, and safety.
- Incidence of treatment-emergent antibodies to *recombinant human hyaluronidase PH20 (*rHuPH20*)* after SC administration relative to the presence at baseline and relationships between antibodies to rHuPH20 and safety.

PHARMACODYNAMIC OBJECTIVE

The pharmacodynamic (PD) objective for this study is to evaluate the effect of SC ocrelizumab compared with IV ocrelizumab on the PD marker for the mechanism of action of ocrelizumab (i.e., B cell depletion) on the basis of the following endpoint:

- Proportion of patients achieving CD19+ B cell level ≤ 5 cells/μL at Weeks 12*,* 24*, 48, and/or 96*.

BIOMARKER OBJECTIVE

The *exploratory* biomarker objective for this study is to evaluate biomarkers that are predictive of response to ocrelizumab (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), can provide evidence of ocrelizumab activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology, on the basis of the following endpoints:

- Levels of biomarkers including but not limited to neurofilament light (NfL) in serum compared between dosing arms at Weeks 12, 24, 48*, and/or 96* compared to baseline.

STUDY DESIGN

DESCRIPTION OF STUDY

CN42097 is a Phase III non-inferiority, randomized, open-label, parallel group, multicenter study to evaluate the pharmacokinetics, pharmacodynamics, safety, immunogenicity, radiological, and clinical effects of SC administration of ocrelizumab compared with the IV infusion of ocrelizumab in patients with either RMS or PPMS.

NUMBER OF PATIENTS

Approximately 232 patients with MS (RMS and PPMS) will be enrolled in this study.

TARGET POPULATION

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Diagnosis of PPMS or relapsing forms of MS (RMS) according to the revised McDonald 2017 criteria (Thompson et al. 2018)
- Signed Informed Consent Form
- Age 18–65 years, inclusive, at time of signing Informed Consent Form
- Ability to comply with the study protocol and schedule of protocol assessments, in the investigator's judgment
- EDSS score, 0–6.5, inclusive, at screening
- Neurological stability for ≥30 days prior to both screening and baseline
- Disease duration from onset of MS symptoms of less than 15 years for patients with EDSS score <2.0 at screening
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use adequate contraception during the treatment period and for 6 or 12 months (as applicable by the ocrelizumab IV [Ocrevus] local label) after the final dose of ocrelizumab. Adherence to local requirements, if more stringent, is required.

  A women is considered to be of childbearing potential if she is postmenarchal, has not reached a post-menopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a woman with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

  As defined by the guidelines, the following contraceptive methods are considered acceptable (failure rate >1%): (1) progesterone-only hormonal contraception, where inhibition of ovulation is not the primary mode of action; (2) male or female condom

with or without spermicide; (3) cap, diaphragm, or sponge with spermicide. (4) combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier method).

Birth control methods that are highly effective (failure rate <1%)may also be used but are not required, and include: (1) oral, intravaginal or transdermal combined hormonal contraception associated with inhibition of ovulation; (2) oral, injectable or implantable progestogen-only hormonal contraception associated with inhibition of ovulation; (3) intrauterine device; (4) intrauterine hormone-releasing system; (5) bilateral tubal occlusion; (6 vasectomized partner; (7) sexual abstinence.

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. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For female patients without reproductive potential:

  Women may be enrolled if

  - post-menopausal (i.e., spontaneous amenorrhea for the past year confirmed by a follicle-stimulating hormone [FSH] level $>$ 40 mIU/mL) unless the patient is receiving a hormonal therapy for her menopause or
  - surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy).

Exclusion Criteria

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

- Any known or suspected active infection at screening or baseline (except nailbed infections), or any major episode of infection requiring hospitalization or treatment with IV antimicrobials within 8 weeks prior to and during screening or treatment with oral antimicrobials within 2 weeks prior to and during screening
- History of confirmed or suspected progressive multifocal leukoencephalopathy (PML)
- History of cancer, including hematologic malignancy and solid tumors, within 10 years of screening
  - Basal or squamous cell carcinoma of the skin that has been excised and is considered cured and in situ carcinoma of the cervix treated with apparent success by curative therapy $>$ 1 year prior to screening is not exclusionary.
- Immunocompromised state, defined as one or more of the following:
  - CD4 count $<$250/μL
  - Absolute neutrophil count $<1.5 \times 10^3/\mu$L
  - Serum IgG $<$4.6 g/L
- Receipt of a live-attenuated vaccine within 6 weeks prior to randomization
  - Influenza vaccination is permitted if the inactivated vaccine formulation is administered.
- Inability to complete an MRI (contraindications for MRI for example, due to, pacemaker, cochlear implants, intracranial vascular clips, surgery within 6 weeks of entry in the study, coronary stent implanted within 8 weeks prior to the time of the intended MRI, etc.) or contraindication to gadolinium administration
- Contraindications to mandatory premedications (i.e., corticosteroids and antihistamines), including closed-angle glaucoma for antihistamines
- Known presence of other neurologic disorders that could interfere with the diagnosis of MS or assessments of efficacy and/or safety during the study, including, but not limited to, the following:
  - History of hemorrhagic or ischemic cerebral or spinal stroke

  - History or known presence of central nervous system (CNS) or spinal cord tumor (e.g., meningioma, glioma)
  - History or known presence of potential metabolic causes of myelopathy (e.g., untreated vitamin B12 deficiency)
  - History or known presence of infectious causes of myelopathy (e.g., syphilis, Lyme disease, HTLV-1, herpes zoster myelopathy)
  - History of genetically inherited progressive CNS degenerative disorder (e.g., hereditary paraparesis, mitochondrial myopathy, encephalopathy, lactic acidosis, stroke [MELAS] syndrome)
  - Neuromyelitis optica
  - History or known presence of systemic autoimmune disorders potentially causing progressive neurologic disease (e.g., lupus, anti-phospholipid antibody syndrome, Sjögren syndrome, Behçet disease)
  - History or known presence of sarcoidosis
  - History of severe, clinically significant brain or spinal cord trauma (e.g., cerebral contusion, spinal cord compression)
- Any concomitant disease that may require chronic treatment with systemic corticosteroids (e.g. mineralocorticoids and glucocorticoids) 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 or gastrointestinal, or any other significant disease that may preclude patient from participating in the study
- History of or currently active primary or secondary (non–drug-related) immunodeficiency
- Pregnant or breastfeeding, or intending to become pregnant during the study and 6 or 12 months (as applicable by the ocrelizumab [Ocrevus] local label) after last administration of the study drug.
  - Females of childbearing potential must have a negative serum and urine pregnancy test result prior to initiation of study drug (negative serum β-CG measured at screening and negative urine β-CG at baseline)
- Lack of peripheral venous access
- History of alcohol or other drug abuse within 12 months prior to screening
- Treatment with any investigational agent within 24 weeks prior to screening or 5 half-lives of the investigational drug (whichever is longer), or treatment with any experimental procedure for MS (e.g., treatment for chronic cerebrospinal venous insufficiency)
- Patients who have previously received anti-CD20s (including ocrelizumab) if the last treatment was less than 2 years before screening, and/or if B-cell count is below lower limit of normal, and/or the discontinuation of the treatment was due to safety reasons or lack of efficacy.
- Previous treatment with cladribine, atacicept, and alemtuzumab
- Previous treatment with fingolimod, siponimod, ponesimod, or ozanimod within 6 weeks of baseline
- Previous treatment with interferons beta (1a or 1b), or glatiramer acetate within 2 weeks of baseline
- Previous treatment with natalizumab within 4.5 months of baseline
- Treatment with mitoxantrone within 2 years prior to baseline visit or evidence of cardiotoxicity following mitoxantrone use or a cumulative lifetime dose of more than 60 mg/m^2

  - Previous treatment with any other immunomodulatory or immunosuppressive medication not already listed above without appropriate washout as described in the applicable local label. If the washout requirements are not described in the applicable local label (washout to be completed prior to baseline), then the wash out period must be 5 times the half-life of the medication. The PD effects of the previous medication must also be considered when determining the required time for washout.
  - Patients screened for this study should not be withdrawn from therapies for the sole purpose of meeting eligibility for the trial.
- Any previous treatment with bone marrow transplantation and hematopoietic stem cell transplantation
- Any previous history of transplantation or anti-rejection therapy
- Treatment with IV Ig or plasmapheresis within 12 weeks prior to randomization
- Systemic corticosteroid therapy within 4 weeks prior to screening
  - The screening period may be extended for patients who have used systemic corticosteroids for MS before screening. For a patient to be eligible, systemic corticosteroids should also not have been administered between screening and baseline.
- Positive screening tests for active, latent, or inadequately treated hepatitis B (as evidenced by either of the following):
  - Positive hepatitis B surface antigen
  - Positive hepatitis B core antibody (total HBcAb) and detectable hepatitis B virus DNA
- Sensitivity or intolerance to any ingredient (including excipients) of ocrelizumab
- Any additional exclusionary criterion as per ocrelizumab (Ocrevus®) local label, if more stringent than the above

END OF STUDY

The end of study will occur when the last participating patient completes the last scheduled visit at the end of the safety follow-up phase, or when the Sponsor decides to discontinue the study or development program.

LENGTH OF STUDY

Each patient will be in the treatment phase for up to 2 years (i.e., 96 weeks) and in the safety follow-up phase for up to 24 weeks after the last ocrelizumab administration.

INVESTIGATIONAL MEDICINAL PRODUCTS

The investigational medicinal product (IMP) for this study is ocrelizumab (comprising both the IV formulation and the SC formulation co-formulated with rHuPH20).

Test Product (Investigational Drug)

Ocrelizumab SC will be provided as a sterile, single-dose liquid at a concentration of 40 mg/mL and contains no preservatives. The ocrelizumab in the ocrelizumab SC formulation is co-formulated with rHuPH20 at a concentration of 1000 U/mL.

For information on the formulation of ocrelizumab SC co-formulated with rHuPH20, see the pharmacy manual and the Ocrelizumab Investigator's Brochure.

Comparator

Ocrelizumab IV will be provided as a sterile, single-dose liquid at a concentration of 30 mg/mL and contains no preservatives.

For information on the formulation of IV ocrelizumab, refer to the Ocrelizumab Investigator's Brochure, local prescribing information, and pharmacy manual.

NON-INVESTIGATIONAL MEDICINAL PRODUCTS

Specific premedications are required prior to the ocrelizumab infusion or injection and include mandatory methylprednisolone or dexamethasone, mandatory diphenhydramine or desloratadine, and optional oral analgesics as needed.

STATISTICAL METHODS

PRIMARY ANALYSIS

The primary objective for this study is to establish the non-inferiority of ocrelizumab SC compared with ocrelizumab IV on the basis of serum ocrelizumab area under the concentration-time curve (AUC) up to Week 12 (AUC_{W1-12}). The geometric mean ratio (GMR) of AUC SC versus AUC IV will be presented, together with the two-sided 90% confidence interval. The non-inferiority would be established if the lower end of the two-sided 90% CI of the GMR of AUC is >0.8. The non-inferiority limit of 0.8 corresponds to a maximal 20% loss in AUC for the SC administration compared with IV. All available results for PK samples obtained during the first 12 weeks will be included in the PK analysis. The primary comparison between SC and IV administered ocrelizumab will be based on the AUC_{W1-12} (i.e., over the first 3 months of the 6 monthly dosing interval after first dose), as absorption is expected to be complete by Week 12.

DETERMINATION OF SAMPLE SIZE

If the observed coefficient of variation (CV) in either the SC or IV arm of the CN41144 study at the time of the data snapshot is greater than these assumed values, then the sample size for this study may be increased to maintain the desired study power.

INTERIM ANALYSES

No interim analyses are planned.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ANC	absolute neutrophil count
AUC	area under the concentration-time curve
AUC_T	area under the curve over the 6-month dosing interval
AUC_{W1-12}	area under the concentration–time curve from Day 1 to Week 12
CCOD	clinical cutoff date
CIS	clinically isolated syndrome
ClinRO	clinician reported outcome
C_{max}	maximum concentration observed
CNS	central nervous system
COVID-19	coronavirus disease-2019
CV	coefficient of variation
DMT	disease-modifying treatments
E.U.	European Union
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EDSS	expanded disability status scale
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
FLAIR	fluid-attenuated inversion recovery
FSH	follicle stimulating hormone
FSS	functional system score
GMR	geometric mean ratio
HBcAb	hepatitis B core antibody
HBcAg	hepatitis B core antigen
HBV	hepatitis B
HIPAA	Health Insurance Portability and Accountability Act
IB	investigator’s brochure
ICH	International Council for Harmonisation
iDMC	internal data monitoring committee
Ig	immunoglobulin
IMP	investigational medicinal product

IND	investigational new drug (Application)
IRB	Institutional Review Board
IRR	infusion-related reaction
ISR	injection site reaction
IV	intravenous
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MN	mobile nursing
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSTPQ	multiple sclerosis treatment preference questionnaire
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NfL	neurofilament light
PCR	polymerase chain reaction
PD	pharmacodynamics
PGI-SF	*patient global impression of satisfaction*
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PMS	progressive multiple sclerosis
PPMS	primary progressive multiple sclerosis
PPQ	Patient Preference Questionnaire
PRO	patient-reported outcome
PT	preferred term
PTP	previously treated patients
RBC	red blood cell
RBR	research biosample repository
rHuPh20	recombinant human hyaluronidase PH20
RMS	relapsing multiple sclerosis
ROW	rest of world
RRMS	relapsing remitting multiple sclerosis
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SFU	safety follow-up
SmPC	summary of product characteristics
SPMS	secondary progressive multiple sclerosis
T1Gd+	gadolinium-enhancing lesions on T1-weighted
TASQ	Treatment Administration Satisfaction Questionnaires

WBC	white blood cell
WES	whole exome sequencing
WGS	whole genome sequencing
U.S.	United States of America
USPI	United States prescribing information

1. BACKGROUND

1.1 BACKGROUND ON MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, and degenerative disease of the central nervous system (CNS) that affects approximately 900,000 people in the United States (Wallin et al. 2019) and 2.8 million worldwide (MSIF 2020).

It is primarily a disease of young adults, with patients usually being diagnosed between the ages of 20 and 40 (Calandri et al. 2019), and a mean age of diagnosis of approximately 30 years (GBD 2016). MS is at least two to three times more frequent in women than in men, except in primary progressive multiple sclerosis (PPMS) where men and women are equally affected (MSIF 2020; Bove and Chitnis 2014).

MS is classified into three clinical phenotypes: relapsing remitting (RRMS), secondary progressive (SPMS), and PPMS (Lublin et al. 2014). These three phenotypes are further subdivided into active and non-active forms based on the presence or absence of disease activity, which in turn is defined by the presence of clinical relapses and/or so-called active lesions on a magnetic resonance imaging (MRI) scan. Active MRI lesions are gadolinium-enhancing lesions on a T1-weighted scan (T1Gd+), or new/enlarging T2-weighted lesions. The term relapsing MS (RMS) encompass RRMS and early stages of (active) SPMS where patient still experience relapses (Lublin et al. 2014); and progressive MS (PMS) forms constitute non-active SPMS and PPMS (Lublin et al. 2014). Evidence available to date suggests that despite the potential heterogeneity of the clinical expression of the disease, PPMS, SPMS, and RRMS belong to the same disease spectrum, and that pathological mechanisms responsible for relapses/disease activity and progression biology are largely identical across the MS spectrum (Lassmann 2018). Although the mechanisms associated with disease progression are assumed to be present from the onset of the disease (Cree et al. 2019), clinical disability progression manifests often later in the course of a patient's disease, most likely due to the degree of brain reserve of the patient. The symptomatic worsening associated with MS disability progression results in a slow, insidious loss of a patient's motor and sensory function, as well as cognitive decline and autonomic dysfunctions (Lassmann 2018).

Disability progression across the spectrum of MS might occur as a result of two concurrent inflammatory mechanisms: acute inflammation and chronic compartmentalized inflammation (Matthews 2019).

Acute inflammation can be observed on an MRI scan (as T1Gd+ lesions or new or enlarging T2 lesions) and clinically manifests as relapses, where it can also lead to step-wise increase of disability due to incomplete relapse recovery. Pathophysiologically, relapsing forms of MS (i.e., RMS) are associated with focal T-cell and B-cell invasion, with blood brain barrier leakage that gives rise to classic active

demyelinating plaques in the white matter. However, RMS also harbors signs of progression biology/chronic compartmentalized inflammation.

In contrast to these acute inflammatory processes, chronic compartmentalized inflammation is responsible for an increase in disability that occurs independently from relapses or radiological disease activity and is characterized by demyelination and axonal loss (progression biology; Lassmann 2019). Progressive forms of MS are associated with a chronic and slow accumulation of T cells and B cells in the connective tissue spaces of the brain, without leakage of the blood brain barrier. There is a typical formation of subpial-demyelinated lesions in the cerebral and cerebellar cortex, with slow expansion of pre-existing lesions in the white matter and diffuse chronic inflammation in the normal-appearing white or gray matter (Lassmann 2019).

1.2 BACKGROUND ON OCRELIZUMAB

Ocrelizumab is a recombinant humanized, glycosylated, monoclonal IgG1 antibody that selectively targets and depletes CD20-expressing B cells, while preserving the capacity of B-cell reconstitution and preexisting humoral immunity. CD20 is a B-cell surface molecule that is restricted in expression to pre–B cells and mature B cells but is not expressed earlier in the development of B cells (Banchereau and Rousset 1992).

Refer to the Ocrelizumab Investigator's Brochure for relevant non-clinical, formulation, and clinical safety information for both IV and SC formulations.

1.2.1 Ocrelizumab Administered Intravenously

Based on the results of Phase III studies in patient populations with RMS and PPMS, ocrelizumab was approved by the U.S. Food and Drug Administration (FDA) on 28 March 2017 for the treatment of adult patients with RMS and PPMS. The indication for RMS was updated in 2019, at the FDA's request, to include clinically isolated syndrome (CIS), RRMS, and active SPMS. Ocrelizumab was approved by the European Medicines Agency (EMA) on 12 January 2018 for patients with active relapsing forms of MS defined by clinical or imaging features and for patients with early PPMS in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.

Two identical randomized, active-controlled studies (OPERA I [Study WA21092] and OPERA II [Study WA21093]) have demonstrated superior efficacy outcomes of ocrelizumab 600 mg versus interferon β-1a in patients with RMS (Hauser et al. 2017); one randomized placebo-controlled study (ORATORIO [Study WA25046]) has demonstrated superior efficacy of ocrelizumab 600 mg in PPMS versus placebo (Montalban et al. 2017). Results of these studies show that depletion of CD20+ B cells leads to a significant impact on a broad range of clinical measures of disease, including disability progression, in addition to an impact on MRI outcomes related to disease progression and reflective of neural tissue loss, thus further supporting the hypothesis that B cells are central to the pathogenesis of both RMS and PPMS. Ocrelizumab has

demonstrated a favorable safety profile in patients with RMS and PPMS (Hauser et al. 2017; Montalban et al. 2017). The proportion of patients with adverse events (AEs) was similar in patients treated with ocrelizumab compared with interferon β-1a (both 83.3%) or placebo (95.1% vs. 90.0%). The proportion of patients experiencing at least one serious adverse event was similar between ocrelizumab and the comparator groups (in RMS: 6.9% [ocrelizumab] and 8.7% [interferon β-1a]; in PPMS: 20.4% [ocrelizumab] and 22.2% [placebo]). Analysis of the data from open-label extension of the pivotal studies supported the long-term consistency of benefit-risk (Hauser et al. 2019).

Ocrelizumab is administered by intravenous (IV) infusion at a dose of 600 mg over 2 to 3.5 hours every 6 months. The first ocrelizumab dose of 600 mg is administered as a divided dose (2×300 mg infusions administered 2 weeks apart) with subsequent doses being administered as a single 600 mg infusion.

1.2.2 Ocrelizumab Administered Subcutaneously

A subcutaneous (SC) formulation of ocrelizumab co-formulated with rHuPH20 (herein ocrelizumab SC) is under development for administration of ocrelizumab as an SC injection. This new route of administration will provide a convenient and faster alternative to the currently approved IV infusion. Ocrelizumab SC formulation is to be administered as a single injection every 6 months. In addition, to support dosing outside of a controlled healthcare setting, including home administration for eligible patients, the Sponsor has started technical development of a medical device (an on-body injector).

A pharmacokinetic (PK)-bridging program composed of OCARINA I (CN41144, ongoing Phase Ib SC dose-selection study) and this proposed study (OCARINA II, CN42097, Phase III SC study) will be conducted in patients with MS, with the overall goal to demonstrate non-inferiority of ocrelizumab exposure between the approved IV dose and the proposed SC dose in terms of area under the concentration-time curve (AUC). Safety, tolerability, pharmacodynamics, and immunogenicity after SC administration of ocrelizumab facilitated by rHuPH20 will be assessed in both OCARINA I and in this study (OCARINA II). The PK non-inferiority is expected to translate into non-inferior efficacy and safety, as per the principle of PK bridging (Shpilberg et al. 2013; Hourcade et al. 2014).

1.2.2.1 Recombinant Human Hyaluronidase (rHuPH20)

rHuPH20 is a human hyaluronidase for injection that has been developed by Halozyme Therapeutics, Inc. rHuPH20 hydrolyzes hyaluronan, a component of the SC matrix, leading to a temporary reduction in the viscosity of the extracellular matrix of the hypodermis. This allows for large volume, rapid delivery of subcutaneously administered drugs. The recombinant human molecule has greater purity than animal-derived hyaluronidases and therefore has higher enzymatic activity per mass (refer to Hylenex® U.S. Prescribing Information (USPI), for additional details on the composition and formulation). rHuPH20 has been approved by the U.S. FDA for various indications,

including increasing the dispersion and absorption of other injected drugs (Hylenex® U.S. USPI) and is used primarily as a permeation enhancer.

To date, four monoclonal antibodies co-formulated with rHuPH20, are approved for SC therapy in the United States and four in the European Union (Phesgo® USPI, Phesgo® Summary of Product Characteristics [SmPC],Darzalex Faspro™ USPI, Herceptin Hylecta® USPI; Herceptin®SC SmPC; Rituxan HYCELA® USPI; Mabthera® SC SmPC).

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Appropriate care and treatment access have been identified by both healthcare providers and patients as key contributing factors to the successful management of MS (Rieckmann 2017). Patients with MS are offered a number of biologic therapies that are provided by different administration routes and in a variety of different settings, ranging from in-office neurology practices, hospital-affiliated settings to even free-standing infusion centers, which offer services to patients afflicted with a variety of medical conditions, such as in hematology and oncology (Foley and Dunne 2011). However, these centers often face considerable challenges when administering infusion therapies; larger scale centers often have to optimize the number of staff, as well as schedule patients who require longer infusion times. Thus, an alternative and more convenient method of administration with a shorter treatment duration is expected to improve access for patients with MS who would prefer another treatment administration besides the approved IV method.

The marketed formulation of ocrelizumab is given by IV infusion over 2 to 3.5 hours and requires monitoring throughout. Patients often have to set aside substantial time to receive an infusion at the hospital when considering transit to and from the institution, lead time for IV premedication, the infusion itself and the 1-hour post-infusion monitoring. This effort creates both a burden on patients (i.e., considerable time for treatment administration before returning to daily activities) and a burden of patient management for healthcare providers. An alternative SC dosing form with a shorter administration time may be preferred by some patients and healthcare providers, and could reduce drug administration related costs and resources (Bax and Postma 2013; Burcombe et al. 2013; Pereira and Santos 2013; Pivot et al. 2013; Tetteh and Morris 2014; Ariza 2015; De Cock et al. 2016; Rule et al. 2017; Rummel et al. 2017; Tjalma et al. 2018).

Ocrelizumab SC co-formulated with rHuPh20 can be administered in a shorter period compared to the approved ocrelizumab IV infusion and has the potential to deliver clinical benefit with reduced treatment burden, improved resource use, and increased patient convenience. In the context of the current global demand for increased efficiencies in healthcare delivery, it also has the potential to relieve stretched capacity at infusion centers. The co-formulation of ocrelizumab SC with rHuPH20 is ready-to-use and planned to allow administration by, or with assistance from, a healthcare professional at the patient's home following initial treatments in the clinic or hospital setting. Moreover, patients with MS often have reduced mobility. Attending a healthcare

institution represents an additional risk for such patients being at peril of falls or other accidents during transit.

Available data for subcutaneously administered monoclonal antibodies (trastuzumab [Herceptin®] and rituximab [MabThera®/Rituxan®]) consistently demonstrate that efficacy remains the same regardless of administration route (Ismael et al. 2012; Davies et al. 2014; Assouline et al. 2015); furthermore, some patients prefer SC to IV administration (Pivot et al. 2013; Rummel et al. 2015).

The proposed study will be conducted in patients with RMS and PPMS, with the overall goal of demonstrating non-inferiority in serum ocrelizumab exposure for the SC route of administration versus IV infusions, and to assess the pharmacodynamics, safety, immunogenicity, and radiological and clinical effects of ocrelizumab after SC injection.

It is expected that SC administration of ocrelizumab will result in reduced treatment burden, increased patient satisfaction, and improved cost-effectiveness, while maintaining an efficacy and safety profile comparable to the approved IV route of administration of ocrelizumab.

The efficacy and the general adverse event profile of the approved IV route of administration of ocrelizumab have been well characterized in the ocrelizumab IV trials and post-marketing experience (see the Ocrelizumab Investigator's Brochure).

The benefit–risk assessment for conducting the current Phase III study with the 920 mg dose of ocrelizumab SC is based on PK and safety data up to the highest tested dose of 1200 mg in all treated patients in the ongoing Phase I study (OCARINA I).

The SC dose of 920 mg was selected so that the 25th percentile in the exposure (AUC_T) distribution matches the 25th percentile in the exposure distribution after 600 mg IV ocrelizumab dosing. Per PK bridging principles, this is expected to translate into non-inferior efficacy, and the OCARINA II study will provide safety information for ocrelizumab SC complemented by clinical and radiological information.

In OCARINA I, as of 7 May 2021, following a conservative dose escalation approach where 21 patients received increasing doses of ocrelizumab SC (40 mg, 200 mg, and 600 mg), a total of 88 patients received ocrelizumab SC as part of the dose escalation. Additionally, a total of 96 patients have received at least one dose of 1200 mg ocrelizumab SC in this study.

No new safety signals have been identified for ocrelizumab SC when compared with ocrelizumab IV. Safety data generated to date confirm that the overall safety profile reported for ocrelizumab SC is comparable to that which is well established for ocrelizumab IV (see the Ocrelizumab Investigator's Brochure).

Risk mitigations measures are in place to closely monitor the overall patient safety during the conduct of this study, including an assessment by an independent Data Monitoring Committee (iDMC).

Overall, the benefits versus the risks for individual participants treated with the ocrelizumab SC dose of 920 mg and study-related procedures remains unchanged compared with IV formulation and support continuation of the SC development program with this identified dose.

1.3.1 Benefit–Risk Assessment of the Conduct of the Study During the COVID-19 Pandemic

An assessment was conducted to determine whether there is any impact of the COVID-19 pandemic on the benefit–risk assessment of this study protocol including, but not limited to, the patient population under study, study treatment(s) and/or treatment combination being evaluated. Based on that assessment, no impact is anticipated and the existing safety monitoring and management guidelines, and risk mitigation measures provided in the study protocol are considered adequate.

The available safety data from patients with MS treated with ocrelizumab to date suggests that COVID-19 follows a similar course in these patients as in the general population, with risk factors for severe COVID-19 that are similar in the general population, the overall MS population, and in those treated with ocrelizumab.

The protocol's eligibility criteria mitigate the known risk factors for severe COVID-19 outcomes, such as older age, more advanced MS disease status, and presence of relevant comorbidities, and exclude patients with MS with any known or suspected active infection (including COVID-19, based on the investigator's assessment) from participating in the study. As per Section 4.3.2.3, absence of active infection is also required for patients to receive further retreatment with ocrelizumab.

A SC dose of ocrelizumab is expected to provide similar benefit for patients in controlling MS disease compared with the approved IV dose.

In summary, protocol-mandated safety monitoring and management guidelines, study eligibility criteria, and the ocrelizumab retreatment criteria are considered appropriate in the context of conducting the study during the COVID-19 pandemic. Investigators should manage COVID-19 in the same way as infections caused by any other pathogen.

1.3.2 Risk Assessment for Concomitant Use of a COVID-19 Vaccine

A benefit–risk assessment was conducted to determine whether there is any impact on the concomitant use of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines on the conduct of this study. Based on this assessment, no interaction between the concomitant use of SARS-CoV-2 vaccines and ocrelizumab has been identified. There is no anticipated impact affecting the efficacy and safety of ocrelizumab

in patients enrolled in ocrelizumab clinical trials. Existing key safety information as described in the protocol (see Sections 4.4.4 and 5.1.1.1), safety monitoring, and risk mitigation measures related to administration of vaccines (including those for SARS-CoV-2) are considered adequate.

As described in Section 5.1.1.1, data from the pivotal Phase III studies of ocrelizumab in RMS and PPMS show that preexisting humoral immunity to common viral and bacterial antigens is not affected by ocrelizumab treatment. Additionally, for patients receiving vaccines while treated with ocrelizumab, the vaccination study BN29739 (VELOCE) showed that people with MS treated with ocrelizumab were able to mount a humoral immune response to non-live vaccines and new antigens. The antibody immune response was considered protective, albeit with reduced levels of antibodies compared to controls. In that study, vaccines were given as early as 12 weeks following the first ocrelizumab infusion (as early as 10 weeks following the second ocrelizumab infusion of the first dose). Booster doses were given at least 4 weeks before the next dose of ocrelizumab. Other immune responses, such as cellular responses were not investigated in the VELOCE study.

Roche is continually collecting evidence from clinical and biological sources to better understand immune response mechanisms of the SARS-CoV-2 vaccine in ocrelizumab-treated patients.

As with any other medication or vaccine, SARS-CoV-2 vaccines should be reported as concomitant medication by using the standard fields in the clinical database (see Section 4.4.4, and medical history, baseline conditions, concomitant medications, and demographic data Section 4.5.2).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the pharmacokinetics, pharmacodynamics, safety, immunogenicity, and radiological and clinical effects of SC administration of ocrelizumab compared with the IV infusion *of ocrelizumab* in patients with either RMS or PPMS. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 PHARMACOKINETIC OBJECTIVE

2.1.1 Primary Pharmacokinetic Objective

The primary PK objective of this study is to demonstrate PK non-inferiority of the SC formulation of ocrelizumab in patients with MS on the basis of the following endpoint:

- Serum ocrelizumab area under the concentration–time curve (AUC_{W1-12}) after SC administration compared to IV infusion from Day 1 to Week 12.

2.1.2 Secondary Pharmacokinetic Objective

The secondary PK objective of this study is to determine the maximum serum concentration (C_{max}) of ocrelizumab SC in patients with MS.

2.2 RADIOLOGICAL AND CLINICAL OBJECTIVES

2.2.1 Secondary Radiological Objective

The secondary radiological objective for this study is to evaluate the radiological effects of ocrelizumab SC compared with ocrelizumab IV in patients with MS on the basis of the following endpoints:

- Total number of T1Gd+ lesions as detected by brain MRI at Weeks 8 and 24
- Total number of new or enlarging T2 lesions as detected by brain MRI at Weeks 12 and 24 relative to the previous scan, respectively

2.2.2 Exploratory Radiological and Clinical Objective

The exploratory radiological and clinical objective for this study is to explore the radiological and clinical effects of ocrelizumab SC compared with ocrelizumab IV in patients with MS on the basis of the following endpoints:

- Total number of T1Gd+ lesions as detected by brain MRI at Week 48 *and Week 96*
- Total number of new or enlarging T2 lesions as detected by brain MRI at Weeks 8, 48, *and 96* relative to the previous scan, respectively
- The annualized protocol-defined relapse rate by Weeks 24, 48, *and 96* in RMS patients
- Change from baseline in the expanded disability status scale (EDSS) at Week*s* 48, *72 and 96*

2.3 PATIENT-REPORTED OBJECTIVE

The exploratory patient-reported outcome (PRO) objective for this study is to evaluate patient preference and satisfaction for ocrelizumab SC and IV in relation to other disease-modifying treatments (DMTs) taken prior to the study, as well as preference for the SC or IV route of administration in a subset of patients:

- Patient satisfaction and experience receiving SC administration (at site and at home) and IV route of administration:
  - Patient administration satisfaction and experience scores using the Treatment Administration Satisfaction Questionnaires (TASQ) for IV Infusion following the first treatment administration in a subset of patients
  - Patient administration satisfaction and experience scores using the TASQ for SC injection
- Patient satisfaction and preference taking ocrelizumab administered SC compared to previous DMTs taken prior to the study:
  - Entry treatment experience questions to report overall treatment satisfaction scores from patients who received an MS treatment prior to the study
  - MS treatment preference score to report overall satisfaction taking ocrelizumab
  - MS treatment preference score to report the proportion of patients with a preference for ocrelizumab SC compared to previously taken DMTs

- Patient preference for the SC or IV route of administration, specifically:
  - Proportion of patients who prefer the SC or IV route of administration using the Patient Preference Questionnaire (PPQ).
- *Patient global impression of overall satisfaction (PGI-SF) for SC ocrelizumab*
  - *Proportion of patients who are satisfied or dissatisfied with ocrelizumab SC as a treatment for their MS symptoms*

2.4 SAFETY OBJECTIVE

The safety objective of this study is to evaluate and compare the safety profile after administration of ocrelizumab SC versus ocrelizumab IV and to assess the safety of ocrelizumab SC at the selected dose in patients with MS on the basis of the following endpoints during the conduct of the study:

- Incidence and severity of adverse events, with severity determined according to the NCI CTCAE version 5.0
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

2.5 IMMUNOGENICITY OBJECTIVE

The immunogenicity objective for this study is to evaluate the immune response to ocrelizumab SC and IV, and rHuPH20, based on the following endpoints:

- Incidence of treatment-emergent anti-drug antibodies (ADAs; formation of ADAs) to ocrelizumab after SC or IV administration relative to the presence of ADAs at baseline
- Relationship between ADA status to ocrelizumab and pharmacokinetics, pharmacodynamics, and safety
- Incidence of treatment-emergent antibodies to rHuPH20 after SC administration relative to the presence at baseline and relationships between antibodies to rHuPH20 and safety

2.6 PHARMACODYNAMIC OBJECTIVE

The pharmacodynamic (PD) objective for this study is to evaluate the effect of SC ocrelizumab compared with IV ocrelizumab on the PD marker for the mechanism of action of ocrelizumab (i.e., B cell depletion) on the basis of the following endpoint:

- Proportion of patients achieving CD19+ B cell level $\leq$5 cells/μL at Weeks 12*, 24, 48, and/or 96*

2.7 BIOMARKER OBJECTIVE

The *exploratory* biomarker objective for this study is to evaluate biomarkers that are predictive of response to ocrelizumab (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), can provide evidence of ocrelizumab activity (i.e., PD

biomarkers), or can increase the knowledge and understanding of disease biology, on the basis of the following endpoints:

- Levels of biomarkers including but not limited to neurofilament light (NfL) in serum compared between dosing arms at Weeks 12, 24, 48, *and/or 96* compared to baseline

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

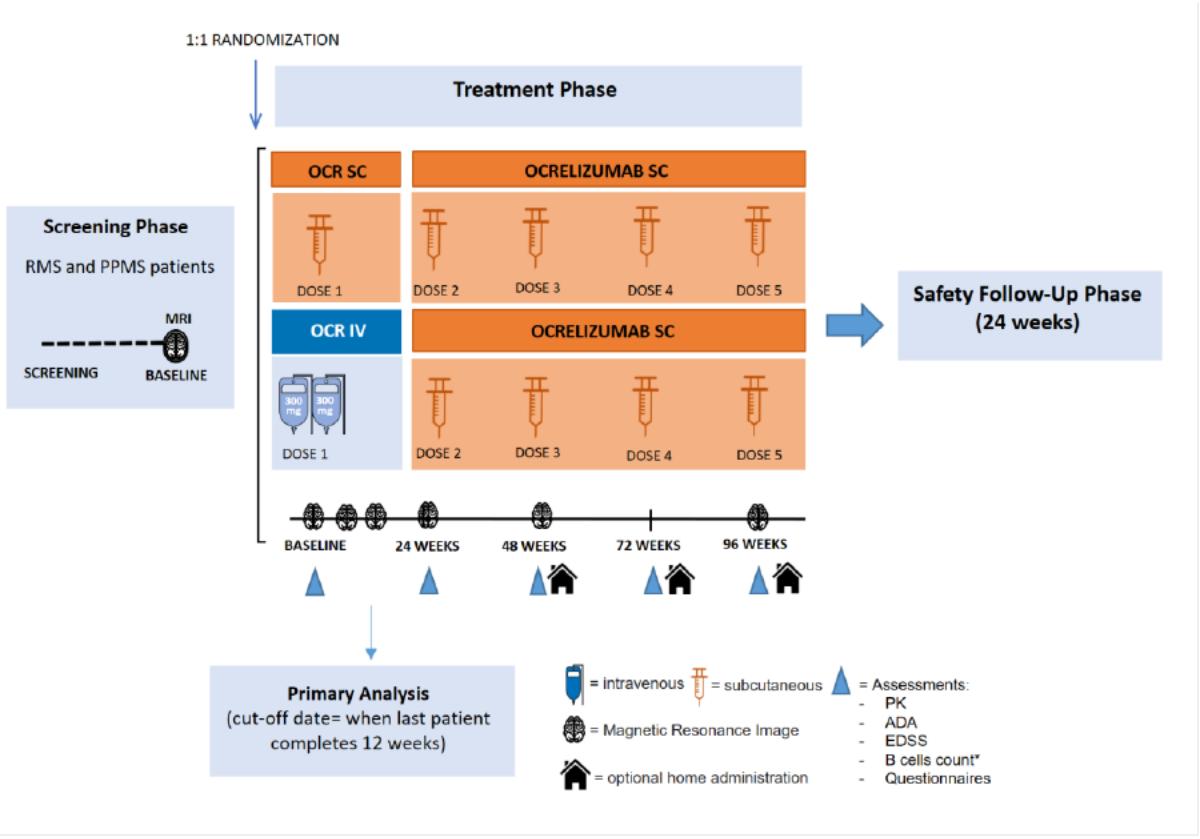
CN42097 is a Phase III non-inferiority, randomized, open-label, parallel group, multicenter study to evaluate the pharmacokinetics, pharmacodynamics, safety, immunogenicity, radiological, and clinical effects of SC administration of ocrelizumab compared with the IV infusion of ocrelizumab in patients with either RMS or PPMS.

The study will consist of the following study phases:

- Screening
- Treatment (controlled period and SC ocrelizumab treatment period)
- Safety follow-up (SFU)

The study design is shown in Figure 1.

Figure 1 Study Schema



ADA=anti-drug antibody; EDSS=expanded disability status scale *(performed at the site)*; IV=intravenous; MRI=Magnetic Resonance Image; OCR=ocrelizumab; PK=pharmacokinetics; PPMS=primary progressive multiple sclerosis; RMS= relapsing multiple sclerosis; SC=subcutaneous.

3.1.1 Overview of Study Phases

3.1.1.1 Screening

The screening phase will last up to 6 weeks. Patients who are candidates for enrollment into the study will also be evaluated by the investigator prior to randomization to ensure all eligibility criteria continue to be met (see Section 4.1, Appendix 1, and Appendix 2). All patients must sign the Informed Consent Form prior to screening and enrollment in the study. Patients providing informed consent will undergo screening prior to the study drug administration.

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for two re-screening opportunities at the investigator's discretion. Patients are not required to re-sign the consent form if they are re-screened within 90 days after previously signing the consent form. The investigator will record reasons for screen failure in the screening log and in the IxRS.

3.1.1.2 Treatment

Patients will be recruited globally.

All patients will receive *five* ocrelizumab doses (Day 1, Week 24*,* Week 48*, Week 72, and Week 96*) during the treatment phase (see Figure 1). Eligible patients will be randomly assigned to one of two treatment arms: ocrelizumab SC dose or ocrelizumab IV dose. Randomization will occur in a 1:1 ratio and will be performed through an interactive voice or web-based response system (IxRS).

The first study drug administration should occur within 24 hours of randomization (in exceptional cases within 48 hours of randomization provided that the investigator assures that all inclusion and exclusion criteria are still met on the day of dosing).

During the controlled period (i.e., time until the Week 24 dose of ocrelizumab SC), the first dose of ocrelizumab SC will be given as one SC injection at a dose of 920 mg. The first dose of ocrelizumab IV will be administered as two 300 mg IV infusions given 2 weeks apart. Every effort should be made to perform all assessments required during the controlled period (e.g., MRI) before the administration of the second dose. The subsequent doses of study drug will be administered as SC injections for all patients, including those initially randomized to ocrelizumab IV (ocrelizumab SC treatment period*, Appendix 3 and Appendix 4*).

For patients randomized in the ocrelizumab IV group, there should be a minimum of 20 weeks between the administration of the final ocrelizumab IV infusion and the first ocrelizumab SC dose (i.e., between the IV infusion at Week 2/Study Day 14 and the first SC dose during Week 24). There should be a minimum of 22 weeks between all SC doses.

To allow for the possibility of home administration at participating sites, *from the third* ocrelizumab dose *onwards* (i.e., Week 48 *onwards*, Appendix 4) *the ocrelizumab dose can* be administered by a healthcare professional at the patient's home or another suitable location. The patient will need to provide an informed consent (refer to Section 4.5.10) and the investigator will determine if the patient is eligible for home administration (Sections 4.5.10 and 4.3.2.3).

Patients who withdraw from treatment during the treatment phase for any reason should return to the site to complete an early termination visit and perform the assessments required during the controlled period (e.g., MRI), as indicated in the schedule of activities (Appendix 1 and Appendix 2). They are encouraged to enter and complete the safety follow-up phase (refer to Section 3.1.1.3).

An iDMC will be employed to monitor and evaluate patient safety throughout the study, until the last patient received their last dose of ocrelizumab. Monitoring details will be described in the iDMC Charter.

3.1.1.3 Safety Follow-Up

Patients who complete the treatment or discontinue from the treatment early will be asked to return to the clinic 24 weeks after the last dose of study drug. Refer to Section 4.3.4 and Section 4.4.2 for treatment options offered to patients.

All patients will be followed for up to *24* weeks after the last ocrelizumab administration. During the safety follow-up visit, a physical examination, neurologic examination, recording of adverse events, hematology, blood chemistry, urinalysis, pharmacokinetics, B cells in blood, biomarker and ADA assessments will be performed.

There is the option to collect information about the patient's planned post-study MS treatment at the 24-week safety follow-up visit.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of study will occur when the last participating patient completes the last scheduled visit at the end of the safety follow-up phase, or when the Sponsor decides to discontinue the study or development program.

Each patient will be in the treatment phase for up to *2* years (i.e., *96* weeks) and in the safety follow-up phase for up to *24* weeks after the last ocrelizumab administration.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Pharmacokinetic Primary Endpoint

Non-inferior ocrelizumab exposure, measured as the AUC, between the SC formulation and the IV formulation is expected to translate into comparable efficacy and safety outcomes, as per the principle of PK bridging (Shpilberg et al. 2013, Hourcade et al. 2014).

The difference between SC and IV administration of ocrelizumab is in the absorption process from the SC injection site versus direct IV infusion. Systemic distribution and elimination is independent of the route of administration. As absorption is expected to be completed within 12 weeks post-injection, AUC up to Week 12 is judged to be representative of the overall ocrelizumab exposure over the 6 monthly dosing interval. Therefore, ocrelizumab $AUC_{W1\text{-}12}$ will be assessed as the primary endpoint in this study.

3.3.2 Rationale for Ocrelizumab SC Dose and Schedule

The dose of 920 mg SC was selected based on the PK and safety data obtained in the currently ongoing Study CN41144 (OCARINA I). In this study, SC doses up to 1200 mg have been administered and were safe and well tolerated. SC bioavailability was estimated with 72%. Rapid B cell depletion in ocrelizumab treatment-naïve patients, and maintenance of B cell depletion throughout the six–month dosing interval in pre-treated patients, was obtained after 1200 mg ocrelizumab SC.

The SC dose of 920 mg was selected such that the ocrelizumab exposure in patients after SC administration matches the exposure after the approved and marketed dose of 600 mg IV. As variability after SC administration is larger than after IV administration, the SC dose of 920 mg was selected so that the 25th percentile in the exposure (AUC_T) distribution matches the 25th percentile in the exposure distribution after IV 600 mg dosing. This ensures that patients on the lower range of the exposure distribution will have adequate exposure.

For the IV administration, the initial 600 mg dose is divided into 2×300 mg. For SC administration, this is not required, as one single dose of up to 1200 mg was well tolerated in ocrelizumab treatment-naïve patients. Therefore, all SC doses in OCARINA II will be given as a single SC injection. Absorption after SC injection is slow (C_{max} between Day 2 and Day 10, based on currently available data from OCARINA I). SC injection of the total dose on Day 1 will help to achieve the onset of efficacy with similar speed versus the IV infusions, for which the systemic availability of the total dose is complete on Day 14.

In conclusion, a dose of 920 mg ocrelizumab SC is expected to provide comparable exposure to the approved 600 mg ocrelizumab IV dose, and has therefore been selected for this study.

3.3.3 Rationale for Control Group

In order to evaluate PK non-inferiority of the SC formulation of ocrelizumab versus the approved 600 mg IV dose, an IV reference arm has been included in the study. This ensures the same PK sample procedures, same bioanalytical assay methods, laboratory assessments, and similar patient population between the test and reference arms.

Treatment with 600 mg IV ocrelizumab has been well characterized in previous clinical studies (for details, refer to the Ocrelizumab Investigator's Brochure), and 600 mg IV ocrelizumab has been approved for treatment of patients with RMS or PPMS (OCREVUS® USPI).

3.3.4 Rationale for Patient Population

The assessment of PK non-inferiority of ocrelizumab SC to ocrelizumab IV will be carried out in a broad MS patient population consistent with the current ocrelizumab indication. Adult patients with relapsing and primary progressive forms of MS with an EDSS score of 0 to 6.5 and with an age range up to 65 years will be enrolled. Available PK data on file does not reveal a difference in the PK profiles of RMS and PPMS patients following treatment with ocrelizumab IV.

3.3.5 Rationale for [redacted] Use of Premedications

An analysis of patients with MS who were treated with ocrelizumab IV revealed that the addition of antihistamines to the pretreatment with methylprednisolone decreased the incidence of IRRs by two-fold (Ocrelizumab Investigator's Brochure). To reduce the

frequency and severity of IRRs, as well as systemic injection reactions or ISRs, patients will be premedicated with corticosteroids and antihistamines prior to administration with ocrelizumab (see Section 4.3.2).

Methylprednisolone (or an alternative steroid in patients where methylprednisolone is contraindicated or not available) and antihistamine will be administered to patients receiving IV ocrelizumab treatment. Dexamethasone and desloratadine (or an alternative steroid or antihistamine in patients where dexamethasone or desloratadine are contraindicated) will be administered to patients receiving SC ocrelizumab treatment. Those recommended oral corticosteroids and antihistamine medications are considered as equivalent in terms of anti-inflammatory potency to the premedication given to patients treated with IV ocrelizumab. The premedication and its administration schedule may be modified by the Sponsor during the study on the basis of emerging clinical evidence for the effectiveness and safety of the proposed premedication schedule.

3.3.5.1 [redacted] Premedication

[redacted] Study CN41144 were almost all CTCAE Grade 1–2 and their incidence decreased after the first injection. The large majority of reactions were local, a minority were systemic, and all were manageable as per the guidelines from the previous versions of the protocol (Section 5.1.1.1 and *Appendix 11*) which continue to apply without any changes.

The most common systemic injection reaction symptom was headache (refer to Section 5.1.1.2). [redacted]

[redacted]

3.3.6 Rationale for Biomarker Assessments

PD biomarkers will be assessed to demonstrate evidence of biologic activity of ocrelizumab in patients, compared between the dosing arms.

B-cells are a direct PD marker for ocrelizumab, and a correlation of the extent of B-cell depletion in blood with exposure levels was observed in the ORCHESTRA Phase III trials (Gibiansky et al. 2020).

NfL, a neuraxonal injury marker, has been correlated with Gd-enhancing MRI lesions and clinical relapses (Burman et al. 2014) and with response to drug treatment in PMS and RMS (Gunnarsson et al. 2011; Axelsson et al. 2014, Kuhle et al. 2019). NfL can be detected in the blood, and blood levels are correlated with cerebral spinal fluid (CSF) level, making NfL an attractive non-invasive biomarker to assess neuronal injury in MS (DiSanto et al. 2017). In addition, NfL is prognostic for worse disability outcome in RMS and PPMS (Kuhle et al. 2019; Bar-Or et al. 2019), and is a PD biomarker for treatment response to ocrelizumab.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 232 patients with MS (RMS and PPMS) will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Diagnosis of PPMS or relapsing forms of MS (RMS) according to the revised McDonald 2017 criteria (Thompson et al. 2018)
- Signed Informed Consent Form
- Age 18–65 years, inclusive, at time of signing Informed Consent Form
- Ability to comply with the study protocol and schedule of protocol assessments, in the investigator's judgment
- EDSS score, 0–6.5, inclusive, at screening
- Neurological stability for ≥30 days prior to both screening and baseline
- Disease duration from onset of MS symptoms of less than 15 years for patients with EDSS score <2.0 at screening
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use adequate contraception during the treatment period and for 6 or 12 months (as applicable by the ocrelizumab IV [Ocrevus] local label) after the final dose of ocrelizumab.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a post-menopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a woman with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

  As defined by the guidelines, the following contraceptive methods are considered acceptable (failure rate >1%): (1) progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action; (2) male or female condom with or without spermicide; (3) cap, diaphragm, or sponge with spermicide;

(4) combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier method).

Birth control methods that are highly effective (i.e. failure rate <1%) may also be used but are not required, and include: (1) oral, intravaginal or transdermal combined hormonal contraception associated with inhibition of ovulation; (2) oral, injectable or implantable progestogen-only hormonal contraception associated with inhibition of ovulation; (3) intrauterine device; (4) intrauterine hormone-releasing system; (5) bilateral tubal occlusion; (6) vasectomized partner; (7) sexual abstinence.

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. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For female patients without reproductive potential:

  Women may be enrolled if

  – Post-menopausal (i.e., spontaneous amenorrhea for the past year confirmed by a follicle-stimulating hormone [FSH] level $>$ 40 mIU/mL) unless the patient is receiving a hormonal therapy for her menopause or

  – Surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy).

4.1.2 Exclusion Criteria

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

- Any known or suspected active infection at screening or baseline (except nailbed infections), or any major episode of infection requiring hospitalization or treatment with IV antimicrobials within 8 weeks prior to and during screening or treatment with oral antimicrobials within 2 weeks prior to and during screening
- History of confirmed or suspected progressive multifocal leukoencephalopathy (PML)
- History of cancer, including hematologic malignancy and solid tumors, within 10 years of screening

  Basal or squamous cell carcinoma of the skin that has been excised and is considered cured and in situ carcinoma of the cervix treated with apparent success by curative therapy $>$ 1 year prior to screening is not exclusionary.
- Immunocompromised state, defined as one or more of the following:
  – CD4 count $<$250/μL
  – Absolute neutrophil count $<1.5 \times 10^3/\mu$L
  – Serum IgG $<$4.6 g/L
- Receipt of a live-attenuated vaccine within 6 weeks prior to randomization

Influenza vaccination is permitted if the inactivated vaccine formulation is administered.

- Inability to complete an MRI (contraindications for MRI for example, due to, pacemaker, cochlear implants, intracranial vascular clips, surgery within 6 weeks of entry in the study, coronary stent implanted within 8 weeks prior to the time of the intended MRI, etc.) or contraindication to gadolinium administration
- Contraindications to mandatory premedications (i.e., corticosteroids and antihistamines), including closed-angle glaucoma for antihistamines
- Known presence of other neurologic disorders that could interfere with the diagnosis of MS or assessments of efficacy and/or safety during the study, including, but not limited to, the following:
  - History of hemorrhagic or ischemic cerebral or spinal stroke
  - History or known presence of CNS or spinal cord tumor (e.g., meningioma, glioma)
  - History or known presence of potential metabolic causes of myelopathy (e.g., untreated vitamin B12 deficiency)
  - History or known presence of infectious causes of myelopathy (e.g., syphilis, Lyme disease, HTLV-1, herpes zoster myelopathy)
  - History of genetically inherited progressive CNS degenerative disorder (e.g., hereditary paraparesis, mitochondrial myopathy, encephalopathy, lactic acidosis, stroke [MELAS] syndrome)
  - Neuromyelitis optica
  - History or known presence of systemic autoimmune disorders potentially causing progressive neurologic disease (e.g., lupus, anti-phospholipid antibody syndrome, Sjögren syndrome, Behçet disease)
  - History or known presence of sarcoidosis
  - History of severe, clinically significant brain or spinal cord trauma (e.g., cerebral contusion, spinal cord compression)
  - Any concomitant disease that may require chronic treatment with systemic corticosteroids (e.g. mineralocorticoids and glucocorticoids) 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 or gastrointestinal, or any other significant disease that may preclude patient from participating in the study
  - History of or currently active primary or secondary (non–drug-related) immunodeficiency

- Pregnant or breastfeeding, or intending to become pregnant during the study and 6 or 12 months (as applicable by the ocrelizumab [Ocrevus] local label) after last administration of the study drug.

    Females of childbearing potential must have a negative serum and urine pregnancy test result prior to initiation of study drug (negative serum β-CG measured at screening and negative urine β-CG at baseline)
- Lack of peripheral venous access
- History of alcohol or other drug abuse within 12 months prior to screening
- Treatment with any investigational agent within 24 weeks prior to screening or 5 half-lives of the investigational drug (whichever is longer), or treatment with any experimental procedure for MS (e.g., treatment for chronic cerebrospinal venous insufficiency)
- Patients who have previously received anti-CD20s (including ocrelizumab) if the last treatment was less than 2 years before screening, and/or if B-cell count is below lower limit of normal, and/or the discontinuation of the treatment was due to safety reasons or lack of efficacy
- Previous treatment with cladribine, atacicept, and alemtuzumab
- Previous treatment with fingolimod, siponimod, ponesimod, or ozanimod within 6 weeks of baseline
- Previous treatment with interferons beta (1a or 1b), or glatiramer acetate within 2 weeks of baseline
- Previous treatment with natalizumab within 4.5 months of baseline
- Treatment with mitoxantrone within 2 years prior to baseline visit or evidence of cardiotoxicity following mitoxantrone use or a cumulative lifetime dose of more than 60 mg/m^2
- Previous treatment with any other immunomodulatory or immunosuppressive medication not already listed above without appropriate washout as described in the applicable local label. If the washout requirements are not described in the applicable local label (washout to be completed prior to baseline), then the wash out period must be 5 times the half-life of the medication. The PD effects of the previous medication must also be considered when determining the required time for washout.

    Patients screened for this study should not be withdrawn from therapies for the sole purpose of meeting eligibility for the trial.
- Any previous treatment with bone marrow transplantation and hematopoietic stem cell transplantation
- Any previous history of transplantation or anti-rejection therapy
- Treatment with IV Ig or plasmapheresis within 12 weeks prior to randomization
- Systemic corticosteroid therapy within 4 weeks prior to screening

    The screening period may be extended for patients who have used systemic corticosteroids for MS before screening. For a patient to be eligible, systemic

corticosteroids should also not have been administered between screening and baseline.

- Positive screening tests for active, latent, or inadequately treated hepatitis B (as evidenced by either of the following):
  - Positive hepatitis B surface antigen
  - Positive hepatitis B core antibody (total HBcAb) and detectable hepatitis B virus DNA
- Sensitivity or intolerance to any ingredient (including excipients) of ocrelizumab
- Any additional exclusionary criterion as per ocrelizumab (Ocrevus®) local label, if more stringent than the above

Re-testing before baseline: In rare cases in which the screening laboratory samples are rejected by the central laboratory (e.g., hemolyzed sample) or the result is not assessable (e.g., indeterminate) or abnormal, the tests need to be repeated as soon as possible, or within the allowed screening period. Any abnormal screening laboratory value that is clinically relevant should be retested to rule out any progressive or uncontrolled underlying condition. The last value before randomization must meet study criteria.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a randomized, open-label study. After initial written informed consent has been obtained, all screening and baseline procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from an interactive voice or web-based response system (IxRS).

Patients who discontinue treatment for any reason will not be replaced. Under no circumstances are patients who enroll in this study and who have completed treatment as specified, permitted to be re-randomized to this study. Patients will be randomly assigned to one of two treatment arms: SC or IV ocrelizumab. Randomization will occur in a 1:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified according to the following criteria:

- Baseline body weight ($<$70 kg vs. $\geq$70 kg)
- Disease subtype (RMS vs. PPMS)
- Region (U.S. vs. rest of world [ROW])

Baseline body weight was identified as the most relevant covariate for the pharmacokinetics in the population PK analysis conducted with the Phase III PK data obtained from approximately 1500 patients with MS treated with IV ocrelizumab. While the disease subtype and region do not influence the pharmacokinetics, inclusion of these

variables as stratification factors would ensure a balanced comparison of the secondary safety and radiological endpoints.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is ocrelizumab (comprising both the IV formulation and the SC formulation co-formulated with rHuPH20).

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Ocrelizumab Subcutaneous Co-Formulated with rHuPH20

Ocrelizumab SC will be provided as a sterile, single-dose liquid at a concentration of 40 mg/mL and contains no preservatives. The ocrelizumab in the ocrelizumab SC formulation is co-formulated with rHuPH20 at a concentration of 1000 U/mL.

For information on the formulation of ocrelizumab SC co-formulated with rHuPH20, see the pharmacy manual and the Ocrelizumab Investigator's Brochure.

4.3.1.2 Ocrelizumab Intravenous

Ocrelizumab IV will be provided as a sterile, single-dose liquid at a concentration of 30 mg/mL and contains no preservatives. For information on the formulation of IV ocrelizumab, refer to the Ocrelizumab Investigator's Brochure, local prescribing information, and pharmacy manual.

4.3.1.3 Non-Investigational Medicinal Products

Specific premedications are required prior to the ocrelizumab infusion or injection. Table 1 shows the premedications that will be used prior to an IV infusion or SC injection of ocrelizumab.

Table 1 Premedications To Be Used Prior to IV Infusion or SC Injection

Prior to IV Administration of Ocrelizumab	Prior to SC Administration of Ocrelizumab
Mandatory methylprednisolone, given by slow IV infusion	Mandatory dexamethasone, given orally
Mandatory diphenhydramine, given orally or IV infusion	Mandatory desloratadine, given orally
Oral analgesic as needed and as tolerated (if using acetaminophen not to exceed 4g/daily per label).	Recommended oral analgesic/as needed/and as tolerated (if using acetaminophen, not to exceed 4g/day, per label)

IV=intravenous; SC=subcutaneous.

For further details on premedication administration, refer to Section 4.3.2.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.1.2.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

At participating sites only, *from* the third ocrelizumab dose *onwards* (i.e., *starting* at Week 48 visit)*, study drug can* be administered by a healthcare professional at the patient's home or another suitable location (refer to Section 4.5.10).

Details on treatment administration (e.g., dose, actual date and time) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.

Guidelines for treatment modification, interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.4.

4.3.2.1 Subcutaneous Ocrelizumab

The 920 mg SC dose of ocrelizumab was determined based on data from the ongoing Phase Ib study (Ocarina I, Section 3.3.2). Detailed information on drug preparation and administration is provided in the pharmacy manual.

The injection of ocrelizumab SC should be administered by an experienced professional with access to appropriate medical support to manage severe injection reactions.

The study drug will be administered by a healthcare professional to patients subcutaneously with a manual syringe or syringe pump through a SC infusion set into the abdominal SC space, except for the 5 cm area directly around the navel (refer to the pharmacy manual) every 24 weeks. A minimum of 22 weeks should be maintained between the first and second SC doses, and between *the next* SC dose.

The patient *will need to remain at the clinic* for *at least* 1 hour after *the* completion of injection for *observation of* potential injection reactions.

Site personnel will contact patients by telephone as indicated in Section 4.5.11 to record potential injection reactions.

Depending on the site and individual participant, some participants will have the option to receive *doses 3-5* of ocrelizumab at home by study staff (i.e., *Weeks 48-96* visits). The investigator will determine whether the participant is eligible for home administration, per Appendix 4, by appropriate study staff (according to local regulations) based on tolerability and suitability (refer to Section 4.3.2.3).

Rescue medications to treat anaphylactic and anaphylactoid reactions must be available at the site or at the dosing location for MN visit (see *Appendix 4).* Participants will be alerted to watch for signs of anaphylactic and anaphylactoid reactions and to contact the study center as soon as possible if any such signs are noted.

Premedication for Patients Treated with Ocrelizumab Subcutaneous

To reduce potential injection reactions, patients treated with ocrelizumab SC will be premedicated with 20 mg dexamethasone and 5 mg desloratadine given orally *30–60 minutes* before *initiating* each ocrelizumab SC *injection*. In the rare case when the use of dexamethasone or desloratadine is contraindicated for the patient or is not available, an equivalent dose of an alternative steroid or antihistaminic should be used as premedication prior to the injection.

Corticosteroids and antihistamine medications are considered as equivalent in terms of anti-inflammatory potency to the premedication given to patients treated with ocrelizumab IV. If using acetaminophen, do not exceed the maximum daily dose or frequency in the label.

4.3.2.2 Intravenous Ocrelizumab

The infusion of ocrelizumab should be initiated and supervised by an experienced healthcare professional with access to appropriate medical support to manage severe reactions such as serious IRRs. The patient will need to remain at the clinic for at least 1 hour after the completion of infusion for observation.

Patients will receive the first dose of ocrelizumab IV as two 300 mg infusions (600 mg in total), each separated by 2 weeks, and from the Week 24 visit onwards patients will receive SC injections, every 24 weeks (refer to Section 4.3.2.1). A minimum interval of 20 weeks should be maintained between the second ocrelizumab infusion (ocrelizumab IV) of Dose 1 (i.e., infusion Day 14, Week 2) and the administration of Dose 2 (i.e., ocrelizumab SC dose on Week 24).

Table 2 Overview of Ocrelizumab IV Dosing and Schedule

Preparation of the Infusion for IV Administration		Infusion Instructions
Infusion 1 at Dose 1	300 mg IV in 250 mL of 0.9% sodium chloride	Initiate the infusion at a rate of 30 mL/hr for 30 minutes. The rate can be increased in 30-mL/hr increments every 30 minutes to a maximum of 180 mL/hr. Each infusion should be given over approximately 2.5 hours.
Infusion 2 (2 weeks later, Dose 1)	300 mg IV in 250 mL of 0.9% sodium chloride	

IV=intravenous.

Premedication for Patients Treated with Ocrelizumab Intravenous

To reduce potential IRRs, all patients who will receive ocrelizumab IV treatment must receive mandatory prophylactic treatment with 100 mg methylprednisolone administered by slow IV infusion to be completed approximately 30 minutes before the start of each ocrelizumab infusion. In the rare case when the use of methylprednisolone is contraindicated for the patient or not available, use of an equivalent dose of an alternative IV steroid should be used as premedication prior to the infusion.

Additionally, a mandatory oral or IV antihistaminic drug (such as 50 mg IV diphenhydramine or an equivalent dose of an alternative) must be administered approximately 30–60 minutes prior to the start of each ocrelizumab infusion.

Oral analgesic is recommended as needed and as tolerated. If using acetaminophen the 4g/day dose, per label, should not be exceed.

Hypotension, as a symptom of IRR, may occur during IV study drug infusions. Therefore, withholding antihypertensive treatments should be considered for 12 hours prior to and throughout each study drug infusion.

4.3.2.3 Retreatment Criteria for Ocrelizumab

A visit prior to any dosing visit will be required to collect blood samples to enable the study investigator to assess whether a patient meets retreatment criteria at the time of treatment with study drug.

The study investigator must ensure he or she has reviewed the central and local laboratory results of the patient prior to retreatment with ocrelizumab.

If study treatment will be administered at patient's home or another suitable location the retreatment criteria must be confirmed by site staff prior to the dose administration.

Prior to retreatment, the following conditions must be met:

- Absence of severe allergic or anaphylactic reaction to the previous ocrelizumab administration
- Absence of any significant or uncontrolled medical condition or treatment-emergent clinically significant laboratory abnormality
- Absence of active infection
- Absolute neutrophil count (ANC) $\geq 1.5 \times 10^3/\mu L$
- CD4 cell count $\geq 250/\mu L$
- IgG ≥ 3.3 g/L
- Negative pregnancy test
- Additional criteria for home administration*:* Absence of any local or systemic injection reaction of Grade ≥ 3 severity or meeting seriousness criteria that occurred during a previous ocrelizumab injection

If any of these criteria are not met prior to retreatment, further administration of ocrelizumab must be suspended until resolved or held indefinitely.

4.3.3 Investigational Medicinal Product Handling and Accountability

All IMPs required for completion of this study will be provided by the Sponsor (ocrelizumab IV and ocrelizumab SC). The study site (i.e., investigator or other authorized personnel [e.g., pharmacist or site personnel]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed

to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and the Ocrelizumab Investigator's Brochure for information on IMP handling, including preparation and storage, and accountability.

4.3.4 Continued Access to Ocrelizumab Subcutaneous

Should SC ocrelizumab not be commercially available or be reasonably accessible for the patient at the end of the treatment phase, the Sponsor may decide to offer access to another study using the Roche IMP, or the Sponsor will offer continued access to Roche IMP (ocrelizumab IV) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Roche IMP (ocrelizumab IV) after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition (e.g., MS) and requires continued Roche IMP treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive Roche IMP (ocrelizumab IV) after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for MS
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for MS
- Provision of the Roche IMP is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Treatment for Symptoms of Multiple Sclerosis

The investigator should attempt to maintain therapies (e.g., physiotherapy) or treatments for symptoms related to MS (e.g., walking ability, spasticity, incontinence, pain, fatigue) reasonably constant throughout the study. However, changes (including starting physiotherapy and/or symptomatic treatment) may be made if appropriate for a patient's well-being in the clinical judgment of the investigator. All such therapies or treatments should be recorded on a designated eCRF.

4.4.2 Therapy for Treatment of Relapses

Patients who experience a relapse during study may receive treatment with IV or oral corticosteroids, if judged to be clinically appropriate by the investigator. The following standardized treatment regimen may be used as warranted: 1 g/day IV methylprednisolone for a maximum of 5 consecutive days (or an equivalent oral dose of prednisolone or methylprednisolone). In addition, at the discretion of the investigator, corticosteroids may be stopped abruptly or tapered over a maximum of 10 days. Such patients should not discontinue the *study treatment solely based on the occurrence of a relapse, unless the patient or investigator deems they have met the criteria for treatment discontinuation (see Section 4.7.1).*

4.4.3 Prohibited Therapy and Alternative Treatments

The following therapies for MS are not permitted while under the study treatment phase: B cell–targeted therapies (e.g., rituximab, atacicept, belimumab, or ofatumumab), natalizumab, sphingosine-1-phosphate receptor modulators, alemtuzumab, cladribine, teriflunomide, dimethyl fumarate, interferons, glatiramer acetate, cyclophosphamide, mitoxantrone, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, total body irradiation, bone marrow transplantation, IV Ig, plasmapheresis, and other approved DMTs or investigational therapies for MS.

After patients have completed (or discontinued) treatment with ocrelizumab, they may receive an alternative treatment for their MS, as judged clinically appropriate by the investigator. However, as sufficient data are not available regarding the risks associated with switching to other products, the following recommendations are given:

- Caution is advised while patients remain B-cell depleted.
- Because of the unknown safety risk of administering DMTs for MS after discontinuation of ocrelizumab, certain treatments for MS, such as lymphocyte-depleting agents or lymphocyte-trafficking blockers (alemtuzumab,

natalizumab, sphingosine-1-phosphate receptor modulators , dimethyl fumarate, cyclophosphamide, azathioprine, cladribine, , etc.) are strongly discouraged for as long as the patient remains B-cell depleted because of unknown effects on the immune system (e.g., increased risk, incidence, or severity of infection).

4.4.4 Immunizations

Physicians are advised to review the immunization status of patients who are considered for treatment with ocrelizumab and follow local/national guidance for adult vaccination against infectious disease. Immunizations should be completed at least 6 weeks prior to first administration of ocrelizumab.

Immunization with any live or live-attenuated vaccine (i.e., measles, mumps, rubella, oral polio vaccine, bacille Calmette-Guérin, typhoid, yellow fever, vaccinia, cold-adapted live influenza strain vaccine, or any other vaccines not yet licensed but belonging to this category) is not recommended during ocrelizumab treatment and for as long as a patient is B cell depleted.

Data from the ocrelizumab IV Phase II and III program currently show that over 2 years after treatment with ocrelizumab, the proportion of patients with positive antibody titers against *Streptococcus pneumoniae*, influenza, mumps, rubella, *Varicella*, and tetanus toxoid was generally similar to the proportion at baseline.

For seasonal influenza vaccines, it is still recommended to vaccinate patients treated with ocrelizumab. Refer to the current version of the Ocrelizumab Investigator's Brochure for further guidance and updates on immunization.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study *are* provided in Appendix 1, Appendix 2, Appendix 3, and *Appendix 4*. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

Patients will be followed using onsite visits, a mobile nursing visit (Section 4.5.10) and telephone calls (Section 4.5.11).

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening and baseline evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator may maintain a *detailed* record of all patients screened and to *document* eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including, but not limited to, clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures) and reproductive status will be recorded at screening and re-confirmed at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Any previous medications taken for the treatment of MS at any time since disease onset, including their start and end dates, and medications taken for the symptoms of MS in the 3-month period prior to the baseline visit will be recorded in the eCRF.

Demographic data will include age, sex, and self-reported race/ethnicity, if allowed per local regulations.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and baseline visits should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified post-baseline visits and as clinically indicated (refer to Appendix 1, Appendix 2, Appendix 3, and *Appendix 4*). Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Limited, symptom-directed physical examinations may be performed by site personnel during MN visit (Appendix 4).

4.5.4 Vital Signs

Vital signs will be measured while the patient is in seated (preferred) or semi-seated position and will include temperature, systolic and diastolic blood pressure, pulse rate and pulse oximetry.

Baseline pulse oximetry should be performed for all patients as follows:

- For newly enrolled patients: Study Day 1 before premedication is given
- For already enrolled patients: At the next visit where vital signs are assessed per the schedule of assessments (Appendices 1, 2 and 3, i.e., Week 12 visit or at the next dosing visit before premedication is given).

Post-baseline pulse oximetry is only required in the event of severe systemic administration reactions including potential hypersensitivity/anaphylactic reaction (Section 5.1.4.4 and Appendix 11).

Blood pressure and pulse rate measurements will be recorded on the appropriate eCRF. Temperature should be measured and recorded in patient's notes only.

Vital sign measurement may be performed by site personnel during the MN visit (Appendix 4).

Clinically significant abnormalities observed at baseline will be recorded on the General Medical History and Baseline Conditions eCRF. At subsequent visits, new or worsened clinically significant abnormalities will be recorded on the Adverse Event eCRF.

4.5.4.1 Ocrelizumab Subcutaneous Administration

Vital signs should be measured prior to premedication (refer to Section 4.3.2.1) with dexamethasone (or an equivalent) and desloratadine (or an equivalent). *In addition, vital signs should also be recorded 1 hour after the end of ocrelizumab SC administration.*

Pulse oximetry should be performed as described above (Section 4.5.4).

On non-dosing days, vital signs should be taken at any time during the visit as indicated.

Additionally, unscheduled vital signs may be collected based on PK and safety data and at the discretion of the investigator at any time during the study as clinically indicated.

4.5.4.2 Ocrelizumab Intravenous Administration

Vital signs should be measured within 45 minutes prior to premedication with methylprednisolone (or an equivalent) infusion. In addition, vital signs should be recorded prior to the ocrelizumab infusion and one hour after the end of infusion.

Only in case of an IRR, vital signs should be recorded in the eCRF every 15 minutes ($\pm$5 minutes) in the first hour after the onset of the IRR, followed by every 30 minutes ($\pm$10 minutes) until 1 hour after the end of the infusion.

For patients randomly allocated to ocrelizumab IV treatment the baseline pulse oximetry should be performed as described in Section 4.5.4, and thereafter only in the event of

severe systemic administration reactions including potential hypersensitivity/anaphylactic reactions (Section 5.1.4.4 and Appendix 11).

On non-dosing days, vital signs should be taken at any time during the visit.

4.5.5 Neurological Examination

A neurologic examination will be performed at the planned visit as indicated in the schedule of activities (Appendix 1, Appendix 2, Appendix 3, and *Appendix 4*). During an unscheduled visit, the neurologic examination will be performed only if deemed necessary. A neurologic examination should include an assessment of mental status, level of consciousness, cranial nerve function, motor function, sensory function, reflexes, and coordination. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

In the presence of newly identified or worsening neurologic symptoms at any given time in the study, a neurologic evaluation should be scheduled promptly and performed within 7 days of onset of the new or worsening neurologic symptom(s).

Study investigators will screen patients for signs and symptoms of PML through evaluation of neurologic deficits localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, hemiparesis, and cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination). Refer to Appendix 12 for guidance on the diagnosis of PML.

Patients with suspected PML, defined as a new or worsening neurologic symptom that necessitates MRI and/or lumbar puncture and CSF analyses to rule out PML, should be withheld from study treatment until PML is ruled out by complete serial clinical evaluations and appropriate diagnostic testing (see Appendix 12). The Medical Monitor should be contacted by email as well as by telephone.

A patient with confirmed PML should be withdrawn from treatment. PML should be reported as a serious adverse event (with all available information) with immediate notification of the Medical Monitor (see also Section 5.1.1.2).

4.5.5.1 Assessment of Disability

Disability in MS is commonly measured by the EDSS (Section 4.5.9). EDSS will be administered at the timepoints indicated in the schedule of activities (see Appendix 1, Appendix 2, Appendix 3, and *Appendix 4*). Additional EDSS assessments for individual patients may be requested between visits (i.e., during an MS relapse, neurological worsening, etc.). All functional system scores (FSS) and total EDSS scores will be captured electronically and completed in real-time *at the site*.

4.5.6 Assessment of Relapse

Patients will be evaluated for relapse by the study investigator at each visit throughout the study and, if necessary, at unscheduled visits to confirm relapse occurring between the visits.

All new or worsening neurological events compatible with MS representing a clinical relapse are to be reported in the appropriate eCRF. Patients with clinical relapses should be referred to the study investigator who will assess the EDSS/FSS independently to allow confirmation as to whether or not the clinical relapse(s) meet the criteria for protocol-defined relapse(s). EDSS should be performed within 7 days from the onset of the relapse.

For this study, a protocol-defined 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 least 30 days. Symptoms must persist for $>$24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reactions to concomitant medications). The new or worsening neurological symptoms must be accompanied by objective neurological worsening consistent with an increase of at least one of the following:

- Half a step (0.5 point) on the EDSS
- Two points on one of the selected FSS as listed below
- One point on two or more of the selected FSS as listed below

The change must affect the following selected FSS: pyramidal, ambulation, cerebellar, brainstem, sensory, or visual. Episodic spasms, sexual dysfunction, fatigue, mood change, or bladder or bowel urgency or incontinence will not suffice to establish a relapse. Note that the following items need not be scored: sexual dysfunction and fatigue.

It should be noted that all patients with new neurological symptoms defined at a visit should be referred to the study investigator considers the symptoms consistent with an intensification of neurological symptoms from a transient systemic infection.

Clinical relapses (i.e., regardless of whether they meet criteria for a protocol-defined relapse) will be recorded in the eCRF.

4.5.7 Brain Magnetic Resonance Imaging

MRI will be used to monitor CNS lesions in patients with MS and potentially other pathophysiology, such as inflammation and neurodegeneration. MRI scans of the brain will be obtained in all patients at study visits as indicated in Appendix 1, Appendix 2, Appendix 3, and *Appendix 4*. The MRI sequences will be analyzed by a central reading facility ensuring the integrity and quality of the acquired data. The centralized reading

center should be blinded to treatment assignment, and the reading will be performed in the absence of clinical information.

If during the screening phase, a MRI scan is required for MS diagnosis, then it can serve as a baseline scan. Note that this MRI scan should be obtained approximately 10 days prior to performing the baseline visit to allow time for the centralized reading center to assess its quality and for potential re-scans if needed.

Patients who prematurely discontinue from study drug treatment during the controlled period will need to return to the clinic to perform the MRI scans required in this period (see Appendix 1 and Appendix 2 for additional details). In addition, MRI scans will be obtained at the Early Termination Visit if one was not performed during the prior 4 weeks.

MRI scans collected during the controlled period should occur within a window of ± 2 weeks of the scheduled visit, as per the schedule of activities (see Appendix 1 and Appendix 2). The remaining MRI scans collected at the Week 48 *and 96 visits*, should occur within a time ± 4 weeks of the scheduled visit (see *Appendix 3* and *Appendix 4*) or can occur 2 weeks of the scheduled MN visit (when patient comes for the Week 46 visit, see *Appendix 4*). If patients receive corticosteroids for a MS relapse, every effort should be made to obtain a scheduled MRI scan prior to the first corticosteroid dose, and there should be an interval of at least 3 weeks between the final dose of corticosteroids and the next scheduled MRI scan.

MRI scans will be read by a centralized reading center for secondary and exploratory endpoints. Further details on scanning acquisition sequences, methods, handling and transmission of the scans, certification of site MRI radiologist/technicians, and the procedures for the analysis of the scans at the central reading center are described in a separate MRI Acquisition Procedures Manual.

MRI assessments will include, but may not be limited to, T1-weighted scans before and after injection of Gd contrast, fluid-attenuated inversion recovery (FLAIR) and T2-weighted scans.

All MRI scans will also be reviewed locally by a radiologist for safety, and the MRI scan report will be provided to the study investigators who in turn will inform the patient about clinically relevant findings. The study investigator will have access to MRI scans.

Non-MS pathology should be reported on the corresponding eCRF, and an adverse event should be reported if clinically relevant.

4.5.8 Laboratory, Biomarker, and Other Biological Samples

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis, unless otherwise indicated, according to schedule of activities (Appendix 1, Appendix 2, Appendix 3, and *Appendix 4*):

- **Hematology**: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count, WBC differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells), and quantitative platelet count.
- **Blood chemistry**: creatinine, amylase, potassium, sodium, and liver function tests (ALT/SGPT, AST/SGOT, γ-glutamyl transferase, ALP, and total bilirubin)
- **Urinalysis:** A urine dipstick will be performed at the site (pH, specific gravity, glucose, protein, ketones, and blood), and a microscopic examination if abnormal and clinically significant.
- **Anti-Drug Antibodies (ADA):** Plasma and serum samples will be collected for determination of antibodies against ocrelizumab or rHuPH20. Because ocrelizumab concentrations affect the ADA assay, the concentration of ocrelizumab will be measured as well at all timepoints with ADA assessment to enable interpretation of the results.
- **Quantitative Ig:** Ig levels (IgG, IgM, and IgA)
- **Pregnancy test**: All females of childbearing potential will have a serum pregnancy test at screening and urine pregnancy test (performed at site) prior to ocrelizumab administration.

  Females of childbearing potential must have regular pregnancy tests. A urine pregnancy test (sensitivity of at least 25 mU/mL on the β-hCG test) will be performed at the specific timepoints. On dosing visits, the urine pregnancy test should be performed prior to the premedication administration. A positive urine pregnancy test should be confirmed with a serum test prior to any further dosing with study drug. If a urine pregnancy test is positive, the patient will not receive the scheduled dose, and confirmatory serum pregnancy test will be performed by the central laboratory.
- **FSH level testing:** only applicable to female patients to confirm the post-menopausal status at screening.
- Serum samples to determine ocrelizumab serum concentration for PK analysis (see Appendix 5)
- **Viral serology and detection**: All patients must have negative hepatitis B surface antigen (HBsAg) test result at screening prior to enrollment. If total HBcAb is positive at screening, hepatitis B virus (HBV) DNA measured by polymerase chain reaction (PCR) must be negative to be eligible.

  For patients enrolled with negative HBsAg and positive total HBcAb, HBV DNA (PCR) must be repeated on a 24-week basis at pre-dosing visits as per the scheduled visits. Patients in whom the viral DNA becomes positive but in whom the quantity is at the lower limit of detection of the assay should have the

test repeated as soon as possible. Patients found to have a confirmed viral DNA-positive test should be referred to a hepatologist for immediate assessment. These patients will not receive further doses of study drug; they will be however further followed up for safety (see Section 4.7.1).

Liver function (i.e., ALT/SGPT, AST/SGOT, gamma-glutamyl transferase, total bilirubin) should be reviewed throughout the study. Patients who develop evidence of liver dysfunction should be assessed for viral hepatitis and, if necessary, referred to a hepatologist or other appropriately qualified expert. Study drug should be withheld until the diagnosis of viral hepatitis has been excluded. Patients who develop hepatitis B should be discontinued from the treatment (see Section 4.7.1). Should treatment be prescribed, this will be recorded in the eCRF. Patients with viral hepatitis due to other agents, such as hepatitis A, may resume treatment after recovery.

- **Biomarker samples:** serum samples will be collected and analysis may include, but may not be limited to, NfL
- **Flow cytometry:** Analysis will include, but may not be limited to, the determination of the B-cell number (CD19+) and T-cell counts (CD3+, CD4+, CD8+). B-cell subsets including but not limited to B-cell memory, naïve, plasmablasts etc. may be measured (e.g., CD27 and CD38).
- Additional samples in the event of severe systemic administration reactions including potential hypersensitivity/anaphylactic reaction: serum samples will be taken for the assessment of tryptase, complement components (C3 and CH50), ADA and PK, as indicated in Section 5.1.4.1 and Appendix 11.

Blood and urine sample collection may be performed by site personnel at a MN visit (see Section 4.5.10).

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.14), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Plasma and serum samples collected for PK and immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood or serum samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if

samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.9 Expanded Disability Status Scale

The EDSS is the most commonly used clinician reported outcome (ClinRO) measure for quantifying changes in the disability level of patients with MS over time. The EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10.0 (death) (Kurtzke 1983; Kappos 2011). The EDSS is based on a standard neurological examination, incorporating functional systems (visual, brainstem, pyramidal, cerebellar< sensory, bowel and bladder, and cerebral [or mental]) that arerated and then scored as a FSS, and ambulation, which is scored as ambulation score. Each FSS is an ordinal clinical rating scale ranging from 0 to 5 or 6 and an ambulation score that is rated from 0 to 16. These ratings are then used in conjunction with observations, as well as information, concerning ambulation and use of assistive devices to determine the total EDSS score. All FSS, ambulation score, and total EDSS scores will be captured electronically and completed in real-time. Note that the following items do not need to be scored for this study: sexual dysfunction and fatigue.

In this study, Neurostatus-eEDSS definitions and calculating algorithms will be used (D'Souza et al. 2017).

4.5.10 Mobile Nursing Visit

At participating sites only, the administration of Dose*s* 3 *onwards* (i.e., the Week 48*, 72, and 96* visit*s*) *can* be performed by a healthcare professional from the study site (if local processes are in place) at the patient's home or another suitable location to improve access and convenience for patients participating in the study (see Appendix 4).
A dedicated informed consent must be obtained and documented in written form (MN Informed Consent Form) before the optional home administration of ocrelizumab SC.

At the participating sites only, the investigator will determine whether the participant is eligible for home administration based on the retreatment criteria (refer to Section 4.3.2.3) and suitability. If at any time the investigator or patient determines that home administration by the site personnel is unsuitable, then study drug must be administered in the clinic. If during a visit the site personnel identifies any change in the patient's health status (e.g., new or worsening neurologic symptoms or any other

situation that may warrant an unscheduled visit), an unscheduled visit will be scheduled as soon as possible with the site (i.e., within 7 days of symptom onset if possible).

4.5.11 Telephone Contact

After each ocrelizumab SC injection, site personnel will have a telephone conversation with the patient to elicit, in a non-leading way, information on adverse events that may have occurred after ocrelizumab SC treatment. On the day of first ocrelizumab SC dose (i.e. Dose 1 for ocrelizumab SC group and Dose 2 for ocrelizumab IV group) the site personnel will contact the patient approximately 6 hours after the injection. On the second and subsequent doses of ocrelizumab SC the site personnel will contact the patient approximately 24 hours after injection. The site personnel should have more frequent calls with a particular patient if considered appropriate by the investigator (e.g. to follow up on potential injection reactions).

4.5.12 Dermatologist Evaluation of Injection Reactions

Any patient who experiences a skin or injection site reaction of Grade ≥3 severity or meeting seriousness criteria will undergo a dermatologist consultation.

4.5.13 Description of Patient-Reported Outcome Assessment Instruments

Five PRO measures (will be included in this study, which include: Entry treatment experience questions, TASQ (IV infusion version and SC injection version), PPQ, an MS treatment preference questionnaire (MSTPQ) *and patient global impression of satisfaction (PGI-SF)*.

All patients will complete the following:

- Entry treatment experience questions at baseline, before their ocrelizumab treatment
- TASQ for SC injection at Weeks 24 and 48, 30-60 minutes after their SC injection
- MSTPQ at Week 48 prior to their ocrelizumab injection
- *PGI-SF at Week 96 prior to their ocrelizumab injection*

A subset of patients will complete the following:

- For patients whose first ocrelizumab treatment is a SC injection, they will complete:

  TASQ for SC at baseline 30-60 minutes after their first SC injection
- For patients whose first ocrelizumab treatment is an IV infusion they will complete:

  TASQ for IV at baseline 30-60 minutes after their first IV infusion of Dose 1

  PPQ at week 48 before their SC injection

4.5.13.1 Entry Treatment Experience Questions

The entry treatment experience questions are reported by the patients at baseline to understand their treatment experience related to the last DMT they were treated with prior to enrollment in this study (see Appendix 6). It consists of four items used to

understand if patients took any previous DMT before starting the study and if so, when they stopped taking their most recent DMT, the reason for stopping this treatment, and how satisfied they were when taking it. Patients will be asked to respond on a 2-, 3-, 4- and 8-point scale, from which each item will be evaluated individually. Entry treatment experience questions will be administered at baseline, prior to ocrelizumab treatment and take approximately 30 seconds–1 minute to complete.

4.5.13.2 Treatment Administration Satisfaction Questionnaires

The TASQ is a patient-reported measure for which there are two versions; an IV Infusion version and a SC Injection version (see Appendix 7 and Appendix 8, respectively). These are adapted from the Rituximab Administration Satisfaction Questionnaire (Theodore-Oklota et al. 2016) and will be used for the patient to evaluate and reflect on his or her last ocrelizumab administration experience. Each version consists of 13 items that are worded the same but include either an IV Infusion or SC Injection item. Items are rated on a 3- or 5-point Likert scale, for which a higher score corresponds to higher satisfaction and more positive experience. Individual items will be evaluated.

The TASQ will be completed by the patient after completion of their ocrelizumab treatment. Patients whose first ocrelizumab treatment was SC injection will complete the TASQ SC at baseline, whereas patients whose first ocrelizumab treatment was IV infusion will complete the TASQ IV at baseline. All patients will complete the TASQ SC at Weeks 24 and 48. It will take between 2–4 minutes to complete.

4.5.13.3 Patient Preference Questionnaire

The PPQ is a patient-reported measure that consists of three items, used to understand whether patients have a preference for SC administered ocrelizumab or IV administered ocrelizumab, the strength of their preference, and the main reasons for this (see Appendix 9). Patients are asked to respond on either 3- or 5- point scale, from which each item will be evaluated individually.

This measure will only be completed by the subset of patients whose first ocrelizumab treatment was administered as an IV infusion. It will be completed prior to the patient's ocrelizumab SC injection at week 48, and will take approximately 30 seconds–1 minute to complete.

4.5.13.4 MS Treatment Preference Questionnaire

The MSTPQ is completed by the patients to provide information about their overall level of satisfaction with ocrelizumab and whether they have a preference for ocrelizumab or the DMT they were most recently treated with prior to the study (see Appendix 10). It consists of three items and is rated on a 4- or 6- point scale, from which each item can be evaluated individually. The MSTPQ will be administered at Week 48 prior to ocrelizumab treatment and will take approximately 30 seconds–1 minute to complete.

4.5.13.5 *New PRO—Patient Global Impression of Satisfaction*

The patient global impression is one item used to assess patient's overall satisfaction (PGI-SF) of ocrelizumab SC as a treatment for their MS symptoms (see Appendix 14). The PGI-SF is rated on a four point Likert scale ranging from Very satisfied (1) to Very dissatisfied (4). It is scored descriptively and takes approximately 30 seconds–1 minute to complete. The PGI-SF will be administered at Week 96 prior to the patient's ocrelizumab treatment.

4.5.14 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.14.1 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.14.1) will not be applicable at that site.

4.5.14.2 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to ocrelizumab SC or IV, diseases, or drug safety:

- PAX gene samples for RNA and genomic DNA

- Whole blood samples for DNA
- Leftover blood, serum, plasma, and/or any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via whole genome sequencing (WGS), whole exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.14.3 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.14.4 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.14.5 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.14.6 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed

Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 OVERVIEW OF CLINICAL VISITS

After the screening, patients who fulfill the entry criteria will be scheduled for baseline assessments. Visits will take place as described in the schedule of *activities* (see Appendix 1, Appendix 2, Appendix 3, and *Appendix 4*).

Patients who cannot receive their study drug at the scheduled visit or within 24 hours of the visit should be rescheduled for a delayed dosing visit (see Section 4.6.1). Additional unscheduled visits for the assessment of disease worsening, new neurological symptoms, or safety events may occur at any time.

4.6.1 Delayed Dosing Visit

Delayed dosing visits may be scheduled only if the study drug cannot be administered (e.g., due to safety events) at the time points defined in the schedule of activities (see Appendix 1, Appendix 2, Appendix 3, and *Appendix 4*). Thus, a patient who had all assessments of a dosing visit performed, but could not receive the study drug, should be rescheduled for the infusion or injection on another day, provided that they meet the retreatment criteria. At the delayed dosing visit, additional tests or assessments, such as routine safety laboratory tests, may be performed as clinically indicated. A minimum interval of 22 weeks should be maintained between the delayed dose and the subsequent dose. However, if the second ocrelizumab IV infusion of Dose 1 (i.e., infusion Day 14, Week 2) happens to be delayed, a minimum interval of 20 weeks should be kept between this infusion and the next administration of Dose 2 (i.e., ocrelizumab SC dose on Week 24 visit).

4.6.2 Unscheduled Visits

Patients who develop new or worsening neurological symptoms should be seen at the investigational site as soon as possible, regardless of the dates of their pre-planned, scheduled study visits and regardless of the study period. The EDSS assessment should be performed for any suspected neurological worsening. If an MS relapse (or any worsening neurological event) is diagnosed or suspected, EDSS assessment should be performed by site investigator (or designee, as applicable) within 7 days from the onset of a new or worsening neurological event (including relapses), in addition to completing the appropriate eCRF (see Section 4.5.5).

Other assessments performed at unscheduled (non-dosing) visits will depend on the clinical needs of the patient. The primary reason for performing an unscheduled visit will be reported in the eCRF.

4.7 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.7.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy: Ocrelizumab treatment will be discontinued for patients who become pregnant during the study. Patients will remain in the study and will have the opportunity to enter the safety follow-up phase.
- Life-threatening (NCI CTCAE Grade 4) infusion- or injection-related event that occurred during a previous ocrelizumab dose
- Develop active hepatitis B infection, either new onset or reactivation
- PML
- Patient's decision to discontinue the treatment

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment will not be replaced.

Patients who prematurely discontinue from study drug treatment will need to return to the clinic for a treatment discontinuation visit (see Appendix 1, Appendix 2, and *Appendix 3* for additional details) and to perform the MRI scans required in the controlled period (Section 4.5.7), if applicable; and are encouraged to enter and complete the safety follow-up phase (refer to Section 3.1.1.3).

After treatment discontinuation, every effort should be made to have the patient enter the safety follow-up phase of the study.

4.7.2 Patient Discontinuation from the Study

Patients will return to the clinic for a treatment discontinuation visit.

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up

- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

If a patient withdraws from the study, the patient should be asked if he or she can still be contacted for further information, unless otherwise specified by the local requirements. The outcome of that discussion should be documented in the medical record. If lost to follow-up, the investigator should contact the patient or a responsible relative by telephone followed by registered mail or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient withdrew from the study.

4.7.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.7.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with ocrelizumab IV and SC from clinical studies as well as post-marketing experience. The anticipated

important safety risks for both ocrelizumab formulations are outlined below. Refer to the ocrelizumab local label and the Ocrelizumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Ocrelizumab

Key information regarding risks is summarized below. For details, please refer to the current version of the Ocrelizumab Investigator Brochure.

5.1.1.1 Identified Risks and Adverse Drug Reactions

Infusion–Related Reactions

All CD20-depleting agents, including ocrelizumab, have been associated with acute IRRs. Symptoms of IRRs may occur during any ocrelizumab infusion but have been more frequently reported during the first IV infusion. Physicians should alert patients that IRRs can occur within 24 hours of the administration.

Across the RMS and PPMS trials, symptoms associated with IRRs included, but are not limited to pruritus, rash, urticaria, erythema, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, tachycardia, and anaphylaxis.

Patients who have received ocrelizumab IV should be observed for at least one hour after the completion of the infusion for observation of any symptom of IRR.

Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

Hypotension, as a symptom of IRR, may occur during IV ocrelizumab infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each study drug infusion.

Patients will be premedicated for ocrelizumab IV administration as described in Section 4.3.2 to minimize the risk of IRRs.

Injection-Site Reactions (subcutaneous formulation)

Injection site reactions (ISRs) were the most frequently reported adverse event in Study CN41144, occurring in 61.5% of the 96 patients who received at least one dose of ocrelizumab 1200 mg SC (CCOD 07 May 2021). All ISRs were Grade 1-2 in intensity,

non-serious, transient, and were not treatment- limiting. The majority of ISRs had resolved within 6 days and symptomatic treatment was provided for 10 out of the 96 patients. The most common ISR symptoms observed in patients who received 1200 mg SC were injection site erythema, pain, swelling, bruising, pruritus, hypersensitivity, and urticaria.

ISRs will continue to be further characterized during this study (e.g., by assessment of the reported ISR and dermatological assessment as indicated in Appendices 1-3 and Section 4.5.12).

The premedication regimen described in Section 4.3.2.1 is expected to minimize the risk of ISRs. See Section 5.3.5.1 for instructions on reporting ISRs.

Infections

Infection is an identified risk associated with ocrelizumab treatment, predominantly involving mild to moderate respiratory tract infections.

During the controlled period of the pivotal trials, the proportion of patients with serious infections in RMS was lower in the ocrelizumab group (1.3%) than in the interferon β-1a group (2.9%); in PPMS, the proportion of patients with serious infections, was similar in both groups: 6.7% in the placebo group compared with 6.2% in the ocrelizumab group.

No opportunistic infections were reported by any MS patient treated with ocrelizumab during the controlled period of the pivotal trials.

Non-disseminated herpes virus-associated infections, mostly mild to moderate, were also reported more frequently with ocrelizumab (approximately 5%–6%, simplex and zoster) than with comparators (approximately 3%).

In interventional clinical studies, there were no reports of hepatitis B reactivation in patients with MS treated with ocrelizumab, but one reported in a patient with RA treated with ocrelizumab. Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with ocrelizumab as per local guidelines. Patients with active HBV should not be treated with ocrelizumab. Patients with positive serology should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Delay ocrelizumab administration in patients with an active infection until the infection is resolved.

In the setting of a pandemic or epidemic, screening for active infections prior to and during study participation should be considered according to local/institutional guidelines or those of applicable professional societies (e.g., MS International Federation, European Academy of Neurology, American Academy of Neurology).

For PML see “Potential risks” below, Section 5.1.1.2.

Impaired Response to Vaccination

After treatment with ocrelizumab over 2 years in pivotal clinical trials, the proportion of patients with positive antibody titers against *Streptococcus pneumoniae*, mumps, rubella, and *Varicella* were generally similar to the proportions at baseline.

The results of the randomized, open-label Phase IIIb study (BN29739) that assessed if ocrelizumab recipients with RMS raise adequate humoral responses to selected vaccines indicate that patients treated with ocrelizumab were able to mount humoral responses, albeit decreased, to tetanus toxoid, 23-valent pneumococcal polysaccharide, keyhole limpet hemocyanin neoantigen, and seasonal influenza vaccines. The results are summarized in the current version of the Ocrelizumab Investigators Brochure.

Physicians should review the immunization status of patients being considered for treatment with ocrelizumab. Patients who require vaccination should complete it at least 6 weeks prior to initiation of ocrelizumab. For seasonal influenza vaccines, it is still recommended to vaccinate patients on ocrelizumab. Vaccination with live or live-attenuated vaccines are not recommended during the treatment with ocrelizumab and until B cells have returned to normal levels.

Due to the potential depletion of B-cells in neonates and infants of mothers, who have been exposed to ocrelizumab during pregnancy, it is recommended that vaccination with live or live-attenuated vaccines should be delayed until B-cells have recovered; therefore, measuring CD19-positive B cell level, in neonates and infants, prior to vaccination is recommended.

It is recommended that all vaccinations other than live or live-attenuated should follow the local immunization schedule and measurement of vaccine-induced response titers should be considered to check whether individuals can mount a protective immune response because the efficacy of the vaccination may be decreased (refer to Section 4.4.4).

Decrease in Immunoglobulins

Treatment with ocrelizumab resulted in a decrease in total immunoglobulins (Ig) over the controlled period of the studies, mainly driven by reduction in IgM. The proportion of patients with decrease in Igs below lower limit of normal (LLN) increased over time and with successive dosing. Based on additional patient exposure, in cases of continuous decrease over time, a higher risk of serious infection cannot be ruled out.

Serious Infections Related to Decrease in Immunoglobulins (Particularly in Patients Previously Exposed to Immunosuppressive/Immunomodulatory Drugs or with Pre-existing Hypogammaglobulinaemia)

The pooled data of the ocrelizumab pivotal clinical studies (RMS and PPMS) and their open-label extensions have shown an apparent association between decrease in

immunoglobulins and serious infections with ocrelizumab treatment and this was most apparent for IgG. There was no difference in the pattern (type, latency, duration, and outcome) of the serious infections reported in this subset of patients compared to the overall serious infections profile. In addition, risk factors for a subset of patients at higher risk of serious infections could not be identified.

Delayed Return of Peripheral B Cells

Treatment with ocrelizumab leads to rapid depletion of CD19+ B cells in blood by 14 days post treatment (first timepoint of assessment) as an expected pharmacologic effect. This was sustained throughout the treatment period. The longest follow-up time after the last ocrelizumab infusion from Phase II Study WA21493 in 51 patients of 600 mg ocrelizumab group indicates that the median time to repletion (returned to baseline/LLN, whichever occurred first) of B cells was 72 weeks (range 27–175 weeks).

5.1.1.2 Potential Risks

Systemic Injection Reactions (subcutaneous formulation)

Injection reactions with systemic symptoms may develop following SC administration of biological therapeutics. The majority of systemic injection reactions were of mild to moderate severity, with headache being the most commonly reported symptom.

Details on management steps and assessments to be performed in the event of severe systemic injection reactions including potential hypersensitivity/anaphylactic reactions are provided in Section 5.1.4.4.

See Section 5.1.4.3 for instructions on reporting injection reactions.

Progressive Multifocal Leukoencephalopathy

JC virus infection, resulting in progressive multifocal leukoencephalopathy (PML) has been reported in patients treated with anti-CD20 antibodies, including ocrelizumab, and mostly associated with risk factors, such as patient population or polytherapy with immunosuppressants. The reporting rate with ocrelizumab has been approximately 1 case per 100,000 patients. Since a risk of PML cannot be ruled out, physicians should be vigilant for early signs and symptoms of PML, which can include any new onset, or worsening of neurological signs or symptoms as these can be similar to an MS relapse. If PML is suspected, dosing with ocrelizumab must be withheld. Evaluation of PML, including MRI scan, preferably with contrast (compared with pre-treatment MRI) confirmatory CSF testing for JC Viral DNA and repeat neurological assessments, should be considered. If PML is confirmed, ocrelizumab must be discontinued permanently. Refer to Appendix 12 for guidance for diagnosis of PML. Also refer to the Ocrelizumab Investigator's Brochure for more details.

Hypersensitivity Reactions

Hypersensitivity may be difficult to distinguish from IRRs or systemic injection reactions in terms of symptoms. A hypersensitivity reaction may present during any

administration, although typically would not present during the first administration. For subsequent administration, more severe symptoms than previously experienced, or new severe symptoms, should prompt consideration of a potential hypersensitivity reaction. If a hypersensitivity reaction is suspected during infusion, the administration must be stopped immediately and permanently. Patients with known IgE-mediated hypersensitivity to ocrelizumab must not be treated.

Precautions and procedures for anaphylaxis are described in Appendix 11. Section 5.1.4.3 details management steps and assessments to be performed in the event of severe systemic injection reactions including potential hypersensitivity/anaphylactic reactions.

Malignancies (Including Breast Cancer)

For US only: An increased risk of malignancy with ocrelizumab may exist. In controlled trials of MS, malignancies, including breast cancer, occurred more frequently in ocrelizumab-treated patients. Breast cancer occurred in 6 of 781 females treated with ocrelizumab and none of 668 females treated with interferon β-1A or placebo.

For all countries: Patients should follow standard breast cancer screening guidelines. Refer to the current Ocrelizumab Investigator's Brochure for more details.

Neutropenia

In the controlled treatment period of the pivotal Phase III Studies WA21092, WA21093 and WA25046, decreased neutrophils were observed in 12% and 15% of patients with MS treated with ocrelizumab, in PPMS and RMS, respectively. Most were mild to moderate in severity, approximately 1% of the patients had Grade 3 or 4 neutropenia; and no temporal association with infections was identified. Based on additional patient exposure, an association between neutropenia and serious infections with ocrelizumab treatment was not observed. Refer to the Ocrelizumab Investigator's Brochure for more details.

5.1.2 Risks Associated with Corticosteroids

The adverse reactions of corticosteroids may result from unwanted glucocorticoid actions, or from inhibition of the hypothalamic-pituitary-adrenal axis. Refer to local prescribing information.

5.1.3 Risks Associated with Antihistamines

The adverse reactions depend on the sedating properties of the antihistamine and include but are not limited to nausea, drowsiness, headaches, dry mouth, and allergic reactions such as rash. Refer to local prescribing information.

5.1.4 Management of Patients Who Experience Adverse Events

5.1.4.1 Dose Modifications

Study drug dose modifications are not foreseen.

5.1.4.2 Treatment Interruption

During the study, ocrelizumab administration may be temporarily suspended in patients who experience relevant adverse events considered to be related to study drug and prevent the patient from retreatment with study drug during the study (see Section 4.3.2.3).

5.1.4.3 Management Guidelines for Injection Site Reactions

ISRs have been reported with other subcutaneously injected monoclonal antibodies, as well as with ocrelizumab SC. ISRs may occur rapidly or with a latency of a few days. Based on experience to date the reaction may manifest as local swelling, tenderness, pain and redness surrounding the injection site. If an ISR develops, patients should be monitored and observed closely, including the measurement of maximum diameter of the skin reaction at each subsequent visit. Symptomatic treatment depending on the severity (Table 3) should be provided as clinically indicated.

In case of a skin or injection reaction of Grade ≥3 severity or meeting seriousness criteria, patients will undergo a dermatologist consultation.

Table 3 Injection Site Reaction Grading

Grade	Description
1	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)
2	Pain; lipodystrophy; edema; phlebitis
3	Ulceration or necrosis; severe tissue damage; operative intervention indicated
4	Life-threatening consequences; urgent intervention indicated
5	Death

Note: Based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v5.0).

5.1.4.4 Management Guidelines for Severe Systemic Injection Reactions, including Potential Hypersensitivity/Anaphylactic Reactions

Precautions and procedures for anaphylaxis are described in Appendix 11. For cases of severe systemic injection reactions including potential hypersensitivity/anaphylactic reactions, the following should be implemented:

- Symptomatic treatment should be provided as clinically indicated
- Ensure that appropriate monitoring is in place, with continuous pulse oximetry monitoring until resolution of symptoms
- Collect serum tryptase, complement components (C3 and CH50), ADA and PK at the time points indicated in Table 4

Table 4 Samples To Be Collected in the Event of a Severe Systemic Injection Reaction Including Potential Hypersensitivity/Anaphylactic Reactions

Assessment	Timepoint related to event			
	As soon as possible but within 1 hour of event onset	3-4 hours post-event onset	24 hours post-event	Within 2 weeks post-event
Serum Tryptase	x	x		X
Serum C3	x	x	x	
Serum CH50	x	x	x	
ADA and PK	x			

ADA = anti-drug antibody; PK = pharmacokinetic.

5.1.4.5 Management Guidelines for Infusion-Related Reactions

Slowing of the infusion rate or interruption of the infusion may be necessary in the event of an infusion reaction. In rare cases, study treatment may need to be discontinued. Refer to ocrelizumab local label for further guidelines.

Handling of IRRs will depend on the intensity of symptoms and shall not depend on the dose administered (see also Table 3 for grading of intensity of IRRs).

For a **mild to moderate (Grade 1 or 2)** non-allergic, infusion-related event, the infusion rate should be reduced to half the rate being given at the time of onset of the event (e.g., from 50 mL/hr to 25 mL/hr or from 100 mL/hr to 50 mL/hr). Once the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to the next closest rate on the patient's infusion schedule and the rate increments resumed.

For a **severe infusion-related event (Grade 3)** or a complex of flushing, fever, and throat pain symptoms, the infusion should be interrupted immediately and the patient should receive aggressive symptomatic treatment. The infusion should be restarted only after all the symptoms have disappeared. The initial infusion rate at restart should be half of the infusion rate that was in progress at the time of onset of the reaction.

For a **life-threatening infusion-related event (Grade 4)** during an infusion, the infusion should be immediately stopped, and the patient should receive appropriate treatment (including use of resuscitation medications and equipment that must be available and used as clinically indicated). The patient will be discontinued from study treatment.

The above examples of dose interruption and slowing (for mild/moderate and severe IRRs) will result in a change in the infusion rate and increase the total duration of the infusion but not the total dose.

Precautions and procedures for management of hypersensitivity and anaphylactic reactions are described in Appendix 11.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Section 5.3.5.9 and Section 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Grade 3 or higher injection site reactions
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.1.2 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

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 (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 48 weeks after the final dose of study drug.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 5 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 5 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 6):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 6 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions or Injection Reactions

Adverse events that occur **during or within 24 hours** after study drug administration and are judged to be related to study drug infusion or injection should be captured as a diagnosis [e.g., "infusion-related reaction", “injection reaction” (which is applicable for local or systemic injection reactions) or "anaphylactic reaction"] on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction or Injection-Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of MS.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to progression of MS, "Multiple Sclerosis progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When

recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Multiple Sclerosis

Medical occurrences or symptoms of deterioration that are anticipated as part of MS should not be recorded as adverse events. However, deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study should be recorded as an adverse event. When recording an unanticipated worsening of MS on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of multiple sclerosis").

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Elective hospitalizations or surgical procedures that are a result of a patient's preexisting condition(s) that have not worsened since receiving trial medication. Examples may include, but are not limited to, cholecystectomy for gallstones and diagnostic testing. Such events should still be recorded as medical procedures on the eCRF.
- Hospitalization to receive study drug unless this is prolonged (more than 24 hours).
- Hospitalization following an MS relapse as long as the reason for hospitalization is to receive standard treatment with IV methylprednisolone.

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria *or qualifies as an adverse event of special interest*, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For ocrelizumab, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with ocrelizumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.

  Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor. Sites are not expected to review the PRO data for adverse events.

5.3.5.14 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Medical Monitors and Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be provided separately. An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week. *The* Emergency Medical Call Center will *connect the investigator with an Emergency Medical Contact,* provide medical translation service if necessary, , and track all calls. *Contact information including t*oll-free numbers for the *Emergency Medical Call Center* will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur Prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported.

The paper Clinical Trial Adverse Event/*Special Situations* Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 48 weeks after the final dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/*Special Situations* Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur more than 48 weeks after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the

course and outcome of the pregnancy becomes available. Information regarding infant health up to 1 year should be collected on the Infant Health Questionnaire (see Appendix 13).

5.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the adverse event reporting period (defined in Section 5.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until Pregnancy Outcome using the Infant Health Questionnaire (see Appendix 13) provided by the Sponsor.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit

to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 48 weeks after the last dose of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/*Special Situations* Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements for expedited safety reporting to regulatory authority (which includes the use of applicable systems, such as EudraVigilance), IRBs, ECs, and investigators.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the Ocrelizumab Investigator's Brochure.

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An iDMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Full details of all statistical issues and planned statistical analyses will be specified in a separate Statistical Analysis Plan, which will be finalized prior to the locking of the study database.

6.1 DETERMINATION OF SAMPLE SIZE

PK data from the pivotal studies (WA21092, WA21093, and WA25046) showed a coefficient of variation (CV) for AUC of approximately 0.30 after the fourth dose of ocrelizumab administered at Week 72, following ocrelizumab IV 600 mg every 24 weeks, in both the RMS and PPMS population.

For treatment-naïve patients, the variability of AUC could be slightly higher during the first dosing cycle, when the patient's B cells have not been depleted. The variability of AUC following SC administration is expected to be higher compared to IV, with the estimated CV to be available following the ongoing Phase Ib study (OCARINA I).

Assuming the CV for the IV and SC administration are 0.50 and 0.75, respectively, an analysis of unequal variance is used, and the true GMR of AUC SC versus AUC IV is 1, 232 patients (116 per treatment arm) need to be enrolled in order to achieve 90% power with a one-sided α of 0.05 for the non-inferiority analysis. The non-inferiority would be established if the lower end of the two-sided 90% CI is $>$0.8. The non-inferiority limit of 0.8 corresponds to a maximum 20% loss in AUC for the SC administration compared with IV. The rationale for the 0.8 non-inferiority margin relies on the standard lower bound recommended in the regulatory guidance documents for demonstration of bioequivalence for PK bridging (EMA "Guideline on the Investigation of Bioequivalence" [2010]/FDA Draft Guidance for Industry, "Bioavailability Studies Submitted in NDAs or INDs—General Considerations" [2019]). If the observed CV in either the SC or IV arm of the CN41144 study at the time of the data snapshot is greater than these assumed values, then the sample size for this study may be increased to maintain the desired study power. In addition to the theoretical PK considerations described above, the proposed sample size also takes into account the adequacy of the safety database to demonstrate the safety profile of ocrelizumab SC in its intended use. The proposed estimated extent of exposure will allow for characterization of common AEs. Given the number of patients exposed and assuming 200 patients had at least one SC dose at the clinical cutoff date (CCOD), any risk of 1.49% or higher can be ruled out with 95% confidence if 0 events are observed in the study.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue treatment or study, or complete the study will be summarized. Reasons for premature treatment and study discontinuation will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, and stratification factors) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment group.

6.4 EFFICACY ANALYSES

6.4.1 Secondary Radiological Estimand

6.4.1.1 Main Estimand

The secondary efficacy analysis will be done separately for each MS subtype (RMS or PPMS), for specific visits, and each variable (T1Gd+ lesions or new and/or enlarging T2 lesions).

Patients will be grouped according to their *planned* treatment and included if receiving, during the controlled period, at least one full or partial dose of either Reference or Experimental treatment.

T1 Gd+ lesions will be performed and analyzed on Week 8 and 24 visits while new and/or enlarging T2 lesions will be analyzed on Week 12 (relative to Week 8) and Week 24 (relative to Week 12).

The estimand for the secondary efficacy analysis follows a combination of while on study and treatment-policy and estimates the treatment effect on the considered MRI variable, regardless of adherence, on the basis of the following attributes:

a) Treatment: Ocrelizumab IV (Reference) versus ocrelizumab SC (Experimental).

b) Population: RMS or PPMS patients defined through the in/exclusion criteria reflecting the target population. The analysis population will consist of all randomized patients who performed a brain MRI scan.

c) Variable: total number of T1 Gd+ lesions (Week 8 or 24) or new and/or enlarging T2 lesions from all subjects at Week 12 or 24. New and/or enlarging T2 lesions are relative to the previous scan, i.e., relative to Week 8 at Week 12 and relative to Week 12 at Week 24.

d) Intercurrent events will be handled as follows:

- Withdrawal from treatment or incomplete dosing: *these intercurrent events will be ignored and* MRI assessment will be collected in all patients.
- *Initiation of treatment for symptoms of multiple sclerosis: the intercurrent event will be ignored.*

e) Population-level-summary estimator

- The estimand variable will be modeled by a negative binomial regression that includes the treatment variable and is adjusted for covariates. Covariates for

variable total number of T1 Gd+ lesions are: baseline T1 Gd+ lesion (present or not), and geographical region (U.S. vs. ROW). Covariate for variable new and/or enlarging T2 lesions *is* geographical region (U.S. vs. ROW). The adjusted Incidence Rates (for each treatment arm) estimated from such models will be reported along with the two-sided 95% CIs.

- If the negative binomial model fails to converge due to an extremely low number of patients with lesions, unadjusted rate and Poisson two-sided 95% CI will be reported instead. *If even the Poisson model does not converge, unadjusted rate and two-sided 95% CI will be reported instead.*
- No formal statistical testing will be done. The estimated rates (adjusted or unadjusted) and two-sided 95% CI will be evaluated to confirm that SC and IV treatment result in similarly low rates of lesions.

f) Handling of missing data

- MRI performed but not possible to read the number of lesions: assessment will not be used in the estimand variable.
- MRI not performed: No data will be imputed.
- Withdrawal from study (missing data): No data will be imputed.

6.4.1.2 Supplementary Estimand Analysis Applying Hypothetical-Policy Strategy

Week 24 assessments should be performed during the controlled treatment period (i.e., before Week 24 SC dosing). It is not ruled out that some MRI assessments are collected after the Week 24 SC dosing has been given (i.e., during the ocrelizumab SC treatment period). This supplementary estimand will apply a hypothetical-policy strategy on such assessments. Hence this supplementary estimand will be performed as the main estimand excluding assessments performed during the ocrelizumab SC treatment period.

6.4.2 Exploratory Radiological and Clinical Endpoints

The parameters defined in Section 2 will be summarized by descriptive statistics by treatment in the RMS and PPMS patient populations and in the overall population.

MRI parameter Total number of new or enlarging T2 lesions as detected by brain MRI at Week 8 relative to the previous scan *(i.e., relative to baseline)* will be analyzed as per secondary radiological main estimand.

6.4.3 Exploratory PRO Endpoints

The parameters defined in Section 2.3 will be summarized by descriptive statistics by treatment in the RMS and PPMS patient populations *where needed*, and in the overall population.

6.5 SAFETY ANALYSES

The safety analysis population and period of exposure will consist of all randomized patients who received at least one infusion (partial or complete) or injection (partial or complete) of study drug (ocrelizumab IV or ocrelizumab SC) with patients grouped according to treatment received at first exposure or being ever exposed to ocrelizumab SC at the selected dose, until when patients receive any other DMTs including commercial ocrelizumab.

In an exploratory analysis, all safety analyses will be conducted on data collected from the first ocrelizumab dose until the end of the study.

Safety will be assessed through summaries of exposure to study treatment, AEs, changes in laboratory test results, and changes in vital signs.

6.5.1 Analyses of Adverse Events

All verbatim AE terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and AE severity will be graded according to CTCAE v5.0.

All AEs, SAEs, AEs leading to death, adverse event of special interest (AESI), and AEs leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent AEs) will be summarized by mapped term, appropriate thesaurus level, and severity grade.

For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

6.5.2 Analyses of Exposure, Laboratory, Vital Sign

Study treatment exposure (such as treatment duration, total dose received, and number of cycles) will be summarized with descriptive statistics.

Relevant laboratory and vital sign (pulse rate, blood pressure, pulse oximetry) data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum post-baseline severity grade.

Changes in vital signs will be summarized.

6.6 PHARMACOKINETIC ANALYSES

All patients who have measurable serum concentrations of ocrelizumab will be included in the PK analysis unless major protocol deviations or unavailability of information (e.g., exact blood sampling time, exact dosing information or incomplete dose administration, missing concentration data) occurred that may interfere with the PK evaluation. Non-linear mixed effects modeling or other appropriate methods, may be used to analyze the

concentration versus time data of ocrelizumab derived from this study. The influence of covariates such as body weight, sex, and B-cell count will be taken into account.

Exposure (AUC) to ocrelizumab and C_{max} will be estimated for each patient. Estimates for these parameters will be tabulated and summarized (mean, standard deviation, coefficient of variation, median, minimum, and maximum).

Additional PK analyses may be conducted as appropriate.

6.6.1 Primary Analysis

The primary objective for this study is to establish the non-inferiority of ocrelizumab SC compared with ocrelizumab IV on the basis of serum ocrelizumab AUC up to Week 12 (AUC_{W1-12}).

The GMR of AUC SC versus AUC IV will be presented, together with the two-sided 90% confidence interval.

The non-inferiority will be established if the lower end of the two-sided 90% CI of the GMR of AUCs is >0.8. The non-inferiority limit of 0.8 corresponds to a maximal 20% loss in AUC for the SC administration compared with IV. All available results for PK samples obtained during the first 12 weeks will be included in the PK analysis.

The primary comparison between SC and IV administered ocrelizumab will be based on the AUC_{W1-12} (i.e., over the first 3 months of the 6 monthly dosing interval after first dose), as absorption is expected to be complete by Week 12.

6.6.1.1 Estimand for Primary Analysis

The estimand for the primary analysis is based on the following attributes:

a) Treatment: Ocrelizumab IV administered at Day 1 and Day 14, 300 mg each visit (Reference), versus ocrelizumab SC at the determined dose at Day 1 (Experimental).

b) Population: RMS and PPMS patients defined through the in/exclusion criteria reflecting the target population. The analysis population will consist of all randomized patients who have received the full assigned dose of ocrelizumab and have available PK data (and all necessary supporting information, i.e., exact dosing administration information, exact blood sampling times), with patients grouped according to their actual treatment. The number of randomized patients excluded from the analysis is expected to be small, falling under the following categories:

- Withdraw after randomization and prior to dosing. Every effort will be made to ensure all randomized patients will receive the treatment on Day 1. Treatment will start within 24 hours of randomization.
- Withdraw from treatment between Day 1 and Day 14 dosing for patients randomized to IV arm. These patients would have received 300 mg only from the Day 1 infusion. Their PK data cannot be compared with the patients who

receive the full 600 mg dose. In the three Phase III IV studies, $<3\%$ patients did not receive the Day 14 dosing in each study. Reasons for treatment discontinuation will be documented.

- Incomplete dosing. A small number of patients may receive incomplete dosing. In the three Phase III IV studies, 0.6%–2% of the patients received $<80\%$ of the planned volume at the Day 1 infusion. No reliable PK comparison can be performed if the received dose is less than the full dose.
- Missing all PK data due to other reasons. Every effort will be made to ensure all PK samples with all supporting information are collected. Among these patients excluded from the analysis, systematic bias in potential exposure levels is not expected compared to all patients. All PK data from all patients in this study will be inspected visually. Samples and/or patients excluded from the analysis will be documented, together with the reason for exclusion.

c) Variable: estimated $AUC_{W1\text{-}12}$, using all available ocrelizumab serum concentrations from the PK samples.

d) Intercurrent events: they are handled within the population specification. Among the patients in the analysis population, there could be some missing individual PK samples due to missed visits, early withdrawal or other reasons. Every effort will be made to collect PK samples on schedule. The non-linear mixed effect model can estimate the AUC with limited PK data, assuming the data are missing at random.

e) Summary measure: GMR and two-sided 90% CI of SC versus IV of AUC between Week 1 and Week 12. Non-inferiority would be established if the lower end of the two-sided 90% CI is >0.8.

The primary analysis will occur once the last patient enrolled has completed the Week 12 visit, to ensure all PK samples in the first 12 weeks are included. A sensitivity analysis will be done using AUC from Week 1 to Week 24, using all available samples collected until CCOD (12 weeks after the last patient enrolled).

6.6.2 Secondary Analysis

The secondary PK objective of this study is to determine C_{max} of ocrelizumab SC in patients with MS.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity assessment will be conducted in all patients with at least one post-baseline ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (post-baseline incidence) will be summarized by treatment group. When determining post-baseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing

data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, pharmacokinetics, and biomarker endpoints will be analyzed and reported via descriptive statistics as appropriate.

6.8 BIOMARKER ANALYSES

Biomarkers will be assessed at baseline and subsequent timepoints following administration of ocrelizumab. Biomarkers will be presented as absolute value over time and/or percent change relative to baseline over time. Biomarker levels at baseline or over time may be compared with efficacy or safety measurements to assess prognostic or predictive properties. Descriptive or summary statistics will be used to describe biomarker assessments. *Baseline is defined as the latest assessment before first ocrelizumab exposure.*

6.9 INTERIM ANALYSES

No interim analyses are planned.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and IxRS data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

EDSS data will be collected through the use of an electronic device provided by a vendor (see Section 7.3 for details).

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 ELECTRONIC PATIENT- AND CLINICAL-REPORTED OUTCOME DATA

EDSS data will be collected electronically. An electronic device or web-based platform will be used to capture EDSS data. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

In the event that the vendor web-based platform or electronic device is unavailable, the paper EDSS should be completed. Once the vendor electronic device or web-based platform is available, all EDSS data must be carefully entered into web-based platform and store the paper version as source documentation.

The electronic data will be available for view access only, via a secure web server. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats that must be kept with the study records as source data. Acknowledgement of receipt of the data is required. In addition, the Sponsor will receive all data in a machine-readable format.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for

the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trials Directive (2001/20/EC) *or Clinical Trials Regulation (536/2014)* and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor has implemented a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. The Sponsor identified potential risks associated with critical trial processes and data and implemented plans for evaluating and controlling these risks. Risk evaluation and control included the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits are provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will

permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 90 sites globally will participate to enroll approximately 232 patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, MRI, biomarker and PK analyses), as specified in Section 4.5.

An iDMC will be employed to monitor and evaluate patient safety throughout the study.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and/*or* other *summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and* reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical *Study Information* at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only.

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Appendix 1
Schedule of Activities–*Controlled Period* (Ocrelizumab IV Group)

	Screen.	BL	Controlled Period						Delayed Dosing Visit [a]	Unschd. Visit [b]	ET Visit [c]	SFU [d]
Dose		**1**						**2**				
Study week		**1**	**2**	**4**	**8**	**12**	**16**	**22**	**24**				
Study day	-42 to -1	1	14	28	56	84	112	154	168				
(Window in days)			±2	±7									
Informed consent [e]	x												
Review of eligibility criteria	x	x											
Demographic data	x												
Medical history and baseline conditions	x												
EDSS score [f]	x	x				x			x		x	x	
Neurological examination [g]	x	x				x			x		x	x	x
Vital signs [h]	x	x	x			x			x	x	x	x	x
Height (in cm) [i]		x	(x) [i]										
Weight		x											
Physical examination [j]	x	x							x	x	x	x	x
Entry treatment experience questions [k]		x											
Hematology, chemistry, urinalysis [l]	x	x				x		x			x	x	x
Flow cytometry (including CD3/4/8/19 count) [m]	x	x	x	x		x	x		x	x	x	x	x
CD4 flow cytometry [m]								x					
IgG, IgA, IgM	x	x						x			x	x	x
Hepatitis B screening [n]	x												
Hepatitis B virus DNA (if required) [n]								x					
Pregnancy test (females) [o]	x	x	x						x	x			
FSH level (if applicable) [p]	x												
Brain MRI [q]	(x)	x			x	x			x		x	x	

Appendix 1 Schedule of Activities—*Controlled Period* (Ocrelizumab IV Group)

	Screen.	BL	Controlled Period						Delayed Dosing Visit [a]	Unschd. Visit [b]	ET Visit [c]	SFU [d]
Dose		**1**						**2**				
Study week		**1**	**2**	**4**	**8**	**12**	**16**	**22**	**24**				
Study day	-42 to -1	1	14	28	56	84	112	154	168				
(Window in days)			±2	±7									
PPQ [r]													
MSPTQ [s]													
Ocrelizumab ADA sample (serum) [t]		x							x	x	x	x	x
rHuPH20 ADA sample (plasma) [t]									x	x	x	x	x
PK sample (serum) [u]		x	x	x	x	x	x		x	x	x	x	x
Biomarker sample (serum) [v]		x				x			x			x	x
RBR DNA collection (optional) [w]		x											
RBR Paxgene RNA collection (optional) [w]		x	x	x	x	x	x		x				
Review of retreatment criteria		x	x						x	x			
Premedication [x]		x	x						x	x			
Ocrelizumab IV administration [y]		x	x							x			
Ocrelizumab SC administration [z]									x	x			
TASQ [aa]		x							x	x			
Telephone contact [bb]									x	x			
Concomitant medications [cc]		x	x	x	x	x	x		x	x	x	x	x
Adverse events [dd]		x	x	x	x	x	x		x	x	x	x	x
Dermatologist evaluation of injection site (for a skin or injection reaction of Grade ≥3 severity or meeting seriousness criteria)	Not Applicable								x				
Optional collection of Information on planned post-study MS treatment [ee]													*(x)*

Appendix 1 Schedule of Activities—*Controlled Period* (Ocrelizumab IV Group)

ADA=anti-drug antibody; BL=baseline; EDSS=Expanded Disability Status Scale; ET=early termination; FSH=follicle-stimulating hormone; IV=intravenous; MRI=magnetic resonance imaging; MS=multiple sclerosis; MSPTQ=MS treatment preference questionnaire; PK=pharmacokinetic; PPQ=Patient Preference Questionnaire; RBR=Roche Biosample Repository; SC=subcutaneous; Screen.=screening; SFU=safety follow-up; TASQ=Treatment Administration Satisfaction Questionnaire; Unschd.=unscheduled.

Notes: All assessments should be performed on the day of the scheduled visit, unless otherwise specified. On dosing day, all assessments should be performed prior to dosing, unless otherwise specified. Study drug will be administered to participants by IV infusion on Days 1 and 14 (i.e., Dose 1), and then by SC injection on Weeks 24*, 48, 72, and 96* (i.e., Doses 2 *to 5*).

[a] A delayed dosing visit will be performed and recorded in the Delayed Dosing Visit eCRF when dosing cannot be administered at the scheduled dosing visit. Other tests or assessments may be performed as appropriate (refer to Section 4.6.1).

[b] Assessments at unscheduled (non-dosing) visits may be performed as clinically appropriate.

[c] Only for patients who decide to discontinue from study treatment. Patients should undergo an early termination (ET) visit, be discontinued from study drug, and enter the safety follow-up phase.

[d] The safety follow-up phase is defined as 24 weeks after the last dose.

[e] Must be obtained and documented in written form before any study-specific screening procedure and initiation of study treatment.

[f] EDSS including functional system scores will be assessed and collected. *All EDSS assessments should be performed at the site.*

[g] Neurological examination will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Potential relapses should be recorded throughout the treatment period.

[h] Vital signs will be measured while the patient is in seated (preferred) or semi-seated position and will include temperature, systolic and diastolic blood pressure, pulse rate, and pulse oximetry. Temperature should be measured and recorded in the patient's notes only. Baseline pulse oximetry should be performed for newly enrolled patients on study Day 1 before premedication is given and for already enrolled patients at the next visit where vital signs are assessed per the schedule of assessments. Post-baseline pulse oximetry is only required in the event of severe systemic administration reactions including potential hypersensitivity/anaphylactic reaction (Section 5.1.4.4 and Appendix 11). On ocrelizumab dosing visits, vital signs should be taken as indicated in Section 4.5.4.1 (ocrelizumab SC administration) or Section 4.5.4.2 (ocrelizumab IV administration). On visits without study drug administration, vital signs may be collected at any time. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF page. At subsequent visits, record new or worsened clinically significant abnormalities on the AE eCRF.

[i] Height will be only collected once during the study; either at baseline for newly enrolled patients or once during the study at the patient's next scheduled patient visit.

[j] At screening and baseline, perform a complete physical examination that should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary (if indicated), and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. During the study conduct, perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the AE eCRF.

[k] Entry treatment experience questions are reported by the patient to provide treatment experience questions related to the last DMT they were treated with prior to enrollment in this study. The entry treatment experience questions will be administered at baseline, prior to ocrelizumab treatment.

[l] Hematology includes hemoglobin, hematocrit, RBC, WBC (absolute and differential: neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells), and quantitative platelet count. Chemistry includes AST, ALT, gamma-glutamyl transferase, total bilirubin, creatinine, amylase, potassium, and sodium. Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, and blood), and a microscopic examination of abnormal and clinically significant abnormalities to be performed at the site.

[m] B-cells and other cell types will be assessed in fresh whole blood using flow cytometry, to be collected prior to the administration of premedication as indicated in Section 4.3.2. This tube will be assessed at the central laboratory for TBNK (B cell count), and B cell subset assays. On visits without study drug administration, sample may be collected at any time.

[n] All patients must have a negative HBsAg test result at screening prior to enrollment. If total HBcAb is positive at screening, HB virus DNA measured by PCR must be negative to be eligible. For those patients enrolled with negative HBsAg and positive total HBcAb, HB virus DNA (PCR) must be repeated every 24 weeks.

[o] All women of childbearing potential will have a serum pregnancy test at screening analyzed by the central laboratory. Urine pregnancy tests (Urine β–human chorionic gonadotropin sensitivity of at least 25 mU/mL) will be performed at the local laboratory at specified subsequent visits. If a urine pregnancy test is positive, the patient will not receive the scheduled dose, and a confirmatory serum pregnancy test will be performed at the central laboratory.

[p] Testing of the FSH level is only applicable to female patients to confirm the post-menopausal status at screening. The sample will be analyzed by the central laboratory.

[q] The baseline and post-baseline MRI scans will be obtained as indicated (refer to Section 4.5.7). If during the screening phase, a MRI scan is required for MS diagnosis then it can serve as a baseline scan. Note that this MRI scan should be obtained approximately 10 days prior to performing the baseline visit to allow time for the centralized reading center to assess its quality and for potential re-scans if needed. MRI scans collected during the controlled period should occur within a window of ±2 weeks of the scheduled visit, as per the schedule of activities. The MRI scans, at the Week 48 and 96 visits should occur within a time ±4 weeks of the scheduled visit. For patients who discontinue from the study treatment during the controlled period, MRI scans should be still obtained as per the schedule of activities. In addition, MRI scans will be obtained in patients who discontinue from the study treatment (at ET visit) if one was not performed during the prior 4 weeks.

[r] Patient preference questionnaire will only be completed by a subset of patients whose first ocrelizumab treatment is administered as an IV infusion. It will be completed prior to the patient's ocrelizumab SC injection at Week 48, and take approximately 30 seconds–1 minute to complete.

[s] Patients will provide overall satisfaction information related ocrelizumab and whether they have a preference for ocrelizumab or the DMT they were most recently on prior to the study. The MSTPQ will be administered prior to ocrelizumab treatment as indicated.

[t] Serum and plasma samples, to be taken prior to the administration of premedication. On visits without study drug administration, sample may be collected at any time.

[u] On study drug infusion days, two serum samples (one prior to the IV methylprednisolone, or an equivalent dose of an alternative, infusion and one 30 minutes (±10 minutes) after completion of study drug infusion) will be collected. PK samples will be collected from the arm opposite to the infusion. On study drug injection days, one serum sample (prior to the oral premedication administration) will be collected (refer to Appendix 5).

[v] Serum samples for biomarkers will be collected prior to the administration of premedication as indicated. On visits without study drug administration, sample may be collected at any time.

[w] These sample types to be collected for research purposes if patient agrees to separate optional RBR consent—a single RBR DNA sample at baseline visit (or any subsequent visit if missed), and an RBR RNA (Paxgene) sample collected prior to the administration of premedication at all indicated visits (refer to Section 4.5.14.2).

[x] Patients will receive mandatory (corticosteroids and antihistamine) and optional (analgesic) prophylactic treatment before the start of each ocrelizumab infusion or injection as indicated in Section 4.3.2.2 or Section 4.3.2.1, respectively, to reduce potential IRR or injections reactions.

[y] Collect vital signs and blood samples (including an unscheduled ADA, PK, tryptase, C3 and CH50 samples), in the event of a severe systemic administration reaction including a potential hypersensitivity/anaphylactic reaction (refer to Appendix 11).

[z] Record vital signs and collect blood samples (including an unscheduled ADA, PK, tryptase, C3 and CH50 samples), in the event of a severe systemic injection reaction including a potential hypersensitivity/anaphylactic reaction (refer to Section 5.1.4.4. These samples should be collected as soon as possible after the event and at the indicated timepoints in (Section 5.1.4.4; Table 4).

[aa] Patients will evaluate and provide their experience on their most recent ocrelizumab administration (TASQ, see Section 4.5.13.2). The TASQ will be completed after completion of their ocrelizumab treatment as indicated.

[bb] After each ocrelizumab SC injection, site personnel will have a telephone conversation with the patient to collect information on AEs that may have occurred after ocrelizumab SC treatment. On the day of first ocrelizumab SC dose (i.e., Dose 2 for ocrelizumab IV group), the site personnel will contact the patient approximately 6 hours after the injection. On the subsequent dose of ocrelizumab SC the site personnel will contact the patient approximately 24 hours after injection. The site personnel should have more frequent calls with a particular patient if considered appropriate by the investigator (e.g. to follow up on potential injection reactions).

[cc] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, and nutritional supplements) used by a patient in addition to protocol-mandated treatment.

[dd] All AEs will be reported for as long as the patient remains in the study. The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[ee] *The option to collect information about the patient's planned post-study MS treatment is provided at this visit.*

Appendix 2
Schedule of Activities–*Controlled Period* (Ocrelizumab SC Group)

	Screen.	BL	Controlled Period												Delayed Dosing Visit [a]	Unschd. Visit [b]	ET Visit [c]	SFU [d]
Dose		**1**												**2**				
Study week			**1**					**2**	**4**	**8**	**12**	**16**	**22**	**24**				
Study day	-42 to -1	1	2	3	5	7	10	14	28	56	84	112	154	168				
(Window in days)								±2	±7									
Informed consent [e]	x																	
Review of eligibility criteria	x	x																
Demographic data	x																	
Medical history and baseline conditions	x																	
EDSS score [f]	x	x									x			x		x	x	
Neurological examination [g]	x	x									x			x		x	x	x
Vital signs [h]	x	x									x			x	x	x	x	x
Height (in cm) [i]		x	(x)															
Weight		x																
Physical examination [j]	x	x												x	x	x	x	x
Entry treatment experience questions [k]		x																
Hematology, chemistry, urinalysis [l]	x	x									x		x			x	x	x
Flow cytometry (including CD3/4/8/19 count) [m]	x	x						x	x		x	x		x	x	x	x	x
CD4 flow cytometry [m]													x					
IgG, IgA, IgM	x	x											x			x	x	x
Hepatitis B screening [n]	x																	
Hepatitis B virus DNA (if required) [n]													x					

Appendix 2 Schedule of Activities—*Controlled Period* (Ocrelizumab SC Group)

	Screen.	BL	Controlled Period												Delayed Dosing Visit [a]	Unschd. Visit [b]	ET Visit [c]	SFU [d]
Dose		**1**												**2**				
Study week			**1**					**2**	**4**	**8**	**12**	**16**	**22**	**24**				
Study day	-42 to -1	1	2	3	5	7	10	14	28	56	84	112	154	168				
(Window in days)								±2	±7									
Pregnancy test (females) [o]	x	x												x	x			
FSH level (if applicable) [p]	x																	
Brain MRI [q]	(x)	x								x	x			x		x	x	
MSPTQ [r]																		
Ocrelizumab ADA sample (serum) [s]		x												x	x	x	x	x
rHuPH20 ADA sample (plasma) [s]		x												x	x	x	x	x
PK sample (serum) [t]		x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x
Biomarker samples (serum) [u]		x									x			x			x	x
RBR DNA collection (optional) [v]		x																
RBR Paxgene RNA collection (optional) [v]		x						x	x	x	x	x		x				
Review of retreatment criteria		x												x	x			
Premedication [w]		x												x	x			
Ocrelizumab SC administration [x]		x												x	x			
TASQ: SC injection [y]		x												x	x			
Telephone contact [z]		x												x	x			
Concomitant medications [aa]		x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x
Adverse events [bb]		x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x

Appendix 2 Schedule of Activities—*Controlled Period* (Ocrelizumab SC Group)

	Screen.	BL	Controlled Period												Delayed Dosing Visit [a]	Unschd. Visit [b]	ET Visit [c]	SFU [d]
Dose		**1**												**2**				
Study week			**1**					**2**	**4**	**8**	**12**	**16**	**22**	**24**				
Study day	-42 to -1	1	2	3	5	7	10	14	28	56	84	112	154	168				
(Window in days)								±2	±7									
Dermatologist evaluation of injection site (for a skin or injection reaction of Grade ≥3 severity or meeting seriousness criteria)		x																
Optional: Information on planned post-study DMT																		*(x)*

ADA=anti-drug antibody; BL=baseline; EDSS=Expanded Disability Status Scale; ET=early termination; FSH=follicle-stimulating hormone; MRI=magnetic resonance imaging; MS=multiple sclerosis; MSPTQ=MS treatment preference questionnaire; PK=pharmacokinetic; PPQ=Patient Preference Questionnaire; RBR=Roche Biosample Repository; SC=subcutaneous; Screen.=screening; TASQ=Treatment Administration Satisfaction Questionnaire; Unschd.=unscheduled.

Note: All assessments should be performed on the day of the scheduled visit, unless otherwise specified. On dosing day, all assessments should be performed prior to dosing, unless otherwise specified. Study drug will be administered to participants by SC injection.

[a] A delayed dosing visit will be performed and recorded in the Delayed Dosing Visit eCRF when dosing cannot be administered at the scheduled dosing visit. Other tests or assessments may be performed as appropriate (refer to Section 4.6.1).

[b] Assessments at unscheduled (non-dosing) visits may be performed as clinically appropriate.

[c] Only for patients who decide to discontinue from study treatment. Patients should undergo an ET visit, be discontinued from study drug, and enter the safety follow-up phase.

[d] The safety follow-up phase is defined as 24 weeks after the last dose.

[e] Must be obtained and documented in written form before any study-specific screening procedure and initiation of study treatment.

[f] EDSS including functional system scores will be assessed and collected. *All EDSS assessments should be performed at the site.*

[g] Neurological examination will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Potential relapses should be recorded throughout the treatment period.

[h] Vital signs will be measured while the patient is in seated (preferred) or semi-seated position and will include temperature, systolic and diastolic blood pressure, pulse rate, and pulse oximetry. Temperature should be measured and recorded in the patient's notes only. Baseline pulse oximetry should be performed for newly enrolled patients on study Day 1 before premedication is given and for already enrolled patients at the next visit where vital signs are assessed per the schedule of assessments. Post-baseline pulse oximetry is only required in the event of severe systemic administration reactions including potential hypersensitivity/anaphylactic reaction (Section 5.1.4.4 and Appendix 11). On ocrelizumab dosing visits, vital signs should be taken as indicated in Section 4.5.4.1 (ocrelizumab SC administration). On visits without study drug administration vital signs may be collected at any time. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF page. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] Height will be only collected once throughout the study either at baseline for newly enrolled patients or once during the study at the patient's next scheduled patient visit.

[j] At screening and baseline, perform a complete physical examination that should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary (if indicated), and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. During the study conduct, perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] Entry treatment experience questions are reported by the patient to provide treatment experience questions related to the last DMT they were treated with prior to enrollment in this study. The entry treatment experience questions will be administered at baseline, prior to ocrelizumab treatment.

[l] Hematology includes hemoglobin, hematocrit, RBC, WBC (absolute and differential: neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells), and quantitative platelet count. Chemistry includes AST, ALT, gamma-glutamyl transferase, total bilirubin, creatinine, amylase, potassium, and sodium. Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, and blood), and a microscopic examination if abnormal and clinically significant abnormalities to be performed at the site.

[m] B-cells and other cell types will be assessed in fresh whole blood using flow cytometry, to be collected prior to the oral premedication as indicated in Section 4.3.2. This tube will be assessed at the central laboratory for TBNK (B cell count), and B cell subset assays. On visits without study drug administration sample may be collected at any time.

[n] All patients must have negative HBsAg test result at screening prior to enrollment. If total HBcAb is positive at screening, HB virus DNA measured by PCR must be negative to be eligible. For those patients enrolled with negative HBsAg and positive total HBcAb, HB virus DNA (PCR) must be repeated every 24 weeks.

[o] All women of childbearing potential will have a serum pregnancy test at screening analyzed by the central laboratory. Urine pregnancy tests (Urine β–human chorionic gonadotropin sensitivity of at least 25 mU/mL) will be performed at the local laboratory at specified subsequent visits. If a urine pregnancy test is positive, the patient will not receive the scheduled dose, and a confirmatory serum pregnancy test will be performed at the central laboratory.

[p] Testing of the FSH level is only applicable to female patients to confirm the post-menopausal status at screening. The sample will be analyzed by the central laboratory.

[q] The baseline and post-baseline MRI scans will be obtained as indicated (refer to Section 4.5.7). If during the screening phase, a MRI scan is required for MS diagnosis then it can serve as a baseline scan. Note that this MRI scan should be obtained approximately 10 days prior to performing the baseline visit to allow time for the centralized reading center to assess its quality and for potential re-scans if needed. MRI scans collected during the controlled period should occur within a window of ±2 weeks of the scheduled visit, as per the schedule of activities. For patients who discontinue from the study treatment during the controlled period, MRI scans should be still obtained as per the schedule of activities.

[r] Patients will provide overall satisfaction information related ocrelizumab and whether they have a preference for ocrelizumab or the DMT they were most recently on prior to the study. The MSTPQ will be administered prior to ocrelizumab treatment as indicated.

[s] Serum and plasma samples, to be taken prior to the oral premedication. On visits without study drug administration, sample may be collected at any time.

[t] On the first dosing day, two serum samples (one prior to the oral premedication administration and another 1 hour [±10 min] after end of injection) will be collected. On the subsequent dosing days, one serum sample (prior to the oral premedication administration) will be collected (see Appendix 5).

[u] Serum samples for biomarkers will be collected prior to the oral premedication as indicated. On visits without study drug administration, sample may be collected at any time.

[v] These sample types to be collected for research purposes if patient agrees to separate optional RBR consent—a single RBR DNA sample at baseline visit (or any subsequent visit if missed), and an RBR RNA (Paxgene) sample collected prior to the administration of premedication at all indicated visits (refer to Section 4.5.14.2).

[w] Patients will receive mandatory (corticosteroids and antihistamine) and optional (analgesic) prophylactic treatment *30-60 minutes* before *initiating* each ocrelizumab injection as indicated in Section 4.3.2.1 to reduce potential injections reactions.

[x] Record vital signs and collect blood samples (including an unscheduled ADA, PK, tryptase, C3 and CH50 samples), in the event of a severe systemic injection reaction including a potential hypersensitivity/anaphylactic reaction (refer to Section 5.1.4.4). These samples should be collected as soon as possible after the event and at the indicated timepoints in (Section 5.1.4.4; Table 4).

[y] Patients will evaluate and provide their experience on their most recent ocrelizumab administration (TASQ, see Section 4.5.13.2). The TASQ will be completed after completion of their ocrelizumab treatment as indicated.

[z] After each ocrelizumab SC injection, site personnel will have a telephone conversation with the patient to collect information on AEs that may have occurred after ocrelizumab SC treatment. On the day of first ocrelizumab SC dose, the site personnel will contact the patient approximately 6 hours after the injection. On the second and subsequent doses of ocrelizumab SC the site personnel will contact the patient approximately 24 hours after injection. The site personnel should have more frequent calls with a particular patient if considered appropriate by the investigator (e.g., to follow up about potential injection reactions).

[aa] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment.

[bb] All AEs will be reported for as long as the patient remains in the study. The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all serious AEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

Appendix 3
Schedule of Activities—Ocrelizumab SC Treatment Period

	Ocrelizumab SC Treatment Period[a]						*Delayed Dosing Visit* [b]	*Unschd. Visit* [c]	*ET Visit* [d]	*SFU*[e]
Dose		**3**		**4**		**5**				
Study week	**46**	**48**	**70**	**72**	**94**	**96**				
Study day	322	336	490	504	658	672				
(Window in days)				± 7						
EDSS score [f]		X		*x*		*x*		X	X	
Neurological examination [g]		X		X		X	X	X	X	*x*
Vital signs [h]		X		X		X	X	X	X	*x*
Physical examination [i]		X		X		X	X	X	X	*x*
Hematology, chemistry, urinalysis [j]	X		X		X			X	X	*x*
Flow cytometry (including CD3/4/8/19 count) [k]		X				*x*	X	X	X	
CD4 flow cytometry [k]	X		X		X					
IgG, IgA, IgM	X		X		X			X	X	*x*
Hepatitis B virus DNA (if required) [l]	X		X		X					
Pregnancy test (females) [m]		X		X		X	X			
Brain MRI [n]		X				*x*		X	X	
Ocrelizumab ADA sample (serum) [o]		X		X		X	X	X	X	*x*
rHuPH20 ADA sample (plasma) [o]		X		X		X	X	X	X	*x*
PK sample (serum) [p]		X		X		X	X	X	X	*x*
Biomarker samples (serum) [q]		X				*x*			X	
RBR Paxgene RNA collection (optional) [r]		X								
Review of retreatment criteria		X		X		X	X			
Premedication [s]		X		X		X	X			
Ocrelizumab SC administration [t]		X		X		X	X			

Appendix 3 Schedule of Activities—*Ocrelizumab SC* Treatment Period

	Ocrelizumab SC Treatment Period[a]						*Delayed Dosing Visit* [b]	*Unschd. Visit* [c]	*ET Visit* [d]	*SFU*[e]
Dose		**3**		**4**		**5**				
Study week	**46**	**48**	**70**	**72**	**94**	**96**				
Study day	322	336	490	504	658	672				
(Window in days)	±7									
TASQ: SC injection [u]		x					x			
PPQ [v]		*x*								
MSPTQ [w]		x								
PGI-SF [x]						x			*x*	
Telephone contact [y]		x		x		x	x			
Concomitant medications [z]		x		x		x	x	x	x	*x*
Adverse events [aa]		x		x		x	x	x	x	*x*
Dermatologist evaluation of injection site (for a skin or injection reaction of Grade ≥3 severity or meeting seriousness criteria)	x									
Optional: Information on planned post-study MS treatment [bb]										*(x)*

Appendix 3 Schedule of Activities—*Ocrelizumab SC* Treatment Period

ADA = anti-drug antibody; *AE = adverse event*; BL = baseline; EDSS = Expanded Disability Status Scale; ET = early termination; FSH = follicle-stimulating hormone; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSTPQ = MS treatment preference questionnaire; *PGI–SF = patient global impression of satisfaction*; PK = pharmacokinetic; PPQ = Patient Preference Questionnaire; RBR = Roche Biosample Repository; SC = subcutaneous; Screen. = screening; TASQ = Treatment Administration Satisfaction Questionnaire; Unschd. = unscheduled.

Note: All assessments should be performed on the day of the scheduled visit, unless otherwise specified. On dosing day, all assessments should be performed prior to dosing, unless otherwise specified. Study drug will be administered to participants by SC injection.

[a] For the schedule of activities for the treatment period with optional home administration of ocrelizumab SC, see Appendix 4.

[b] A delayed dosing visit will be performed and recorded in the Delayed Dosing Visit eCRF when dosing cannot be administered at the scheduled dosing visit. Other tests or assessments may be performed as appropriate (refer to Section 4.6.1).

[c] Assessments at unscheduled (non-dosing) visits may be performed as clinically appropriate.

[d] Only for patients who decide to discontinue from study treatment. Patients should undergo an ET visit, be discontinued from study drug, and enter the safety follow-up phase.

[e] The safety follow-up phase is defined as 24 weeks after the last dose.

[f] EDSS including functional system scores will be assessed and collected. All EDSS assessments should be performed at the site.

[g] Neurological examination will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Potential relapses should be recorded throughout the treatment period.

[h] Vital signs will be measured while the patient is in seated (preferred) or semi-seated position and will include temperature, systolic and diastolic blood pressure, pulse rate, and pulse oximetry. Temperature should be measured and recorded in the patient's notes only. Baseline pulse oximetry should be performed for newly enrolled patients on study Day 1 before premedication is given and for already enrolled patients at the next visit where vital signs are assessed per the schedule of assessments. Post-baseline pulse oximetry is only required in the event of severe systemic administration reactions including potential hypersensitivity/anaphylactic reaction (Section 5.1.4.4 and Appendix 11). On ocrelizumab dosing visits, vital signs should be taken as indicated in Section 4.5.4.1 (ocrelizumab SC administration). On visits without study drug administration vital signs may be collected at any time. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF page. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] During the study conduct, perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[j] Hematology includes hemoglobin, hematocrit, RBC, WBC (absolute and differential: neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells), and quantitative platelet count. Chemistry includes AST, ALT, gamma-glutamyl transferase, total bilirubin, creatinine, amylase, potassium, and sodium. Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, and blood), and a microscopic examination if abnormal and clinically significant abnormalities to be performed at the site.

[k] B-cells and other cell types will be assessed in fresh whole blood using flow cytometry, to be collected prior to the oral premedication as indicated in Section 4.3.2. This tube will be assessed at the central laboratory for TBNK (B cell count), and B cell subset assays. On visits without study drug administration sample may be collected at any time.

[l] All patients must have negative HBsAg test result at screening prior to enrollment. If total HBcAb is positive at screening, HB virus DNA measured by PCR must be negative to be eligible. For those patients enrolled with negative HBsAg and positive total HBcAb, HB virus DNA (PCR) must be repeated every 24 weeks.

[m] Urine pregnancy tests (Urine β–human chorionic gonadotropin sensitivity of at least 25 mU/mL) will be performed at the local laboratory at specified visits. If a urine pregnancy test is positive, the patient will not receive the scheduled dose, and a confirmatory serum pregnancy test will be performed at the central laboratory.

[n] The MRI scans at Week 48 and Week 96 should occur within a time ±4 weeks of the scheduled visit. In addition, MRI scans will be obtained in patients who discontinue from the study treatment (at ET visit) if one was not performed during the prior 4 weeks.

[o] Serum and plasma samples, to be taken prior to the oral premedication. On visits without study drug administration, sample may be collected at any time.

[p] On study drug injection days, one serum sample (prior to the oral premedication administration) will be collected (refer to Appendix 5).

[q] Serum samples for biomarkers will be collected prior to the oral premedication as indicated. On visits without study drug administration, sample may be collected at any time.

[r] These sample types to be collected for research purposes if patient agrees to separate optional RBR consent—a single RBR DNA sample at baseline visit (or any subsequent visit if missed), and an RBR RNA (Paxgene) sample collected prior to the administration of premedication at all indicated visits (refer to Section 4.5.14.2).

[s] Patients will receive mandatory (corticosteroids and antihistamine) and optional (analgesic) prophylactic treatment *30-60 minutes* before initiating each ocrelizumab injection as indicated in Section 4.3.2.1 to reduce potential injection reactions.

[t] Record vital signs and collect blood samples (including an unscheduled ADA, PK, tryptase, C3 and CH50 samples), in the event of a severe systemic injection reaction including a potential hypersensitivity/anaphylactic reaction (refer to Section 5.1.4.4). These samples should be collected as soon as possible after the event and at the indicated timepoints in (Section 5.1.4.4; Table 4).

[u] Patients will evaluate and provide their experience on their most recent ocrelizumab administration (TASQ, see Section 4.5.13.2). The TASQ will be completed after completion of their ocrelizumab treatment as indicated.

[v] *Patient preference questionnaire will only be completed by a subset of patients whose first ocrelizumab treatment is administered as an IV infusion. It will be completed prior to the patient's ocrelizumab SC injection at the Week 48, and take approximately 30 seconds -1 minute to complete.*

[w] *Patients will provide overall satisfaction information related ocrelizumab and whether they have a preference for ocrelizumab or the DMT they were most recently on prior to the study. The MSTPQ will be administered prior to ocrelizumab treatment as indicated.*

[x] *The PGI-SF (see Section 4.5.13.5) is completed by patients to assess their overall satisfaction of ocrelizumab SC as a treatment for their MS symptoms throughout the study. This will be administered prior to ocrelizumab treatment as indicated.*

[y] *After each ocrelizumab SC injection, site personnel will have a telephone conversation with the patient to collect information on AEs that may have occurred after ocrelizumab SC treatment. The site personnel will contact the patient approximately 24 hours after injection. The site personnel should have more frequent calls with a particular patient if considered appropriate by the investigator (e.g., to follow up about potential injection reactions).*

[z] *Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment.*

[aa] *All AEs will be reported for as long as the patient remains in the study. The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all serious AEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.*

[bb] *The option to collect information about the patient's planned post-study MS treatment is provided at this visit.*

Appendix 4
Schedule of Activities—Treatment Period with Optional Home Administration of SC Ocrelizumab

	Ocrelizumab SC Treatment Period [a]					
Dose		**3**		**4**		**5**
Study week	**46**	**48**	**70**	**72**	**94**	**96**
Study day	322	336	490	504	658	672
(Window in days)	±7					
Visit type	Site	MN	Site	MN	Site	MN
MN Informed consent [b]	x		*x*		*x*	
EDSS score [c]		x [c]		*x*[c]		*x*[c]
Neurological examination [d]	x	(x)	*x*	(x)	*x*	(x)
Vital signs [e]		x		x		x
Physical examination [f]		x		x		x
Hematology, chemistry, urinalysis [g]	x		x		x	
Flow cytometry (including CD3/4/8/19 count) [h]		x				*x*
CD4	x		x		x	
IgG, IgA, IgM	x		x		x	
Hepatitis B virus DNA (if required) [i]	*x*		*x*		*x*	
Pregnancy test (females) [j]		x		x		x
Brain MRI [k]		x [k]				*x*[k]
PPQ [l]		x				
MSPTQ [m]		x				
PGI-SF [n]						x
Ocrelizumab ADA sample (serum) [o]		x		x		x
rHuPH20 ADA sample (plasma) [o]		x		x		x
PK sample (serum) [p]		x		x		x
Biomarker serum samples [q]		x				*x*
RBR Paxgene RNA collection (optional) [r]		x				
Review of retreatment criteria		x		x		x
Premedication [s]		x		x		x
Ocrelizumab SC administration [t]		x		x		x
TASQ: SC injection [u]		x				
Telephone contact [v]		x		x		x
Concomitant medications [w]		x		x		x
Adverse events [x]		x		x		x
Dermatologist evaluation of injection site (for a skin or injection reaction of Grade ≥3 severity or meeting seriousness criteria)	x					

ADA=anti-drug antibody; EDSS=Expanded Disability Status Scale; MN=mobile nursing; MRI=magnetic resonance imaging; MS=multiple sclerosis; MSPTQ=MS treatment preference questionnaire; *PGI–SF=patient global impression of satisfaction*; PK=pharmacokinetic; PPQ=Patient Preference Questionnaire; RBR=Roche Biosample Repository; SC=subcutaneous; TASQ=Treatment Administration Satisfaction Questionnaire.

Note: All assessments should be performed on the day of the scheduled visit, unless otherwise specified. On dosing day, all assessments should be performed prior to dosing, unless otherwise specified. Study drug will be administered to participants by SC injection.

[a] For the schedule of activities before and after the treatment period with optional home administration of ocrelizumab SC, see Appendix 1 Appendix 2, and *Appendix 3. All EDSS assessments should be performed at the site.*

[b] Must be obtained and documented in written form before the optional home administration of ocrelizumab SC by a healthcare professional from the study site (if local processes are in place) at the patient's home or another suitable location (refer to Section 4.5.10). The investigator will determine whether the participant is eligible for home administration based on the eligibility criteria (i.e., absence of any local or systemic injection reaction of Grade ≥3 severity or meeting seriousness criteria that occurred during a previous ocrelizumab injection and suitability).

[c] EDSS including functional system scores will be assessed and collected. The EDSS collected at the Week 48*/72/96* MN visit *should* be performed at site when *the* patient comes for the Week 46*/70/94* visit*, respectively*.

[d] Neurological examination will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Potential relapses should be recorded throughout the treatment period. The neurological examination can be alternatively performed at the Week 48*/72/96* MN visit*s*.

[e] Vital signs will be measured while the patient is in seated (preferred) or semi-seated position and will include temperature, systolic and diastolic blood pressure, pulse rate, and pulse oximetry. Temperature should be measured and recorded in the patient's notes only. Baseline pulse oximetry should be performed for newly enrolled patients on study Day 1 before premedication is given and for already enrolled patients at the next visit where vital signs are assessed per the schedule of assessments. Post-baseline pulse oximetry is only required in the event of severe systemic administration reactions including potential hypersensitivity/anaphylactic reaction (Section 5.1.4.4 and Appendix 11) On ocrelizumab dosing visits, vital signs should be taken as indicated in Section 4.5.4.1 (ocrelizumab SC administration).

[f] During the study conduct, perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[g] Hematology includes hemoglobin, hematocrit, RBC, WBC (absolute and differential: neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells), and quantitative platelet count. Chemistry includes AST, ALT, gamma-glutamyl transferase, total bilirubin, creatinine, amylase, potassium, and sodium. Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, and blood), and a microscopic examination if abnormal and clinically significant to be performed at the site.

[h] B-cells and other cell types will be assessed in fresh whole blood using flow cytometry, to be collected prior to the oral premedication as indicated in Section 4.3.2. This tube will be assessed at the central laboratory for TBNK (B cell count), and B cell subset assays. On visits without study drug administration, sample may be collected at any time.

[i] All patients must have negative HBsAg test result at screening prior to enrollment. If total HBcAb is positive at screening, HB virus DNA measured by PCR must be negative to be eligible. For those patients enrolled with negative HBsAg and positive total HBcAb, HB virus DNA (PCR) must be repeated every 24 weeks.

[j] If a urine pregnancy test is positive, the patient will not receive the scheduled dose, and a confirmatory serum pregnancy test will be performed at the central laboratory.

[k] The MRI scan will be obtained as indicated (refer to Section 4.5.6). The MRI scan collected at the Week 48 visit can be performed at site when patient comes for the Week 46 visit, if needed.

[l] Patient preference questionnaire will only be completed by a subset of patients whose first ocrelizumab treatment is administered as an IV infusion. It will be completed prior to the patient's ocrelizumab SC injection at the Week 48 MN visit, and take approximately 30 seconds–1 minute to complete.

[m] Patients will provide overall satisfaction information related ocrelizumab and whether they have a preference for ocrelizumab or the DMT they were most recently on prior to the study. The MSTPQ will be administered prior to ocrelizumab treatment as indicated.

[n] *The PGI-SF (see Section 4.5.13.5) is completed by patients to assess their overall satisfaction of ocrelizumab SC as a treatment for their MS symptoms throughout the study. This will be administered prior to ocrelizumab treatment as indicated.*

[o] Serum and plasma samples, to be taken prior to the oral premedication.

[p] On the dosing day, one serum sample (prior to the oral premedication administration) will be collected.

[q] Serum sample for biomarkers will be collected prior to the oral premedication as indicated.

[r] This sample to be collected for research purposes if patient agrees to separate optional RBR consent—an RBR RNA (Paxgene) sample collected prior to the administration of premedication (refer to Section 4.5.14.2).

[s] Patients will receive mandatory (corticosteroids and antihistamine) and optional (analgesic) prophylactic treatment *30-60 minutes* before *initiating each ocrelizumab* injection as indicated in Section *4.3.2.1* to reduce potential injection reactions.

[t] Record vital signs and collect blood samples (including an unscheduled ADA, PK, tryptase, C3 and CH50 samples), in the event of a severe systemic injection reaction including a potential hypersensitivity/anaphylactic reaction (refer to Section 5.1.4.4). These samples should be collected as soon as possible after the event and at the indicated timepoints in (Section 5.1.4.4; Table 4).

[u] Patients will evaluate and provide their experience on their most recent ocrelizumab administration (TASQ, see Section 4.5.13.2). The TASQ will be completed after completion of their ocrelizumab treatment as indicated.

[v] Approximately 24 hours after ocrelizumab SC injection, site personnel will have a telephone conversation with the patient to collect information on adverse events that may have occurred after ocrelizumab SC treatment. The site personnel should have more frequent calls with a particular patient if considered appropriate by the investigator (e.g., to follow up about injection reactions).

[w] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment.

[x] All AEs will be reported for as long as the patient remains in the study. The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all serious AEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

Appendix 5
Schedule of Pharmacokinetic Samples at Dosing Visits

Scheduled Timepoint	Ocrelizumab SC Injection	Ocrelizumab IV Infusion
Day 1/Baseline	Before premedication prior to the ocrelizumab injection 1 hour (±10 minutes) postdose after completion of the ocrelizumab injection	Before premedication prior to the ocrelizumab infusion 30 minutes (±10 minutes) postdose after completion of the ocrelizumab infusion
Day 14/Week 2	At any time	Before premedication prior to the ocrelizumab infusion 30 minutes (±10 minutes) postdose after completion of the ocrelizumab infusion
Subsequent visits	Prior to premedication (refer to Appendix 1, Appendix 2, Appendix 3, and *Appendix 4*)	NA

IV=intravenous; SC=subcutaneous; NA=not applicable.

Appendix 6
Sample Entry Treatment Experience Questions

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Entry Treatment Experience Questions

Instructions: Please complete the following questions based on the most recent MS treatment you took before starting this study

1. **Did you receive any MS treatment before starting this study?**

☐ Yes ☐ No

If you responded 'No' then this is the end of the questionnaire.
If you responded 'Yes' then please continue to questions 2, 3 and 4.

2. **When did you stop taking your most recent MS treatment?**

☐ 0-3 months ago ☐ 4-12 months ago ☐ More than 12 months ago

3. **What was the main reason(s) for stopping your most recent MS treatment? Select up to TWO responses**

☐ I stopped treatment so I could enroll in this study

☐ MS symptoms were worsening

☐ MS symptoms were not improving as expected

☐ Side effects bothered me

☐ Treatment administration was too frequent

☐ All things considered, it took too much of my time

☐ Treatment administration was uncomfortable

☐ Other

4. **Taking all things into consideration, how satisfied or dissatisfied were you with the most recent MS treatment you received to treat your MS symptoms?**

☐	☐	☐	☐
Very satisfied	Satisfied	Dissatisfied	Very dissatisfied

Appendix 7
Sample Treatment Administration Satisfaction Questionnaire—IV

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Treatment administration satisfaction questionnaire - Intravenous infusion

Instructions: Please complete the following questions based on your last ocrelizumab treatment. Your treatment was given through a thin plastic tube and a needle that was put directly into a vein in your arm, called an intravenous or IV infusion. Please answer the questions **based on your most recent IV infusion**.

1. Thinking about the ocrelizumab IV infusion, how **satisfied** or **dissatisfied** are you with the **IV infusion** procedure?

☐	☐	☐	☐	☐
Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied

2. Thinking about the ocrelizumab IV infusion, how do you rate the **pain** you experienced **during** the **IV infusion process?**

☐	☐	☐	☐	☐
None	Mild	Moderate	Severe	Very Severe

3. Thinking about the ocrelizumab IV infusion, how do you rate the **pain** you experienced at the **site of the drug infusion?**

☐	☐	☐	☐	☐
None	Mild	Moderate	Severe	Very Severe

4. Thinking about the ocrelizumab IV infusion, how do you rate the **swelling** you experienced **at the site of the drug infusion?**

☐	☐	☐	☐	☐
None	Mild	Moderate	Severe	Very Severe

5. Thinking about the ocrelizumab IV infusion, how do you rate the **redness** you experienced at **the site of the drug infusion?**

☐	☐	☐	☐	☐
None	Mild	Moderate	Severe	Very Severe

6. Thinking about the ocrelizumab IV infusion, are the **side effects** of the **IV infusion** as you expected?

☐	☐	☐	☐	☐
Much less than expected	Somewhat less than expected	Met my expectations	Somewhat worse than my expectations	Much worse than my expectations

7. Thinking about the ocrelizumab IV infusion, how do you feel about the **amount of time** it takes for you to get your IV infusion?

☐	☐	☐
Too short	Just right	Too long

8. Thinking about the ocrelizumab IV infusion, do you feel that the **length of time** to get your IV infusion was **as you expected?**

☐	☐	☐	☐	☐
Much shorter than expected	Somewhat shorter than expected	As expected	Somewhat longer than expected	Much longer than expected

9. Thinking about your last ocrelizumab IV infusion, how **bothered** are you by the **amount of time** it takes to get the infusion?

☐	☐	☐	☐	☐
Not at all bothered	A little bothered	Moderately bothered	Quite bothered	Very bothered

10. After receiving the ocrelizumab IV infusion, do you feel **physically restricted** by any side effects at the site of drug infusion?

☐	☐	☐	☐	☐
Not at all	A little bit	Somewhat	Quite a bit	Very much

11. How **convenient** was it for you to **get your IV infusion**?

☐	☐	☐	☐	☐
Very convenient	Convenient	Neither convenient nor inconvenient	Inconvenient	Very inconvenient

12. When you received the ocrelizumab infusion, were you able to **talk** to your **nurse and/or doctor as much as** you would **like** about your illness? (please only select ONE answer)

☐ Yes, I had more than enough time to talk to my nurse and/or doctor.

☐ Yes, but I would have liked more time to talk to my nurse and/or doctor.

☐ It does not matter to me if I have time to talk to my nurse and/or doctor during my treatment.

☐ No, I did not have enough time to talk to my nurse and/or doctor.

☐ No, I did not talk to my nurse and/or doctor at all.

13. Thinking about the ocrelizumab treatment, would you **recommend** the way you received the treatment (**IV infusion**) to another patient?

☐	☐	☐	☐	☐
Definitely yes	Probably yes	I don't know	Probably not	Definitely not

Appendix 8
Sample Treatment Administration Satisfaction Questionnaire—SC

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Treatment administration satisfaction questionnaire - Subcutaneous injection

Instructions: Please complete the following questions based on your last ocrelizumab treatment. Your treatment was given through a needle injected into your abdomen (or belly) area called a subcutaneous or SC injection. Please answer the questions **based on your most recent SC injection.**

1. Thinking about your last ocrelizumab SC injection, how **satisfied** or **dissatisfied** are you with the **SC injection** procedure?

☐	☐	☐	☐	☐
Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied

2. Thinking about your last ocrelizumab SC injection, how do you rate the **pain** you experienced **during the SC injection process?**

☐	☐	☐	☐	☐
None	Mild	Moderate	Severe	Very Severe

3. Thinking about your last ocrelizumab SC injection, how do you rate the **pain** you experienced at the **site of the drug injection?**

☐	☐	☐	☐	☐
None	Mild	Moderate	Severe	Very Severe

4. Thinking about your last ocrelizumab SC injection, how do you rate the **swelling** you experienced **at the site of the drug injection?**

☐	☐	☐	☐	☐
None	Mild	Moderate	Severe	Very Severe

5. Thinking about your last ocrelizumab SC injection, how do you rate the **redness** you experienced at **the site of the drug injection?**

☐	☐	☐	☐	☐
None	Mild	Moderate	Severe	Very Severe

TASQ-SC version 4.0

6. Thinking about your last ocrelizumab SC injection, are the **side effects** of the **SC injection** as you expected?

☐	☐	☐	☐	☐
Much less than expected	Somewhat less than expected	Met my expectations	Somewhat worse than my expectations	Much worse than my expectations

7. Thinking about your last ocrelizumab SC injection, how do you feel about the **amount of time** it takes for you to get your SC injection?

☐	☐	☐
Too short	Just right	Too long

8. Thinking about your last ocrelizumab SC injection, do you feel that the **length of time** to get your SC injection was **as you expected**?

☐	☐	☐	☐	☐
Much shorter than expected	Somewhat shorter than expected	As expected	Somewhat longer than expected	Much longer than expected

9. Thinking about your last ocrelizumab SC injection, **how bothered** are you by the **amount of time** it took to get the injection?

☐	☐	☐	☐	☐
Not at all bothered	A little bothered	Moderately bothered	Quite bothered	Very bothered

10. After receiving your last ocrelizumab SC injection, do you feel **physically restricted** by any side effects at the site of drug injection?

☐	☐	☐	☐	☐
Not at all	A little bit	Somewhat	Quite a bit	Very much

Appendix 8 Sample Treatment Administration Satisfaction Questionnaire – SC

11. How **convenient** was it for you to get your most recent SC injection?

☐	☐	☐	☐	☐
Very convenient	Convenient	Neither convenient nor inconvenient	Inconvenient	Very inconvenient

12. When you received your last ocrelizumab treatment, were you able to **talk** to your **nurse and/or doctor as much as** you would **like** about your illness? (Please select only ONE answer.)

☐ Yes, I had more than enough time to talk to my nurse and/or doctor.

☐ Yes, but I would have liked more time to talk to my nurse and/or doctor.

☐ It does not matter to me if I have time to talk to my nurse and/or doctor during my treatment.

☐ No, I did not have enough time to talk to my nurse and/or doctor.

☐ No, I did not talk to my nurse and/or doctor at all.

13. Thinking about your last ocrelizumab treatment, **would you recommend** the way you received the SC treatment to another patient?

☐	☐	☐	☐	☐
Definitely yes	Probably yes	I don't know	Probably not	Definitely not

Appendix 9
Sample Patient Preference Questionnaire

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

PATIENT PREFERENCE QUESTIONNAIRE

You have now received the drug ocrelizumab in two different ways:

- through a thin plastic tube and a needle that was put directly into a vein in your arm, called an intravenous or IV infusion
- given through a needle injected into your abdomen (or stomach) area, called a subcutaneous or SC injection

Please answer the following questions about your experiences and your preferences.
There are not any right or wrong answers.

1) All things considered which method of administration did you prefer?

☐ IV ☐ SC ☐ No preference

If you have responded 'No preference,' this is the end of the questionnaire.
If you have a preference, please respond to questions 2 and 3.

2) If you have a preference for one of the administration routes, how strong is this preference?

☐ Very strong ☐ Fairly strong ☐ Not very strong

3) If you have a preference for one of the administration routes, what are the main reasons for your preference? Select up to TWO responses

☐ Feels less emotionally distressing

☐ Requires less time in the clinic

☐ Lower level of injection-site pain

☐ Feels more comfortable during administration

☐ Other reason

Appendix 10
Sample MS Treatment Preference Questionnaire

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

MS treatment preference questionnaire

Instructions: Please complete the following questions based on your experience with ocrelizumab and the most recent MS treatment you received prior to enrolling in this study

1. **Taking all things into consideration, how satisfied or dissatisfied are you with ocrelizumab as a treatment for your MS symptoms?**

☐ Very satisfied ☐ Satisfied ☐ Dissatisfied ☐ Very dissatisfied

2. **All things considered, based on your experience with ocrelizumab and the most recent MS treatment you took prior to the study, which did you prefer?**

☐ I had not taken any MS treatment prior to this study

☐ Preference for ocrelizumab

☐ Preference for MS treatment I had taken prior to the study

☐ No preference

3. **What is the reason for your preference? (Select all responses that apply)**

☐ It treats my MS symptoms more effectively

☐ Less side effects

☐ All things considered, it takes less of my time

☐ It is administered less frequently

☐ Treatment administration is more comfortable

☐ Other

Appendix 11
Precautions and Procedures For Severe Systemic Administration Reactions Including Hypersensitivity/Anaphylactic Reactions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion:

- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Monitoring devices: electrocardiogram (ECG) monitor, blood pressure monitor, pulse oximeter monitor (record values in the eCRF), and thermometer
- Oxygen
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment administration, the following procedures should be performed:

1. Stop the study treatment administration, if applicable.
2. Call for additional medical assistance, as required.
3. Maintain an adequate airway.
4. Administer epinephrine if anaphylaxis is suspected.
5. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
6. Administer antihistamines, corticosteroids, IV fluids or other medications as required by patient status and as directed by the physician in charge.
7. Continue to observe the patient and document observations until resolution.
8. Collect serum tryptase, complement components (C3 and CH50), ADA and PK at the time points indicated in Table 1.

Table 1 Samples to be Collected in the Event of a Severe Systemic Administration Reactions Including Potential Hypersensitivity/Anaphylactic Reactions

Assessment	Timepoint related to event			
	As soon as possible but within 1 hour of event onset	3–4 hours post-event onset	24 hours post-event	Within 2 weeks post-event
Serum Tryptase	x	x		x
Serum C3	x	x	x	
Serum CH50	x	x	x	
ADA and PK	x			

ADA = anti-drug antibody; PK = pharmacokinetic

Appendix 12
Progressive Multifocal Leukoencephalopathy: Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy

Action Steps if PML Is Suspected

- If the clinical presentation is suggestive of progressive multifocal leukoencephalopathy (PML) further investigations should include brain magnetic resonance imaging (MRI) evaluation as soon as possible (see Table 1). If MRI evaluation reveals lesions suspicious for PML (Berger et al. 2013; see Figure 1), a lumbar puncture with evaluation of the cerebrospinal fluid (CSF) should be undertaken for the detection of JC virus (JCV) DNA by polymerase chain reaction using a validated sensitive assay. A diagnosis of PML can potentially be made by evaluating clinical and MRI findings plus the identification of JCV in the CSF.
- For details, please refer to the most up-to-date laboratory manual providing sample handling and shipment instructions.
- There is no known treatment or cure for PML. Treatment considerations are discussed in the medical literature (Calabrese et al. 2007).

Magnetic Resonance Imaging Assessment

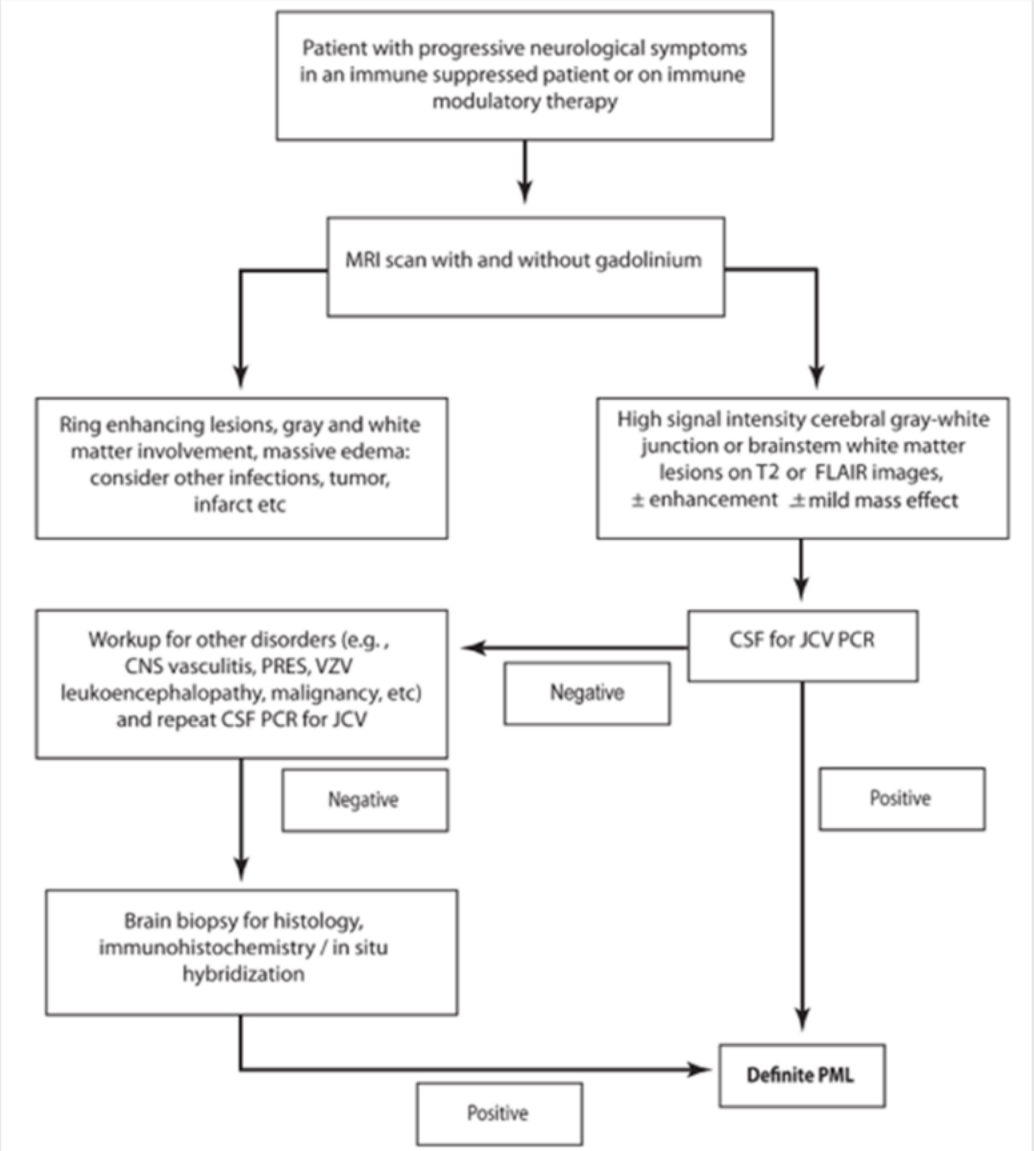
- Although there are no pathognomonic findings that differentiate PML from multiple sclerosis (MS), a brain MRI scan that includes fluid-attenuated inversion recovery and T2-weighted and T1-weighted sequences, with and without gadolinium, should be performed to assess patients with neurologic changes suggestive of PML (see Figure 1).
- Comparison with baseline scan may assist with interpretation of the findings on the newly acquired MRI for differences in lesion characteristics that may help differentiate between PML and MS (see Table 2).

Cerebrospinal Fluid Assessment

- The detection of JCV DNA in the CSF of a patient with clinical and MRI features suggestive of PML establishes the diagnosis of PML.
- If JCV DNA is not detected in CSF and if clinical suspicion of PML remains high, a repeat lumbar puncture should be performed.
- If diagnosis remains uncertain and suspicion of PML remains high, a brain biopsy may be considered to establish a definitive diagnosis.

Appendix 12 Progressive Multifocal Leukoencephalopathy: Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy

Figure 1 Diagnostic Algorithm Framework for PML



FLAIR = fluid-attenuated inversion recovery; JCV = JC virus; PML = progressive multifocal leukoencephalopathy; PRES = posterior reversible encephalopathy syndrome; VZV = varicella-zoster virus.

Source: Berger et al. 2013.

Table 1 Clinical Signs and Symptoms Typical of Multiple Sclerosis and Progressive Multifocal Leukoencephalopathy

Onset	MS Acute	PML Subacute
Evolution	• Over hours to days • Normally stabilized • Resolve spontaneously even without therapy	• Over weeks • Progressive
Clinical presentation	• Diplopia • Paresthesia • Paraparesis • Optic neuritis • Myelopathy	• Cortical symptoms/signs • Behavioral and neuropsychological alteration • Retrochiasmal visual defects • Hemiparesis • Cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination)

MS=multiple sclerosis; PML=progressive multifocal leukoencephalopathy.
Adapted from: Kappos et al. 2007.

Table 2 MRI Lesion Characteristics Typical of PML and MS

Feature	Multiple Sclerosis	PML
Location of new lesions	Mostly focal; may affect entire brain and spinal cord, in white and possibly gray matter; posterior cranial fossa lesions are rarely seen	Diffuse lesions, mainly subcortical and rarely periventricular, located almost exclusively in white matter, although occasional extension to gray matter has been seen; posterior fossa frequently involved (cerebellum)
Borders	Sharp edges; mostly round or finger-like in shape (especially periventricular lesions), confluent with other lesions; U-fibers may be involved	Ill-defined edges; infiltrating; irregular in shape; confined to white matter, sparing gray matter; pushing against the cerebral cortex; U-fibers destroyed
Mode of extension	Initially focal, lesions enlarge within days or weeks and later decrease in size within months	Lesions are diffuse and asymmetric, extending homogeneously; no confluence with other lesions; confined to white matter tracks, sparing the cortex; continuous progression
Mass effect	Acute lesions show some mass effect	No mass effect even in large lesions (but lesion slightly abuts cerebral cortex)
On T_2-weighted sequence	• Acute lesions: hyperintense center, isointense ring, discrete hyperintensity outside the ring structure • Subacute and chronic lesions: hyperintense, with no ring structure	Diffuse hyperintensity, slightly increased intensity of newly involved areas compared with old areas, little irregular signal intensity of lesions
On T_1-weighted sequence	Acute lesions: densely hypointense (large lesions) or isointense (small lesions); increasing signal intensity over time in 80%; decreasing signal intensity (axonal loss) in about 20%	Slightly hypointense at onset, with signal intensity decreasing over time and along the affected area; no reversion of signal intensity
On FLAIR sequence	Hyperintense, sharply delineated	Hyperintensity more obvious, true extension of abnormality more clearly visible than in T_2-weighted images
With enhancement	• Acute lesions: dense homogeneous enhancement, sharp edges • Subacute lesions: ring enhancement • Chronic lesions: no enhancement	Usually no enhancement even in large lesions; in patients with HIV, some peripheral enhancement is possible, especially under therapy
Atrophy	Focal atrophy possible, due to focal white matter degeneration; no progression	No focal atrophy

FLAIR = fluid-attenuated inversion recovery; MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy.

Adapted from: Yousry et al. 2006.

Appendix 13
Pregnancy Outcome and Infant Health Information on First Year of Life

Do not reproduce or distribute. The Sponsor will provide sites with all forms to be completed in this study.

Pregnancy Outcome and Infant Health Information on First Year of Life

If twin or multi-gestational pregnancy, this questionnaire has to be filled out separately for each baby born in the multi-gestational pregnancy.

Please check all that apply and provide detailed information on complications in infant on last page.

Table 1: Parent's (or Person with Parental Responsibility in Law) Consent to Data Collection

Has parent's (or person's with parental responsibility in law) data authorization form been signed?	☐Yes ☐No	Date signed _____	Other – comment _____
	Date consent withdrawn: (if applicable)		

Table 2: Information on Birth

Mode of birth	☐Vaginal delivery Forceps / vacuum: - Yes ☐ - No ☐ ☐Cesarean section (CS) - scheduled CS ☐ - emergency CS ☐	Reason for assisted delivery/Cesarean section_____
Gestational age at birth	_____ weeks - since conception ☐ - since LMP ☐	Induced labor - Yes ☐ - No ☐

Table 3: Growth Alteration, Congenital Anomalies and Functional Deficits

Date of Assessment			
Growth alteration - Yes ☐ - No ☐	☐Small for gestational age (SGA) ☐Low birth weight ☐Short birth length	If Growth alteration present: Specify weight:_____ Specify length: _____	Contributing factors:
Congenital anomalies - Yes ☐ - No ☐	☐ Major structural malformation A defect that has either cosmetic or functional significance to the child	Specify: _____ _____	Contributing factors:
	☐ Minor structural malformation A defect that occurs infrequently but has neither cosmetic nor functional significance to the child	Specify: _____ _____	Contributing factors:
	☐ Deformation A defect attributable to deformation of a structure, which had previously formed normally (usually due to mechanical force)	Specify: _____ _____	Contributing factors:
	☐ Disruption A defect due to destruction of a structure, which has previously formed normally (may be of vascular, infectious, or mechanical origin)	Specify: _____ _____	Contributing factors:
Functional deficit (except for infections, which should be described in separate table below) - Yes ☐ - No ☐	☐Functional deficit	Specify: _____ _____ _____	Contributing factors: _____ _____

Infant status at the time of latest follow-up (at birth, 3 months, 6 months, 12 months)

Table 4: Status of Infant

Date of Assessment		Contributing factors/ Comments
Status of infant	☐Normal ☐Abnormal, specify abnormality: _____ ☐Neonatal/infant death, specify cause and date of death: _____	_____ _____
Nursing status	☐Exclusive breastfeeding ☐Mixed feeding (partial breastfeeding along with infant formula and/or baby food), specify date since when: _____ ☐Fully weaned, specify date since when: _____	_____

Infections in neonate and infant during first year of life

Any infection detected at birth?

☐ Yes

☐ No

☐ Unknown

If available, please provide CD19 count (B cell values) at birth (regardless of infection). Are the results (select one option below)____?

☐ Normal

☐ Abnormal

☐ Unknown

If abnormal, specify test result:

If abnormal, date of test:

If infection detected at birth then Tables 5 and 6 should to be filled out and additional detailed information may be provided on last page.

If no infection detected at birth, however an infection developed later during the first year of live, please move directly to Table 7.

If no infection detected at birth, and if also no infection developed during the first 12 months then move directly to Table 8.

Table 5: Information on Infection in Neonate at Birth

Specify the event term:	**Event number**		
Location of infection present in neonate at birth? Site of infection (specify):		**Outcome of infection?**	**Duration of infection?**
		☐Resolved ☐Improving ☐Fatal ☐Persisting ☐Unknown	**Duration**:_____
Intensity of infection (Grade 1-5 NCI CTCAE)?	**Seriousness of infection?**	**Treatment with anti-infective?**	**Pathogen causing infection known?**
Severity: ☐Mild (Grade 1) ☐Moderate (Grade 2) ☐Severe (Grade 3) ☐Life-threatening (Grade 4) ☐Death (Grade 5)	Serious: ☐Yes ☐No	☐Yes, specify: _____ ☐No ☐Unknown	☐Yes, specify: _____ ☐No ☐Unknown
Relevant laboratory test results (in newborn infant):			
CD19 count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
IgG levels	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
White blood cell count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Neutrophil count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Lymphocyte count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Other, specify:	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____

Table 6: Maternal risk factors for neonatal infection (during most recent pregnancy, if infant developed neonatal infection at birth)

Maternal risk factors for neonatal infection	**Date of diagnosis**	If **diagnosed, was pregnant mother treated with anti-infective prior to delivery?**
☐Maternal intrapartum colonization or infection with group B streptococcus (GBS) ☐Maternal listeriosis ☐Premature rupture of membranes (PROM) ☐Meconium in amniotic fluid (meconium-stained liquid) ☐Active genital herpes infection ☐CMV ☐HPV (papilloma virus) Other, specify	_____ _____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____ _____

Relevant laboratory test results in pregnant mother:			
CD19 count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
IgG levels	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
White blood cell count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Neutrophil count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Lymphocyte count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Other, specify: (e.g., any specific antibodies and their titers)	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____

Any infection detected during first year of infant's life?

☐ Yes

☐ No

☐ Unknown

If infection detected during first year of infant's life, then Table 7 should to be filled out and additional detailed information may be provided on last page. If no infection developed during first 12 months of life, then please move directly to Table 8.

Table 7: Information on infection detected during first year of infant's life

Specify the event term:	**Event number (automatically populated by the system?)**		
Location of infection?	**Infant's age on day of onset of infection?**	**Outcome of infection?**	**Duration of infection?**
Site of infection (specify): _____ _____	**Age:** _____	☐Resolved ☐Improving ☐Fatal ☐Persisting ☐Unknown	**Duration:**_____
Intensity of infection (Grade 1-5 NCI CTCAE)?	**Seriousness of infection?**	**Treatment with anti- infective?**	**Pathogen causing infection known?**
Severity: ☐Mild (Grade 1) ☐Moderate (Grade 2) ☐Severe (Grade 3) ☐Life-threatening (Grade 4) ☐Death (Grade 5)	Serious: ☐Yes ☐No	☐Yes, specify: _____ ☐No ☐Unknown	☐Yes (specify): _____ ☐No ☐Unknown
Relevant laboratory test results (in infant):			
CD19 count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
IgG levels	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
White blood cell count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Neutrophil count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Lymphocyte count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Other, specify:	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____

Table 8: Vaccinations administered to infant at birth and during first year of age

Vaccinations administered at birth and during first year of age	Date administered	Infant's age on day of vaccination	Comments (abnormal outcome, reason for postponing vaccination, etc.)
☐Hepatitis B			
☐Rotavirus			
☐Diphtheria, tetanus, and pertussis			
☐Hemophilus influenza type b			
☐Pneumococcal			
☐Poliovirus ☐Attenuated oral polio vaccine ☐Inactivated polio vaccine			
☐Meningococcal group B bacteria			
☐Tuberculosis (Bacille Calmette Guérin, BCG) bacteria			
☐Other vaccination, specify: _____			

Table 9: Fetal/neonatal abnormalities in previous pregnancies

Fetal/neonatal abnormalities (in previous pregnancies)			Please, provide specifics including contributing factors
None ☐	Yes ☐	Unknown ☐	
Infection; if yes, specify			
Death in utero; if yes, specify reason			
Birth defects; if yes, specify			
Family history of birth defects; if yes, specify			
Small for gestational age at birth (or Intrauterine growth retardation)			
Premature delivery (before 37 weeks)			
Other; specify			

Detailed information on health-related findings in infant during first year of life

Please enter text in the free text box below.

Appendix 14
Sample: Patient Global Impression of Satisfaction

Do not reproduce or distribute. The Sponsor will provide sites with all forms to be completed in this study.

Taking all things into consideration, how satisfied or dissatisfied are you with ocrelizumab SC as a treatment for your MS symptoms?

☐	☐	☐	☐
Very satisfied	Satisfied	Dissatisfied	Very dissatisfied

Signature Page for Protocol - CN42097 - OCREVUS - v4 - United States - Published
System identifier: RIM-CLIN-493468

Approval Task	[redacted] 07-Jul-2023 16:16:34 GMT+0000

PROTOCOL

TITLE:	**A PHASE III, NON-INFERIORITY, RANDOMIZED, OPEN-LABEL, PARALLEL GROUP, MULTICENTER STUDY TO INVESTIGATE THE PHARMACOKINETICS, PHARMACODYNAMICS, SAFETY AND RADIOLOGICAL AND CLINICAL EFFECTS OF SUBCUTANEOUS OCRELIZUMAB VERSUS INTRAVENOUS OCRELIZUMAB IN PATIENTS WITH MULTIPLE SCLEROSIS**
PROTOCOL NUMBER:	CN42097
STUDY NAME:	OCARINA II
VERSION NUMBER:	*3*
EUDRACT NUMBER:	2020-005448-48
IND NUMBER:	100,593
NCT NUMBER:	NCT05232825
TEST PRODUCT:	Ocrelizumab (RO4964913)
SPONSOR:	F. Hoffmann-La Roche Ltd
***APPROVAL*:**	See electronic *signature and* date stamp *on the final page of this document*.

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
3	*See electronic date stamp on the final page of this document*
2	*24 February 2022*
1	21 January 2021

PROTOCOL AMENDMENT, VERSION 3: RATIONALE

Protocol CN42097 has been amended primarily [redacted] based on data from the ongoing Phase Ib Study CN41144 (OCARINA I). The SC treatment period has also been extended from 48 weeks to 96 weeks. Changes to the protocol, along with a rationale for each change, are summarized below

- [redacted] The large majority of reactions were local, a minority were systemic, and all were manageable as per the guidelines from the previous versions of the protocol (Section 5.1.4 and Appendix 11) which continue to apply without any changes. [redacted]
- [redacted] As mentioned above, safety information from Study CN41144 shows a decreasing incidence of local and systemic injection reactions after the first ocrelizumab SC injection. All local and systemic reactions to date have been non-serious. Local reactions were all CTCAE Grade 1–2. Systemic injection reactions with onset less than 1 hour after the start of injection (most commonly: headache) have been Grade 1 or 2, non-serious, and resolved with standard treatments. [redacted]
- The treatment period has been extended from 48 weeks to a maximum of 96 weeks for continued assessment of safety and tolerability, immunogenicity, home administration, radiological and clinical effects, pharmacodynamics, biomarkers, and patient-reported outcomes after longer-term SC administration of ocrelizumab (Section 3.1.1.2, Appendix 3). Endpoints for the exploratory radiological and clinical objective, patient reported objective, pharmacodynamic objective and biomarker objective have been modified accordingly to include assessments at later visits during the extended treatment period (Section 2.2, 2.3, 2.6, 2.7).
- Home administration of ocrelizumab can occur from the third ocrelizumab dose onwards (i.e. Week 48, Week 72, Week 96; Section 3.1.1.2, Appendix 4) and there is no longer a maximum number of patients. In the mobile nursing schedule of

assessments it has been clarified that EDSS assessment must occur at the site (i.e. at Week 46, Week 70 or Week 94 visits) and cannot be performed at the patient's home or other dosing location (Appendix 4).

- A new patient-reported outcome has been included at Week 96 during the extended treatment period to assess patients' global impression of overall satisfaction of SC ocrelizumab as a treatment for their MS symptoms during the study (Section 2.3, 4.5.13, Appendix 3, Appendix 14).
- Potential risks have been updated with current information about PML (Section 5.1.1.2).
- The duration of the Safety Follow Up (SFU) period has been shortened from 48 weeks to 24 weeks after last dose of study drug (Section 3.1.1.3 and 3.2). No safety concerns post last dose (e.g. withdrawal syndrome, immune reconstitution inflammatory syndrome, rebound in MS activity/progression) have been identified from the SFU periods of the ocrelizumab intravenous (IV) studies, and differences are not expected between SC and IV with respect to safety after the last dose. An extended SFU period in the SC studies will not contribute to the further characterization of the risks of local and systemic injection reactions, which are the only risks specific to this route of administration. In addition, shortening the SFU period will avoid unnecessarily delaying patient access to post-study treatment indicated for their multiple sclerosis (MS).
- The option to collect information about the patient's planned post-study MS treatment has been added to the 24-week SFU visit (Section 3.1.1.3).
- The email address for withdrawal from the Research Biosample Repository after site closure has been corrected (Section 4.5.14.5).
- Language has been added to clarify that adverse events associated with a special situation that also qualify as adverse events of special interest should be reported within 24 hours (Section 5.3.5.12).
- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol (Section 5.4.1). Medical Monitor contact information has been replaced with a sentence indicating that this information will be provided separately to sites.
- A description of the technical and organizational security measures taken to protect personal data has been added to align with CTR requirements (Section 8.4).
- Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access in addition to redacted Clinical Study Reports (Section 9.6).
- The name of a Roche policy on data sharing has been corrected (Section 9.6).

Substantive new information appears in *italics*. This amendment represents cumulative changes to the original protocol.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL ACCEPTANCE FORM

TITLE:	**A PHASE III, NON-INFERIORITY, RANDOMIZED, OPEN-LABEL, PARALLEL GROUP, MULTICENTER STUDY TO INVESTIGATE THE PHARMACOKINETICS, PHARMACODYNAMICS, SAFETY AND RADIOLOGICAL AND CLINICAL EFFECTS OF SUBCUTANEOUS OCRELIZUMAB VERSUS INTRAVENOUS OCRELIZUMAB IN PATIENTS WITH MULTIPLE SCLEROSIS**
PROTOCOL NUMBER:	CN42097
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EUDRACT NUMBER:	2020-005448-48
IND NUMBER:	100,593
NCT NUMBER:	NCT05232825
TEST PRODUCT:	Ocrelizumab (RO4964913)
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, NON-INFERIORITY, RANDOMIZED, OPEN-LABEL, PARALLEL GROUP, MULTICENTER STUDY TO INVESTIGATE THE PHARMACOKINETICS, PHARMACODYNAMICS, SAFETY AND RADIOLOGICAL AND CLINICAL EFFECTS OF SUBCUTANEOUS OCRELIZUMAB VERSUS INTRAVENOUS OCRELIZUMAB IN PATIENTS WITH MULTIPLE SCLEROSIS**
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IND NUMBER:	100,593
NCT NUMBER:	NCT05232825
TEST PRODUCT:	Ocrelizumab (RO4964913)
PHASE:	Phase III
INDICATION:	Multiple Sclerosis
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

This study will evaluate the pharmacokinetics, pharmacodynamics, safety, immunogenicity, and radiological and clinical effects of subcutaneous (SC) administration of ocrelizumab compared with the intravenous (IV) infusion of ocrelizumab in patients with either relapsing multiple sclerosis (RMS) or primary progressive multiple sclerosis (PPMS). Specific objectives and corresponding endpoints for the study are outlined below.

PRIMARY PHARMACOKINETIC OBJECTIVE

The primary PK objective of this study is to demonstrate PK non-inferiority of the SC formulation of ocrelizumab in patients with multiple sclerosis (MS) on the basis of the following endpoint:

- Serum ocrelizumab area under the concentration–time curve (AUC_{W1-12}) after SC administration compared to IV infusion from Day 1 to Week 12.

SECONDARY PHARMACOKINETIC OBJECTIVE

The secondary PK objective of this study is to determine the maximum serum concentration (C_{max}) of ocrelizumab SC in patients with MS.

SECONDARY RADIOLOGICAL OBJECTIVE

The secondary radiological objective for this study is to evaluate the radiological effects of ocrelizumab SC compared with ocrelizumab IV in patients with MS on the basis of the following endpoints:

- Total number of T1Gd+ lesions as detected by brain MRI at Weeks 8 and 24.
- Total number of new or enlarging T2 lesions as detected by brain MRI at Weeks 12 and 24 relative to the previous scan, respectively.

EXPLORATORY RADIOLOGICAL AND CLINICAL OBJECTIVE

The exploratory radiological and clinical objective for this study is to explore the radiological and clinical effects of ocrelizumab SC compared with ocrelizumab IV in patients with MS on the basis of the following endpoints:

- Total number of T1Gd+ lesions as detected by brain MRI at Week 48 *and Week 96*.
- Total number of new or enlarging T2 lesions as detected by brain MRI at Weeks 8*,* 48*, and 96* relative to the previous scan, respectively.
- The annualized protocol-defined relapse rate by Weeks 24*,* 48*, and 96* in RMS patients.
- Change from baseline in the expanded disability status scale (EDSS) at Week*s* 48*, 72, and 96*.

PATIENT-REPORTED OBJECTIVE

The exploratory patient-reported outcome (PRO) objective for this study is to evaluate patient preference and satisfaction for ocrelizumab SC and IV in relation to other disease-modifying treatments (DMTs) taken prior to the study, as well as preference for the SC or IV route of administration in a subset of patients:

- Patient satisfaction and experience receiving SC administration (at site and at home) and IV route of administration:
  - Patient administration satisfaction and experience scores using the Treatment Administration Satisfaction Questionnaires (TASQ) for IV Infusion following the first treatment administration in a subset of patients
  - Patient administration satisfaction and experience scores using the TASQ for SC injection
- Patient satisfaction and preference taking ocrelizumab administered SC compared to previous DMTs taken prior to the study:
  - Entry treatment experience questions to report overall treatment satisfaction scores from patients who received an MS treatment prior to the study
  - MS treatment preference score to report overall satisfaction taking ocrelizumab
  - MS treatment preference score to report the proportion of patients with a preference for ocrelizumab SC compared to previously taken DMTs.
- Patient preference for the SC or IV route of administration, specifically:
  - Proportion of patients who prefer the SC or IV route of administration using the Patient Preference Questionnaire (PPQ)
- *Patient global impression of overall satisfaction (PGI-SF) for SC ocrelizumab*
  - *Proportion of patients who are satisfied or dissatisfied with ocrelizumab SC as a treatment for their MS symptoms*

SAFETY OBJECTIVE

The safety objective of this study is to evaluate and compare the safety profile after administration of ocrelizumab SC versus ocrelizumab IV and to assess the safety of ocrelizumab SC at the selected dose in patients with MS on the basis of the following endpoints during the conduct of the study:

- Incidence and severity of adverse events, with severity determined according to the NCI CTCAE, version 5.0.
- Change from baseline in targeted vital signs.
- Change from baseline in targeted clinical laboratory test results.

IMMUNOGENICITY OBJECTIVE

The immunogenicity objective for this study is to evaluate the immune response to ocrelizumab SC and IV, and rHuPH0, based on the following endpoints:

- Incidence of treatment-emergent anti-drug antibodies (ADAs; formation of ADAs) to ocrelizumab after SC or IV administration relative to the presence of ADAs at baseline.
- Relationship between ADA status to ocrelizumab and pharmacokinetics, pharmacodynamics, and safety.
- Incidence of treatment-emergent antibodies to rHuPH20 after SC administration relative to the presence at baseline and relationships between antibodies to rHuPH20 and safety.

PHARMACODYNAMIC OBJECTIVE

The pharmacodynamic (PD) objective for this study is to evaluate the effect of SC ocrelizumab compared with IV ocrelizumab on the PD marker for the mechanism of action of ocrelizumab (i.e., B cell depletion) on the basis of the following endpoint:

- Proportion of patients achieving CD19+ B cell level ≤ 5 cells/μL at Weeks 12*,* 24*, 48, and/or 96*.

BIOMARKER OBJECTIVE

The biomarker objective for this study is to evaluate biomarkers that are predictive of response to ocrelizumab (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), can provide evidence of ocrelizumab activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology, on the basis of the following endpoints:

- Levels of biomarkers including but not limited to neurofilament light (NfL) in serum compared between dosing arms at Weeks 12, 24, 48*, and/or 96* compared to baseline.

STUDY DESIGN

DESCRIPTION OF STUDY

CN42097 is a Phase III non-inferiority, randomized, open-label, parallel group, multicenter study to evaluate the pharmacokinetics, pharmacodynamics, safety, immunogenicity, radiological, and clinical effects of SC administration of ocrelizumab compared with the IV infusion of ocrelizumab in patients with either RMS or PPMS.

NUMBER OF PATIENTS

Approximately 232 patients with MS (RMS and PPMS) will be enrolled in this study.

TARGET POPULATION

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Diagnosis of PPMS or relapsing forms of MS (RMS) according to the revised McDonald 2017 criteria (Thompson et al. 2018)
- Signed Informed Consent Form
- Age 18–65 years, inclusive, at time of signing Informed Consent Form
- Ability to comply with the study protocol and schedule of protocol assessments, in the investigator's judgment
- EDSS score, 0–6.5, inclusive, at screening
- Neurological stability for ≥30 days prior to both screening and baseline
- Disease duration from onset of MS symptoms of less than 15 years for patients with EDSS score <2.0 at screening
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use adequate contraception during the treatment period and for 6 or 12 months (as applicable by the ocrelizumab IV [Ocrevus] local label) after the final dose of ocrelizumab. Adherence to local requirements, if more stringent, is required.

  A women is considered to be of childbearing potential if she is postmenarchal, has not reached a post-menopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery

(i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a woman with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

As defined by the guidelines, the following contraceptive methods are considered acceptable (failure rate >1%): (1) progesterone-only hormonal contraception, where inhibition of ovulation is not the primary mode of action; (2) male or female condom with or without spermicide; (3) cap, diaphragm, or sponge with spermicide. (4) combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier method).

Birth control methods that are highly effective (failure rate <1%)may also be used but are not required, and include: (1) oral, intravaginal or transdermal combined hormonal contraception associated with inhibition of ovulation; (2) oral, injectable or implantable progestogen-only hormonal contraception associated with inhibition of ovulation; (3) intrauterine device; (4) intrauterine hormone-releasing system; (5) bilateral tubal occlusion; (6 vasectomized partner; (7) sexual abstinence.

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. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For female patients without reproductive potential:

  Women may be enrolled if

  - post-menopausal (i.e., spontaneous amenorrhea for the past year confirmed by a follicle-stimulating hormone [FSH] level $>$ 40 mIU/mL) unless the patient is receiving a hormonal therapy for her menopause or
  - surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy).

Exclusion Criteria

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

- Any known or suspected active infection at screening or baseline (except nailbed infections), or any major episode of infection requiring hospitalization or treatment with IV antimicrobials within 8 weeks prior to and during screening or treatment with oral antimicrobials within 2 weeks prior to and during screening
- History of confirmed or suspected progressive multifocal leukoencephalopathy (PML)
- History of cancer, including hematologic malignancy and solid tumors, within 10 years of screening
  - Basal or squamous cell carcinoma of the skin that has been excised and is considered cured and in situ carcinoma of the cervix treated with apparent success by curative therapy $>$ 1 year prior to screening is not exclusionary.
- Immunocompromised state, defined as one or more of the following:
  - CD4 count $<$250/μL
  - Absolute neutrophil count $<1.5 \times 10^3/\mu$L
  - Serum IgG $<$4.6 g/L
- Receipt of a live-attenuated vaccine within 6 weeks prior to randomization
  - Influenza vaccination is permitted if the inactivated vaccine formulation is administered.
- Inability to complete an MRI (contraindications for MRI for example, due to, pacemaker, cochlear implants, intracranial vascular clips, surgery within 6 weeks of entry in the study, coronary stent implanted within 8 weeks prior to the time of the intended MRI, etc.) or contraindication to gadolinium administration

- Contraindications to mandatory premedications (i.e., corticosteroids and antihistamines), including closed-angle glaucoma for antihistamines
- Known presence of other neurologic disorders that could interfere with the diagnosis of MS or assessments of efficacy and/or safety during the study, including, but not limited to, the following:
  - History of hemorrhagic or ischemic cerebral or spinal stroke
  - History or known presence of central nervous system (CNS) or spinal cord tumor (e.g., meningioma, glioma)
  - History or known presence of potential metabolic causes of myelopathy (e.g., untreated vitamin B12 deficiency)
  - History or known presence of infectious causes of myelopathy (e.g., syphilis, Lyme disease, HTLV-1, herpes zoster myelopathy)
  - History of genetically inherited progressive CNS degenerative disorder (e.g., hereditary paraparesis, mitochondrial myopathy, encephalopathy, lactic acidosis, stroke [MELAS] syndrome)
  - Neuromyelitis optica
  - History or known presence of systemic autoimmune disorders potentially causing progressive neurologic disease (e.g., lupus, anti-phospholipid antibody syndrome, Sjögren syndrome, Behçet disease)
  - History or known presence of sarcoidosis
  - History of severe, clinically significant brain or spinal cord trauma (e.g., cerebral contusion, spinal cord compression)
- Any concomitant disease that may require chronic treatment with systemic corticosteroids (e.g. mineralocorticoids and glucocorticoids) 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 or gastrointestinal, or any other significant disease that may preclude patient from participating in the study
- History of or currently active primary or secondary (non–drug-related) immunodeficiency
- Pregnant or breastfeeding, or intending to become pregnant during the study and 6 or 12 months (as applicable by the ocrelizumab [Ocrevus] local label) after last administration of the study drug.
  - Females of childbearing potential must have a negative serum and urine pregnancy test result prior to initiation of study drug (negative serum β-CG measured at screening and negative urine β-CG at baseline)
- Lack of peripheral venous access
- History of alcohol or other drug abuse within 12 months prior to screening
- Treatment with any investigational agent within 24 weeks prior to screening or 5 half-lives of the investigational drug (whichever is longer), or treatment with any experimental procedure for MS (e.g., treatment for chronic cerebrospinal venous insufficiency)
- Patients who have previously received anti-CD20s (including ocrelizumab) if the last treatment was less than 2 years before screening, and/or if B-cell count is below lower limit of normal, and/or the discontinuation of the treatment was due to safety reasons or lack of efficacy.
- Previous treatment with cladribine, atacicept, and alemtuzumab
- Previous treatment with fingolimod, siponimod, ponesimod, or ozanimod within 6 weeks of baseline
- Previous treatment with interferons beta (1a or 1b), or glatiramer acetate within 2 weeks of baseline
- Previous treatment with natalizumab within 4.5 months of baseline

- Treatment with mitoxantrone within 2 years prior to baseline visit or evidence of cardiotoxicity following mitoxantrone use or a cumulative lifetime dose of more than 60 mg/m^2
  - Previous treatment with any other immunomodulatory or immunosuppressive medication not already listed above without appropriate washout as described in the applicable local label. If the washout requirements are not described in the applicable local label (washout to be completed prior to baseline), then the wash out period must be 5 times the half-life of the medication. The PD effects of the previous medication must also be considered when determining the required time for washout.
  - Patients screened for this study should not be withdrawn from therapies for the sole purpose of meeting eligibility for the trial.
- Any previous treatment with bone marrow transplantation and hematopoietic stem cell transplantation
- Any previous history of transplantation or anti-rejection therapy
- Treatment with IV Ig or plasmapheresis within 12 weeks prior to randomization
- Systemic corticosteroid therapy within 4 weeks prior to screening
  - The screening period may be extended for patients who have used systemic corticosteroids for MS before screening. For a patient to be eligible, systemic corticosteroids should also not have been administered between screening and baseline.
- Positive screening tests for active, latent, or inadequately treated hepatitis B (as evidenced by either of the following):
  - Positive hepatitis B surface antigen
  - Positive hepatitis B core antibody (total HBcAb) and detectable hepatitis B virus DNA
- Sensitivity or intolerance to any ingredient (including excipients) of ocrelizumab
- Any additional exclusionary criterion as per ocrelizumab (Ocrevus®) local label, if more stringent than the above

END OF STUDY

The end of study will occur when the last participating patient completes the last scheduled visit at the end of the safety follow-up phase, or when the Sponsor decides to discontinue the study or development program.

LENGTH OF STUDY

Each patient will be in the treatment phase for up to *2* year*s* (i.e., *96* weeks) and in the safety follow-up phase for up to *24* weeks after the last ocrelizumab administration.

INVESTIGATIONAL MEDICINAL PRODUCTS

The investigational medicinal product (IMPs) for this study is ocrelizumab (comprising both the IV formulation and the SC formulation co-formulated with rHuPH20).

Test Product (Investigational Drug)

Ocrelizumab SC will be provided as a sterile, single-dose liquid at a concentration of 40 mg/mL and contains no preservatives. The ocrelizumab in the ocrelizumab SC formulation is co-formulated with rHuPH20 at a concentration of 1000 U/mL.

For information on the formulation of ocrelizumab SC co-formulated with rHuPH20, see the pharmacy manual and the Ocrelizumab Investigator's Brochure.

Comparator

Ocrelizumab IV will be provided as a sterile, single-dose liquid at a concentration of 30 mg/mL and contains no preservatives.

For information on the formulation of IV ocrelizumab, refer to the Ocrelizumab Investigator's Brochure, local prescribing information, and pharmacy manual.

NON-INVESTIGATIONAL MEDICINAL PRODUCTS

Specific premedications are required prior to the ocrelizumab infusion or injection and include mandatory methylprednisolone or dexamethasone, mandatory diphenhydramine or desloratadine, and optional oral analgesics as needed.

STATISTICAL METHODS

PRIMARY ANALYSIS

The primary objective for this study is to establish the non-inferiority of ocrelizumab SC compared with ocrelizumab IV on the basis of serum ocrelizumab area under the concentration-time curve (AUC) up to Week 12 (AUC_{W1-12}). The geometric mean ratio (GMR) of AUC SC versus AUC IV will be presented, together with the two-sided 90% confidence interval. The non-inferiority would be established if the lower end of the two-sided 90% CI of the GMR of AUC is $>$0.8. The non-inferiority limit of 0.8 corresponds to a maximal 20% loss in AUC for the SC administration compared with IV. All available results for PK samples obtained during the first 12 weeks will be included in the PK analysis. The primary comparison between SC and IV administered ocrelizumab will be based on the AUC_{W1-12} (i.e., over the first 3 months of the 6 monthly dosing interval after first dose), as absorption is expected to be complete by Week 12.

DETERMINATION OF SAMPLE SIZE

If the observed coefficient of variation (CV) in either the SC or IV arm of the CN41144 study at the time of the data snapshot is greater than these assumed values, then the sample size for this study may be increased to maintain the desired study power.

INTERIM ANALYSES

No interim analyses are planned.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ANC	absolute neutrophil count
AUC	area under the concentration-time curve
AUC_T	area under the curve over the 6-month dosing interval
AUC_{W1-12}	area under the concentration–time curve from Day 1 to Week 12
CCOD	clinical cutoff date
CIS	clinically isolated syndrome
ClinRO	clinician reported outcome
C_{max}	maximum concentration observed
CNS	central nervous system
COVID-19	coronavirus disease-2019
CV	coefficient of variation
DMT	disease-modifying treatments
E.U.	European Union
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EDSS	expanded disability status scale
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
FLAIR	fluid-attenuated inversion recovery
FSH	follicle stimulating hormone
FSS	functional system score
GMR	geometric mean ratio
HBcAb	hepatitis B core antibody
HBcAg	hepatitis B core antigen
HBV	hepatitis B
HIPAA	Health Insurance Portability and Accountability Act
IB	investigator’s brochure
ICH	International Council for Harmonisation
iDMC	internal data monitoring committee
Ig	immunoglobulin
IMP	investigational medicinal product

IND	investigational new drug (Application)
IRB	Institutional Review Board
IRR	infusion-related reaction
ISR	injection site reaction
IV	intravenous
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MN	mobile nursing
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSTPQ	multiple sclerosis treatment preference questionnaire
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NfL	neurofilament light
PCR	polymerase chain reaction
PD	pharmacodynamics
PGI-SF	*patient global impression of satisfaction*
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PMS	progressive multiple sclerosis
PPMS	primary progressive multiple sclerosis
PPQ	Patient Preference Questionnaire
PRO	patient-reported outcome
PT	preferred term
PTP	previously treated patients
RBC	red blood cell
RBR	research biosample repository
rHuPh20	recombinant human hyaluronidase PH20
RMS	relapsing multiple sclerosis
ROW	rest of world
RRMS	relapsing remitting multiple sclerosis
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SFU	safety follow-up
SmPC	summary of product characteristics
SPMS	secondary progressive multiple sclerosis
T1Gd+	gadolinium-enhancing lesions on T1-weighted

TASQ	Treatment Administration Satisfaction Questionnaires
WBC	white blood cell
WES	whole exome sequencing
WGS	whole genome sequencing
U.S.	United States of America
USPI	United States prescribing information

1. BACKGROUND

1.1 BACKGROUND ON MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, and degenerative disease of the central nervous system (CNS) that affects approximately 900,000 people in the United States (Wallin et al. 2019) and 2.8 million worldwide (MSIF 2020).

It is primarily a disease of young adults, with patients usually being diagnosed between the ages of 20 and 40 (Calandri et al. 2019), and a mean age of diagnosis of approximately 30 years (GBD 2016). MS is at least two to three times more frequent in women than in men, except in primary progressive multiple sclerosis (PPMS) where men and women are equally affected (MSIF 2020; Bove and Chitnis 2014).

MS is classified into three clinical phenotypes: relapsing remitting (RRMS), secondary progressive (SPMS), and PPMS (Lublin et al. 2014). These three phenotypes are further subdivided into active and non-active forms based on the presence or absence of disease activity, which in turn is defined by the presence of clinical relapses and/or so-called active lesions on a magnetic resonance imaging (MRI) scan. Active MRI lesions are gadolinium-enhancing lesions on a T1-weighted scan (T1Gd+), or new/enlarging T2-weighted lesions. The term relapsing MS (RMS) encompass RRMS and early stages of (active) SPMS where patient still experience relapses (Lublin et al. 2014); and progressive MS (PMS) forms constitute non-active SPMS and PPMS (Lublin et al. 2014). Evidence available to date suggests that despite the potential heterogeneity of the clinical expression of the disease, PPMS, SPMS, and RRMS belong to the same disease spectrum, and that pathological mechanisms responsible for relapses/disease activity and progression biology are largely identical across the MS spectrum (Lassmann 2018). Although the mechanisms associated with disease progression are assumed to be present from the onset of the disease (Cree et al. 2019), clinical disability progression manifests often later in the course of a patient's disease, most likely due to the degree of brain reserve of the patient. The symptomatic worsening associated with MS disability progression results in a slow, insidious loss of a patient's motor and sensory function, as well as cognitive decline and autonomic dysfunctions (Lassmann 2018).

Disability progression across the spectrum of MS might occur as a result of two concurrent inflammatory mechanisms: acute inflammation and chronic compartmentalized inflammation (Matthews 2019).

Acute inflammation can be observed on an MRI scan (as T1Gd+ lesions or new or enlarging T2 lesions) and clinically manifests as relapses, where it can also lead to step-wise increase of disability due to incomplete relapse recovery. Pathophysiologically, relapsing forms of MS (i.e., RMS) are associated with focal T-cell and B-cell invasion, with blood brain barrier leakage that gives rise to classic active demyelinating plaques in the white matter. However, RMS also harbors signs of progression biology/chronic compartmentalized inflammation.

In contrast to these acute inflammatory processes, chronic compartmentalized inflammation is responsible for an increase in disability that occurs independently from relapses or radiological disease activity and is characterized by demyelination and axonal loss (progression biology; Lassmann 2019). Progressive forms of MS are associated with a chronic and slow accumulation of T cells and B cells in the connective tissue spaces of the brain, without leakage of the blood brain barrier. There is a typical formation of subpial-demyelinated lesions in the cerebral and cerebellar cortex, with slow expansion of pre-existing lesions in the white matter and diffuse chronic inflammation in the normal-appearing white or gray matter (Lassmann 2019).

1.2 BACKGROUND ON OCRELIZUMAB

Ocrelizumab is a recombinant humanized, glycosylated, monoclonal IgG1 antibody that selectively targets and depletes CD20-expressing B cells, while preserving the capacity of B-cell reconstitution and preexisting humoral immunity. CD20 is a B-cell surface molecule that is restricted in expression to pre–B cells and mature B cells but is not expressed earlier in the development of B cells (Banchereau and Rousset 1992).

Refer to the Ocrelizumab Investigator's Brochure for relevant non-clinical, formulation, and clinical safety information for both IV and SC formulations.

1.2.1 Ocrelizumab Administered Intravenously

Based on the results of Phase III studies in patient populations with RMS and PPMS, ocrelizumab was approved by the U.S. Food and Drug Administration (FDA) on 28 March 2017 for the treatment of adult patients with RMS and PPMS. The indication for RMS was updated in 2019, at the FDA's request, to include clinically isolated syndrome (CIS), RRMS, and active SPMS. Ocrelizumab was approved by the European Medicines Agency (EMA) on 12 January 2018 for patients with active relapsing forms of MS defined by clinical or imaging features and for patients with early PPMS in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.

Two identical randomized, active-controlled studies (OPERA I [Study WA21092] and OPERA II [Study WA21093]) have demonstrated superior efficacy outcomes of ocrelizumab 600 mg versus interferon β-1a in patients with RMS (Hauser et al. 2017); one randomized placebo-controlled study (ORATORIO [Study WA25046]) has demonstrated superior efficacy of ocrelizumab 600 mg in PPMS versus placebo (Montalban et al. 2017). Results of these studies show that depletion of CD20+ B cells leads to a significant impact on a broad range of clinical measures of disease, including disability progression, in addition to an impact on MRI outcomes related to disease progression and reflective of neural tissue loss, thus further supporting the hypothesis that B cells are central to the pathogenesis of both RMS and PPMS. Ocrelizumab has demonstrated a favorable safety profile in patients with RMS and PPMS (Hauser et al. 2017; Montalban et al. 2017). The proportion of patients with adverse events (AEs) was

similar in patients treated with ocrelizumab compared with interferon β-1a (both 83.3%) or placebo (95.1% vs. 90.0%). The proportion of patients experiencing at least one serious adverse event was similar between ocrelizumab and the comparator groups (in RMS: 6.9% [ocrelizumab] and 8.7% [interferon β-1a]; in PPMS: 20.4% [ocrelizumab] and 22.2% [placebo]). Analysis of the data from open-label extension of the pivotal studies supported the long-term consistency of benefit-risk (Hauser et al. 2019).

Ocrelizumab is administered by intravenous (IV) infusion at a dose of 600 mg over 2 to 3.5 hours every 6 months. The first ocrelizumab dose of 600 mg is administered as a divided dose (2×300 mg infusions administered 2 weeks apart) with subsequent doses being administered as a single 600 mg infusion.

1.2.2 Ocrelizumab Administered Subcutaneously

A subcutaneous (SC) formulation of ocrelizumab co-formulated with rHuPH20 (herein ocrelizumab SC) is under development for administration of ocrelizumab as an SC injection. This new route of administration will provide a convenient and faster alternative to the currently approved IV infusion. Ocrelizumab SC formulation is to be administered as a single injection every 6 months. In addition, to support dosing outside of a controlled healthcare setting, including home administration for eligible patients, the Sponsor has started technical development of a medical device (an on-body injector).

A pharmacokinetic (PK)-bridging program composed of OCARINA I (CN41144, ongoing Phase Ib SC dose-selection study) and this proposed study (OCARINA II, CN42097, Phase III SC study) will be conducted in patients with MS, with the overall goal to demonstrate non-inferiority of ocrelizumab exposure between the approved IV dose and the proposed SC dose in terms of area under the concentration-time curve (AUC). Safety, tolerability, pharmacodynamics, and immunogenicity after SC administration of ocrelizumab facilitated by rHuPH20 will be assessed in both OCARINA I and in this study (OCARINA II). The PK non-inferiority is expected to translate into non-inferior efficacy and safety, as per the principle of PK bridging (Shpilberg et al. 2013; Hourcade et al. 2014).

1.2.2.1 Recombinant Human Hyaluronidase (rHuPH20)

rHuPH20 is a human hyaluronidase for injection that has been developed by Halozyme Therapeutics, Inc. rHuPH20 hydrolyzes hyaluronan, a component of the SC matrix, leading to a temporary reduction in the viscosity of the extracellular matrix of the hypodermis. This allows for large volume, rapid delivery of subcutaneously administered drugs. The recombinant human molecule has greater purity than animal-derived hyaluronidases and therefore has higher enzymatic activity per mass (refer to Hylenex® U.S. Prescribing Information (USPI), for additional details on the composition and formulation). rHuPH20 has been approved by the U.S. FDA for various indications, including increasing the dispersion and absorption of other injected drugs (Hylenex® U.S. USPI) and is used primarily as a permeation enhancer.

To date, four monoclonal antibodies co-formulated with rHuPH20, are approved for SC therapy in the United States and four in the European Union (Phesgo® USPI, Phesgo® Summary of Product Characteristics [SmPC],Darzalex Faspro™ USPI, Herceptin Hylecta® USPI; Herceptin®SC SmPC; Rituxan HYCELA® USPI; Mabthera® SC SmPC).

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Appropriate care and treatment access have been identified by both healthcare providers and patients as key contributing factors to the successful management of MS (Rieckmann 2017). Patients with MS are offered a number of biologic therapies that are provided by different administration routes and in a variety of different settings, ranging from in-office neurology practices, hospital-affiliated settings to even free-standing infusion centers, which offer services to patients afflicted with a variety of medical conditions, such as in hematology and oncology (Foley and Dunne 2011). However, these centers often face considerable challenges when administering infusion therapies; larger scale centers often have to optimize the number of staff, as well as schedule patients who require longer infusion times. Thus, an alternative and more convenient method of administration with a shorter treatment duration is expected to improve access for patients with MS who would prefer another treatment administration besides the approved IV method.

The marketed formulation of ocrelizumab is given by IV infusion over 2 to 3.5 hours and requires monitoring throughout. Patients often have to set aside substantial time to receive an infusion at the hospital when considering transit to and from the institution, lead time for IV premedication, the infusion itself and the 1-hour post-infusion monitoring. This effort creates both a burden on patients (i.e., considerable time for treatment administration before returning to daily activities) and a burden of patient management for healthcare providers. An alternative SC dosing form with a shorter administration time may be preferred by some patients and healthcare providers, and could reduce drug administration related costs and resources (Bax and Postma 2013; Burcombe et al. 2013; Pereira and Santos 2013; Pivot et al. 2013; Tetteh and Morris 2014; Ariza 2015; De Cock et al. 2016; Rule et al. 2017; Rummel et al. 2017; Tjalma et al. 2018).

Ocrelizumab SC co-formulated with rHuPh20 can be administered in a shorter period compared to the approved ocrelizumab IV infusion and has the potential to deliver clinical benefit with reduced treatment burden, improved resource use, and increased patient convenience. In the context of the current global demand for increased efficiencies in healthcare delivery, it also has the potential to relieve stretched capacity at infusion centers. The co-formulation of ocrelizumab SC with rHuPH20 is ready-to-use and planned to allow administration by, or with assistance from, a healthcare professional at the patient's home following initial treatments in the clinic or hospital setting. Moreover, patients with MS often have reduced mobility. Attending a healthcare institution represents an additional risk for such patients being at peril of falls or other accidents during transit.

Available data for subcutaneously administered monoclonal antibodies (trastuzumab [Herceptin®] and rituximab [MabThera®/Rituxan®]) consistently demonstrate that efficacy remains the same regardless of administration route (Ismael et al. 2012; Davies et al. 2014; Assouline et al. 2015); furthermore, some patients prefer SC to IV administration (Pivot et al. 2013; Rummel et al. 2015).

The proposed study will be conducted in patients with RMS and PPMS, with the overall goal of demonstrating non-inferiority in serum ocrelizumab exposure for the SC route of administration versus IV infusions, and to assess the pharmacodynamics, safety, immunogenicity, and radiological and clinical effects of ocrelizumab after SC injection.

It is expected that SC administration of ocrelizumab will result in reduced treatment burden, increased patient satisfaction, and improved cost-effectiveness, while maintaining an efficacy and safety profile comparable to the approved IV route of administration of ocrelizumab.

The efficacy and the general adverse event profile of the approved IV route of administration of ocrelizumab have been well characterized in the ocrelizumab IV trials and post-marketing experience (see the Ocrelizumab Investigator's Brochure).

The benefit–risk assessment for conducting the current Phase III study with the 920 mg dose of ocrelizumab SC is based on PK and safety data up to the highest tested dose of 1200 mg in all treated patients in the ongoing Phase I study (OCARINA I).

The SC dose of 920 mg was selected so that the 25th percentile in the exposure (AUC_T) distribution matches the 25th percentile in the exposure distribution after 600 mg IV ocrelizumab dosing. Per PK bridging principles, this is expected to translate into non-inferior efficacy, and the OCARINA II study will provide safety information for ocrelizumab SC complemented by clinical and radiological information.

In OCARINA I, as of 07 May 2021, following a conservative dose escalation approach where 21 patients received increasing doses of ocrelizumab SC (40 mg, 200 mg, and 600 mg), a total of 88 patients received ocrelizumab SC as part of the dose escalation. Additionally, a total of 96 patients have received at least one dose of 1200 mg ocrelizumab SC in this study.

No new safety signals have been identified for ocrelizumab SC when compared with ocrelizumab IV. Safety data generated to date confirm that the overall safety profile reported for ocrelizumab SC is comparable to that which is well established for ocrelizumab IV (see the Ocrelizumab Investigator's Brochure).

Risk mitigations measures are in place to closely monitor the overall patient safety during the conduct of this study, including an assessment by an independent Data Monitoring Committee (iDMC).

Overall, the benefits versus the risks for individual participants treated with the ocrelizumab SC dose of 920 mg and study-related procedures remains unchanged compared with IV formulation and support continuation of the SC development program with this identified dose.

1.3.1 Benefit–Risk Assessment of the Conduct of the Study During the COVID-19 Pandemic

An assessment was conducted to determine whether there is any impact of the COVID-19 pandemic on the benefit–risk assessment of this study protocol including, but not limited to, the patient population under study, study treatment(s) and/or treatment combination being evaluated. Based on that assessment, no impact is anticipated and the existing safety monitoring and management guidelines, and risk mitigation measures provided in the study protocol are considered adequate.

The available safety data from patients with MS treated with ocrelizumab to date suggests that COVID-19 follows a similar course in these patients as in the general population, with risk factors for severe COVID-19 that are similar in the general population, the overall MS population, and in those treated with ocrelizumab.

The protocol's eligibility criteria mitigate the known risk factors for severe COVID-19 outcomes, such as older age, more advanced MS disease status, and presence of relevant comorbidities, and exclude patients with MS with any known or suspected active infection (including COVID-19, based on the investigator's assessment) from participating in the study. As per Section 4.3.2.3, absence of active infection is also required for patients to receive further retreatment with ocrelizumab.

A SC dose of ocrelizumab is expected to provide similar benefit for patients in controlling MS disease compared with the approved IV dose.

In summary, protocol-mandated safety monitoring and management guidelines, study eligibility criteria, and the ocrelizumab retreatment criteria are considered appropriate in the context of conducting the study during the COVID-19 pandemic. Investigators should manage COVID-19 in the same way as infections caused by any other pathogen.

1.3.2 Risk Assessment for Concomitant Use of a COVID-19 Vaccine

A benefit–risk assessment was conducted to determine whether there is any impact on the concomitant use of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines on the conduct of this study. Based on this assessment, no interaction between the concomitant use of SARS-CoV-2 vaccines and ocrelizumab has been identified. There is no anticipated impact affecting the efficacy and safety of ocrelizumab in patients enrolled in ocrelizumab clinical trials. Existing key safety information as described in the protocol (see Sections 4.4.4 and 5.1.1.1), safety monitoring, and risk mitigation measures related to administration of vaccines (including those for SARS-CoV-2) are considered adequate.

As described in Section 5.1.1.1, data from the pivotal Phase III studies of ocrelizumab in RMS and PPMS show that preexisting humoral immunity to common viral and bacterial antigens is not affected by ocrelizumab treatment. Additionally, for patients receiving vaccines while treated with ocrelizumab, the vaccination study BN29739 (VELOCE) showed that people with MS treated with ocrelizumab were able to mount a humoral immune response to non-live vaccines and new antigens. The antibody immune response was considered protective, albeit with reduced levels of antibodies compared to controls. In that study, vaccines were given as early as 12 weeks following the first ocrelizumab infusion (as early as 10 weeks following the second ocrelizumab infusion of the first dose). Booster doses were given at least 4 weeks before the next dose of ocrelizumab. Other immune responses, such as cellular responses were not investigated in the VELOCE study.

Roche is continually collecting evidence from clinical and biological sources to better understand immune response mechanisms of the SARS-CoV-2 vaccine in ocrelizumab-treated patients.

As with any other medication or vaccine, SARS-CoV-2 vaccines should be reported as concomitant medication by using the standard fields in the clinical database (see Section 4.4.4, and medical history, baseline conditions, concomitant medications, and demographic data Section 4.5.2).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the pharmacokinetics, pharmacodynamics, safety, immunogenicity, and radiological and clinical effects of SC administration of ocrelizumab compared with the IV infusion in patients with either RMS or PPMS. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 PHARMACOKINETIC OBJECTIVE

2.1.1 Primary Pharmacokinetic Objective

The primary PK objective of this study is to demonstrate PK non-inferiority of the SC formulation of ocrelizumab in patients with MS on the basis of the following endpoint:

- Serum ocrelizumab area under the concentration–time curve (AUC_{W1-12}) after SC administration compared to IV infusion from Day 1 to Week 12.

2.1.2 Secondary Pharmacokinetic Objective

The secondary PK objective of this study is to determine the maximum serum concentration (C_{max}) of ocrelizumab SC in patients with MS.

2.2 RADIOLOGICAL AND CLINICAL OBJECTIVES

2.2.1 Secondary Radiological Objective

The secondary radiological objective for this study is to evaluate the radiological effects of ocrelizumab SC compared with ocrelizumab IV in patients with MS on the basis of the following endpoints:

- Total number of T1Gd+ lesions as detected by brain MRI at Weeks 8 and 24
- Total number of new or enlarging T2 lesions as detected by brain MRI at Weeks 12 and 24 relative to the previous scan, respectively

2.2.2 Exploratory Radiological and Clinical Objective

The exploratory radiological and clinical objective for this study is to explore the radiological and clinical effects of ocrelizumab SC compared with ocrelizumab IV in patients with MS on the basis of the following endpoints:

- Total number of T1Gd+ lesions as detected by brain MRI at Week 48 *and Week 96*
- Total number of new or enlarging T2 lesions as detected by brain MRI at Weeks 8, 48, *and 96* relative to the previous scan, respectively
- The annualized protocol-defined relapse rate by Weeks 24, 48, *and 96* in RMS patients
- Change from baseline in the expanded disability status scale (EDSS) at Week*s* 48, *72 and 96*

2.3 PATIENT-REPORTED OBJECTIVE

The exploratory patient-reported outcome (PRO) objective for this study is to evaluate patient preference and satisfaction for ocrelizumab SC and IV in relation to other disease-modifying treatments (DMTs) taken prior to the study, as well as preference for the SC or IV route of administration in a subset of patients:

- Patient satisfaction and experience receiving SC administration (at site and at home) and IV route of administration:
  - Patient administration satisfaction and experience scores using the Treatment Administration Satisfaction Questionnaires (TASQ) for IV Infusion following the first treatment administration in a subset of patients
  - Patient administration satisfaction and experience scores using the TASQ for SC injection
- Patient satisfaction and preference taking ocrelizumab administered SC compared to previous DMTs taken prior to the study:
  - Entry treatment experience questions to report overall treatment satisfaction scores from patients who received an MS treatment prior to the study
  - MS treatment preference score to report overall satisfaction taking ocrelizumab
  - MS treatment preference score to report the proportion of patients with a preference for ocrelizumab SC compared to previously taken DMTs

- Patient preference for the SC or IV route of administration, specifically:
  - Proportion of patients who prefer the SC or IV route of administration using the Patient Preference Questionnaire (PPQ).
- *Patient global impression of overall satisfaction (PGI-SF) for SC ocrelizumab*
  - *Proportion of patients who are satisfied or dissatisfied with ocrelizumab SC as a treatment for their MS symptoms*

2.4 SAFETY OBJECTIVE

The safety objective of this study is to evaluate and compare the safety profile after administration of ocrelizumab SC versus ocrelizumab IV and to assess the safety of ocrelizumab SC at the selected dose in patients with MS on the basis of the following endpoints during the conduct of the study:

- Incidence and severity of adverse events, with severity determined according to the NCI CTCAE version 5.0
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

2.5 IMMUNOGENICITY OBJECTIVE

The immunogenicity objective for this study is to evaluate the immune response to ocrelizumab SC and IV, and rHuPH20, based on the following endpoints:

- Incidence of treatment-emergent anti-drug antibodies (ADAs; formation of ADAs) to ocrelizumab after SC or IV administration relative to the presence of ADAs at baseline
- Relationship between ADA status to ocrelizumab and pharmacokinetics, pharmacodynamics, and safety
- Incidence of treatment-emergent antibodies to rHuPH20 after SC administration relative to the presence at baseline and relationships between antibodies to rHuPH20 and safety

2.6 PHARMACODYNAMIC OBJECTIVE

The pharmacodynamic (PD) objective for this study is to evaluate the effect of SC ocrelizumab compared with IV ocrelizumab on the PD marker for the mechanism of action of ocrelizumab (i.e., B cell depletion) on the basis of the following endpoint:

- Proportion of patients achieving CD19+ B cell level *<5* cells/μL at Weeks 12*,* 24*, 48, and/or 96*

2.7 BIOMARKER OBJECTIVE

The biomarker objective for this study is to evaluate biomarkers that are predictive of response to ocrelizumab (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), can provide evidence of ocrelizumab activity (i.e., PD biomarkers), or can

increase the knowledge and understanding of disease biology, on the basis of the following endpoints:

- Levels of biomarkers including but not limited to neurofilament light (NfL) in serum compared between dosing arms at Weeks 12, 24, 48 *and/or 96* compared to baseline

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

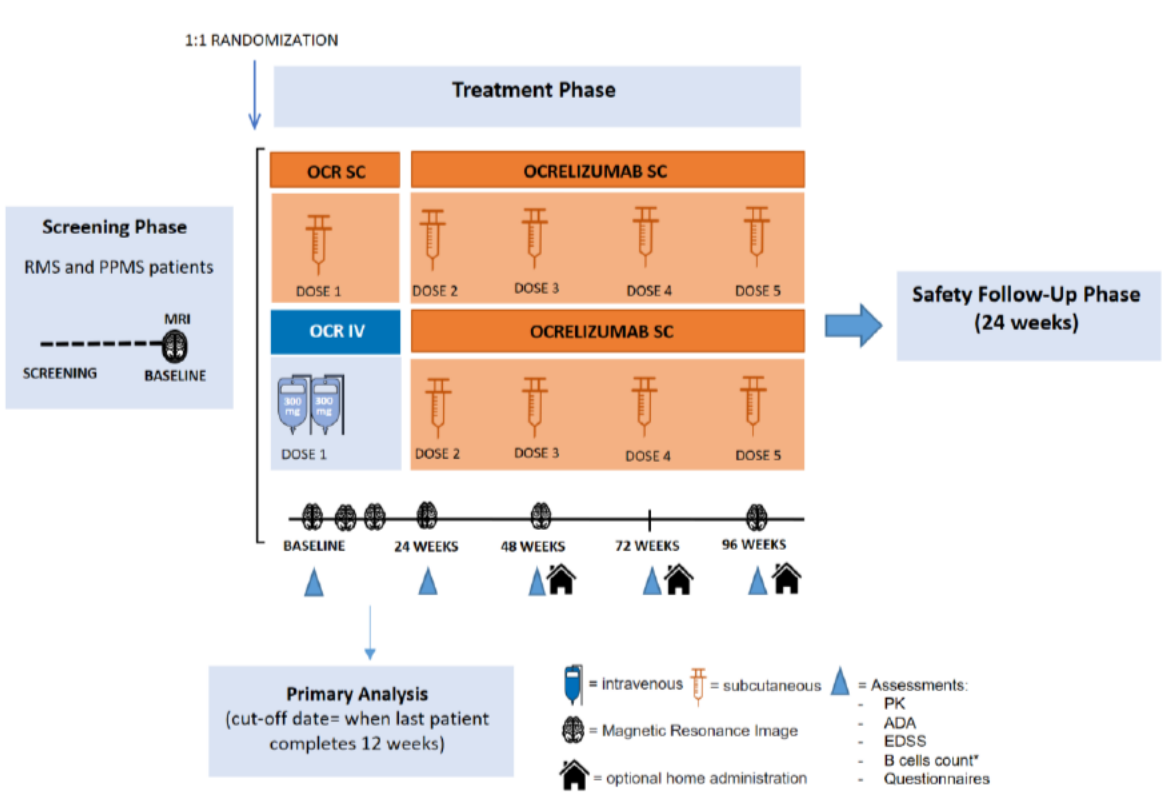
CN42097 is a Phase III non-inferiority, randomized, open-label, parallel group, multicenter study to evaluate the pharmacokinetics, pharmacodynamics, safety, immunogenicity, radiological, and clinical effects of SC administration of ocrelizumab compared with the IV infusion of ocrelizumab in patients with either RMS or PPMS.

The study will consist of the following study phases:

- Screening
- Treatment (controlled period and SC ocrelizumab treatment period)
- Safety follow-up (SFU)

The study design is shown in Figure 1.

Figure 1 Study Schema



ADA=anti-drug antibody; EDSS=expanded disability status scale *(performed at the site)*; IV=intravenous; MRI=Magnetic Resonance Image; OCR=ocrelizumab; PK=pharmacokinetics; PPMS=primary progressive multiple sclerosis; RMS= relapsing multiple sclerosis; SC=subcutaneous.

3.1.1 Overview of Study Phases

3.1.1.1 Screening

The screening phase will last up to 6 weeks. Patients who are candidates for enrollment into the study will also be evaluated by the investigator prior to randomization to ensure all eligibility criteria continue to be met (see Section 4.1, Appendix 1, and Appendix 2). All patients must sign the Informed Consent Form prior to screening and enrollment in the study. Patients providing informed consent will undergo screening prior to the study drug administration.

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for two re-screening opportunities at the investigator's discretion. Patients are not required to re-sign the consent form if they are re-screened within 90 days after previously signing the consent form. The investigator will record reasons for screen failure in the screening log and in the IxRS.

3.1.1.2 Treatment

Patients will be recruited globally.

All patients will receive *five* ocrelizumab doses (Day 1, Week 24*,* Week 48*, Week 72 and Week 96*) during the treatment phase (see Figure 1). Eligible patients will be randomly assigned to one of two treatment arms: ocrelizumab SC dose or ocrelizumab IV dose. Randomization will occur in a 1:1 ratio and will be performed through an interactive voice or web-based response system (IxRS).

The first study drug administration should occur within 24 hours of randomization (in exceptional cases within 48 hours of randomization provided that the investigator assures that all inclusion and exclusion criteria are still met on the day of dosing).

During the controlled period (i.e., time until the Week 24 dose of ocrelizumab SC), the first dose of ocrelizumab SC will be given as one SC injection at a dose of 920 mg. The first dose of ocrelizumab IV will be administered as two 300 mg IV infusions given 2 weeks apart. Every effort should be made to perform all assessments required during the controlled period (e.g., MRI) before the administration of the second dose. The subsequent doses of study drug will be administered as SC injections for all patients, including those initially randomized to ocrelizumab IV (ocrelizumab SC treatment period).

For patients randomized in the ocrelizumab IV group, there should be a minimum of 20 weeks between the administration of the final ocrelizumab IV infusion and the first ocrelizumab SC dose (i.e., between the IV infusion at Week 2/Study Day 14 and the first SC dose during Week 24). There should be a minimum of 22 weeks between all SC doses.

To allow for the possibility of home administration at participating sites, *from the third* ocrelizumab dose *onwards* (i.e., Week 48 *onwards*, Appendix 4) *the ocrelizumab dose can* be administered by a healthcare professional at the patient's home or another suitable location. The patient will need to provide an informed consent (refer to Section 4.5.10) and the investigator will determine if the patient is eligible for home administration (Sections 4.5.10 and 4.3.2.3).

Patients who withdraw from treatment during the treatment phase for any reason should return to the site to complete an early termination visit and perform the assessments required during the controlled period (e.g. MRI), as indicated in the schedule of activities (Appendix 1, Appendix 2, and Appendix 3). They are encouraged to enter and complete the safety follow-up phase (refer to Section 3.1.1.3).

An iDMC will be employed to monitor and evaluate patient safety throughout the study, until the last patient received their last dose of ocrelizumab. Monitoring details will be described in the iDMC Charter.

3.1.1.3 Safety Follow-Up

Patients who complete the treatment or discontinue from the treatment early will be asked to return to the clinic 24 weeks after the last dose of study drug. Refer to Section 4.3.4 and Section 4.4.2 for treatment options offered to patients.

All patients will be followed for up to *24* weeks after the last ocrelizumab administration. During the safety follow-up visit, a physical examination, neurologic examination, recording of adverse events, hematology, blood chemistry, urinalysis, pharmacokinetics, B cells in blood, biomarker and ADA assessments will be performed.

There is the option to collect information about the patient's planned post-study MS treatment at the 24-week safety follow-up visit.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of study will occur when the last participating patient completes the last scheduled visit at the end of the safety follow-up phase, or when the Sponsor decides to discontinue the study or development program.

Each patient will be in the treatment phase for up to *2* year*s* (i.e., *96* weeks) and in the safety follow-up phase for up to *24* weeks after the last ocrelizumab administration.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Pharmacokinetic Primary Endpoint

Non-inferior ocrelizumab exposure, measured as the AUC, between the SC formulation and the IV formulation is expected to translate into comparable efficacy and safety outcomes, as per the principle of PK bridging (Shpilberg et al. 2013, Hourcade et al. 2014).

The difference between SC and IV administration of ocrelizumab is in the absorption process from the SC injection site versus direct IV infusion. Systemic distribution and elimination is independent of the route of administration. As absorption is expected to be completed within 12 weeks post-injection, AUC up to Week 12 is judged to be representative of the overall ocrelizumab exposure over the 6 monthly dosing interval. Therefore, ocrelizumab $AUC_{W1\text{-}12}$ will be assessed as the primary endpoint in this study.

3.3.2 Rationale for Ocrelizumab SC Dose and Schedule

The dose of 920 mg SC was selected based on the PK and safety data obtained in the currently ongoing Study CN41144 (OCARINA I). In this study, SC doses up to 1200 mg have been administered and were safe and well tolerated. SC bioavailability was estimated with 72%. Rapid B cell depletion in ocrelizumab treatment-naïve patients, and maintenance of B cell depletion throughout the six month dosing interval in pre-treated patients, was obtained after 1200 mg ocrelizumab SC.

The SC dose of 920 mg was selected such that the ocrelizumab exposure in patients after SC administration matches the exposure after the approved and marketed dose of 600 mg IV. As variability after SC administration is larger than after IV administration, the SC dose of 920 mg was selected so that the 25th percentile in the exposure (AUC_T) distribution matches the 25th percentile in the exposure distribution after IV 600 mg dosing. This ensures that patients on the lower range of the exposure distribution will have adequate exposure.

For the IV administration, the initial 600 mg dose is divided into 2 x 300 mg. For SC administration, this is not required, as one single dose of up to 1200 mg was well tolerated in ocrelizumab treatment-naïve patients. Therefore, all SC doses in OCARINA II will be given as a single SC injection. Absorption after SC injection is slow (C_{max} between Day 2 and Day 10, based on currently available data from OCARINA I). SC injection of the total dose on Day 1 will help to achieve the onset of efficacy with similar speed versus the IV infusions, for which the systemic availability of the total dose is complete on Day 14.

In conclusion, a dose of 920 mg ocrelizumab SC is expected to provide comparable exposure to the approved 600 mg ocrelizumab IV dose, and has therefore been selected for this study.

3.3.3 Rationale for Control Group

In order to evaluate PK non-inferiority of the SC formulation of ocrelizumab versus the approved 600 mg IV dose, an IV reference arm has been included in the study. This ensures the same PK sample procedures, same bioanalytical assay methods, laboratory assessments, and similar patient population between the test and reference arms.

Treatment with 600 mg IV ocrelizumab has been well characterized in previous clinical studies (for details, refer to the Ocrelizumab Investigator's Brochure), and 600 mg IV ocrelizumab has been approved for treatment of patients with RMS or PPMS (OCREVUS® USPI).

3.3.4 Rationale for Patient Population

The assessment of PK non-inferiority of ocrelizumab SC to ocrelizumab IV will be carried out in a broad MS patient population consistent with the current ocrelizumab indication. Adult patients with relapsing and primary progressive forms of MS with an EDSS score of 0 to 6.5 and with an age range up to 65 years will be enrolled. Available PK data on file does not reveal a difference in the PK profiles of RMS and PPMS patients following treatment with ocrelizumab IV.

3.3.5 Rationale for [redacted] Use of Premedications

An analysis of patients with MS who were treated with ocrelizumab IV revealed that the addition of antihistamines to the pretreatment with methylprednisolone decreased the incidence of IRRs by two-fold (Ocrelizumab Investigator's Brochure). To reduce the

frequency and severity of IRRs, as well as systemic injection reactions or ISRs, patients will be premedicated with corticosteroids and antihistamines prior to administration with ocrelizumab (see Section 4.3.2).

Methylprednisolone (or an alternative steroid in patients where methylprednisolone is contraindicated or not available) and antihistamine will be administered to patients receiving IV ocrelizumab treatment. Dexamethasone and desloratadine (or an alternative steroid or antihistamine in patients where dexamethasone or desloratadine are contraindicated) will be administered to patients receiving SC ocrelizumab treatment. Those recommended oral corticosteroids and antihistamine medications are considered as equivalent in terms of anti-inflammatory potency to the premedication given to patients treated with IV ocrelizumab. The premedication and its administration schedule may be modified by the Sponsor during the study on the basis of emerging clinical evidence for the effectiveness and safety of the proposed premedication schedule.

3.3.5.1 [redacted] Premedication

[redacted] Study CN41144 were almost all CTCAE Grade 1–2 and their incidence decreased after the first injection. The large majority of reactions were local, a minority were systemic, and all were manageable as per the guidelines from the previous versions of the protocol (Section 5.1.1.1 and Appendix 4) which continue to apply without any changes.

The most common systemic injection reaction symptom was headache (refer to Section 5.1.1.2). [redacted]

[redacted]

3.3.6 Rationale for Biomarker Assessments

PD biomarkers will be assessed to demonstrate evidence of biologic activity of ocrelizumab in patients, compared between the dosing arms.

B-cells are a direct PD marker for ocrelizumab, and a correlation of the extent of B-cell depletion in blood with exposure levels was observed in the ORCHESTRA Phase III trials (Gibiansky et al. 2020).

NfL, a neuraxonal injury marker, has been correlated with Gd-enhancing MRI lesions and clinical relapses (Burman et al. 2014) and with response to drug treatment in PMS and RMS (Gunnarsson et al. 2011; Axelsson et al. 2014, Kuhle et al. 2019). NfL can be detected in the blood, and blood levels are correlated with cerebral spinal fluid (CSF) level, making NfL an attractive non-invasive biomarker to assess neuronal injury in MS (DiSanto et al. 2017). In addition, NfL is prognostic for worse disability outcome in RMS and PPMS (Kuhle et al. 2019; Bar-Or et al. 2019), and is a PD biomarker for treatment response to ocrelizumab.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 232 patients with MS (RMS and PPMS) will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Diagnosis of PPMS or relapsing forms of MS (RMS) according to the revised McDonald 2017 criteria (Thompson et al. 2018)
- Signed Informed Consent Form
- Age 18–65 years, inclusive, at time of signing Informed Consent Form
- Ability to comply with the study protocol and schedule of protocol assessments, in the investigator's judgment
- EDSS score, 0–6.5, inclusive, at screening
- Neurological stability for ≥30 days prior to both screening and baseline
- Disease duration from onset of MS symptoms of less than 15 years for patients with EDSS score <2.0 at screening
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use adequate contraception during the treatment period and for 6 or 12 months (as applicable by the ocrelizumab IV [Ocrevus] local label) after the final dose of ocrelizumab.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a post-menopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a woman with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

  As defined by the guidelines, the following contraceptive methods are considered acceptable (failure rate >1%): (1) progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action; (2) male or female condom with or without spermicide; (3) cap, diaphragm, or sponge with spermicide;

(4) combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier method).

Birth control methods that are highly effective (i.e. failure rate <1%) may also be used but are not required, and include: (1) oral, intravaginal or transdermal combined hormonal contraception associated with inhibition of ovulation; (2) oral, injectable or implantable progestogen-only hormonal contraception associated with inhibition of ovulation; (3) intrauterine device; (4) intrauterine hormone-releasing system; (5) bilateral tubal occlusion; (6) vasectomized partner; (7) sexual abstinence.

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. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For female patients without reproductive potential:

  Women may be enrolled if

  – Post-menopausal (i.e., spontaneous amenorrhea for the past year confirmed by a follicle-stimulating hormone [FSH] level $>$ 40 mIU/mL) unless the patient is receiving a hormonal therapy for her menopause or

  – Surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy).

4.1.2 Exclusion Criteria

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

- Any known or suspected active infection at screening or baseline (except nailbed infections), or any major episode of infection requiring hospitalization or treatment with IV antimicrobials within 8 weeks prior to and during screening or treatment with oral antimicrobials within 2 weeks prior to and during screening
- History of confirmed or suspected progressive multifocal leukoencephalopathy (PML)
- History of cancer, including hematologic malignancy and solid tumors, within 10 years of screening

  Basal or squamous cell carcinoma of the skin that has been excised and is considered cured and in situ carcinoma of the cervix treated with apparent success by curative therapy $>$ 1 year prior to screening is not exclusionary.
- Immunocompromised state, defined as one or more of the following:
  – CD4 count $<$250/μL
  – Absolute neutrophil count $<1.5 \times 10^3/\mu$L
  – Serum IgG $<$4.6 g/L
- Receipt of a live-attenuated vaccine within 6 weeks prior to randomization

Influenza vaccination is permitted if the inactivated vaccine formulation is administered.

- Inability to complete an MRI (contraindications for MRI for example, due to, pacemaker, cochlear implants, intracranial vascular clips, surgery within 6 weeks of entry in the study, coronary stent implanted within 8 weeks prior to the time of the intended MRI, etc.) or contraindication to gadolinium administration
- Contraindications to mandatory premedications (i.e., corticosteroids and antihistamines), including closed-angle glaucoma for antihistamines
- Known presence of other neurologic disorders that could interfere with the diagnosis of MS or assessments of efficacy and/or safety during the study, including, but not limited to, the following:
  - History of hemorrhagic or ischemic cerebral or spinal stroke
  - History or known presence of CNS or spinal cord tumor (e.g., meningioma, glioma)
  - History or known presence of potential metabolic causes of myelopathy (e.g., untreated vitamin B12 deficiency)
  - History or known presence of infectious causes of myelopathy (e.g., syphilis, Lyme disease, HTLV-1, herpes zoster myelopathy)
  - History of genetically inherited progressive CNS degenerative disorder (e.g., hereditary paraparesis, mitochondrial myopathy, encephalopathy, lactic acidosis, stroke [MELAS] syndrome)
  - Neuromyelitis optica
  - History or known presence of systemic autoimmune disorders potentially causing progressive neurologic disease (e.g., lupus, anti-phospholipid antibody syndrome, Sjögren syndrome, Behçet disease)
  - History or known presence of sarcoidosis
  - History of severe, clinically significant brain or spinal cord trauma (e.g., cerebral contusion, spinal cord compression)
- Any concomitant disease that may require chronic treatment with systemic corticosteroids (e.g. mineralocorticoids and glucocorticoids) 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 or gastrointestinal, or any other significant disease that may preclude patient from participating in the study
- History of or currently active primary or secondary (non–drug-related) immunodeficiency

- Pregnant or breastfeeding, or intending to become pregnant during the study and 6 or 12 months (as applicable by the ocrelizumab [Ocrevus] local label) after last administration of the study drug.

    Females of childbearing potential must have a negative serum and urine pregnancy test result prior to initiation of study drug (negative serum β-CG measured at screening and negative urine β-CG at baseline)
- Lack of peripheral venous access
- History of alcohol or other drug abuse within 12 months prior to screening
- Treatment with any investigational agent within 24 weeks prior to screening or 5 half-lives of the investigational drug (whichever is longer), or treatment with any experimental procedure for MS (e.g., treatment for chronic cerebrospinal venous insufficiency)
- Patients who have previously received anti-CD20s (including ocrelizumab) if the last treatment was less than 2 years before screening, and/or if B-cell count is below lower limit of normal, and/or the discontinuation of the treatment was due to safety reasons or lack of efficacy
- Previous treatment with cladribine, atacicept, and alemtuzumab
- Previous treatment with fingolimod, siponimod, ponesimod, or ozanimod within 6 weeks of baseline
- Previous treatment with interferons beta (1a or 1b), or glatiramer acetate within 2 weeks of baseline
- Previous treatment with natalizumab within 4.5 months of baseline
- Treatment with mitoxantrone within 2 years prior to baseline visit or evidence of cardiotoxicity following mitoxantrone use or a cumulative lifetime dose of more than 60 mg/m^2
- Previous treatment with any other immunomodulatory or immunosuppressive medication not already listed above without appropriate washout as described in the applicable local label. If the washout requirements are not described in the applicable local label (washout to be completed prior to baseline), then the wash out period must be 5 times the half-life of the medication. The PD effects of the previous medication must also be considered when determining the required time for washout.

    Patients screened for this study should not be withdrawn from therapies for the sole purpose of meeting eligibility for the trial.
- Any previous treatment with bone marrow transplantation and hematopoietic stem cell transplantation
- Any previous history of transplantation or anti-rejection therapy
- Treatment with IV Ig or plasmapheresis within 12 weeks prior to randomization
- Systemic corticosteroid therapy within 4 weeks prior to screening

    The screening period may be extended for patients who have used systemic corticosteroids for MS before screening. For a patient to be eligible, systemic

corticosteroids should also not have been administered between screening and baseline.

- Positive screening tests for active, latent, or inadequately treated hepatitis B (as evidenced by either of the following):
  - Positive hepatitis B surface antigen
  - Positive hepatitis B core antibody (total HBcAb) and detectable hepatitis B virus DNA
- Sensitivity or intolerance to any ingredient (including excipients) of ocrelizumab
- Any additional exclusionary criterion as per ocrelizumab (Ocrevus®) local label, if more stringent than the above

Re-testing before baseline: In rare cases in which the screening laboratory samples are rejected by the central laboratory (e.g., hemolyzed sample) or the result is not assessable (e.g., indeterminate) or abnormal, the tests need to be repeated as soon as possible, or within the allowed screening period. Any abnormal screening laboratory value that is clinically relevant should be retested to rule out any progressive or uncontrolled underlying condition. The last value before randomization must meet study criteria.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a randomized, open-label study. After initial written informed consent has been obtained, all screening and baseline procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from an interactive voice or web-based response system (IxRS).

Patients who discontinue treatment for any reason will not be replaced. Under no circumstances are patients who enroll in this study and who have completed treatment as specified, permitted to be re-randomized to this study. Patients will be randomly assigned to one of two treatment arms: SC or IV ocrelizumab. Randomization will occur in a 1:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified according to the following criteria:

- Baseline body weight (<70 kg vs. ≥70 kg)
- Disease subtype (RMS vs. PPMS)
- Region (U.S. vs. rest of world [ROW])

Baseline body weight was identified as the most relevant covariate for the pharmacokinetics in the population PK analysis conducted with the Phase III PK data obtained from approximately 1500 patients with MS treated with IV ocrelizumab. While the disease subtype and region do not influence the pharmacokinetics, inclusion of these

variables as stratification factors would ensure a balanced comparison of the secondary safety and radiological endpoints.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is ocrelizumab (comprising both the IV formulation and the SC formulation co-formulated with rHuPH20).

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Ocrelizumab Subcutaneous Co-Formulated with rHuPH20

Ocrelizumab SC will be provided as a sterile, single-dose liquid at a concentration of 40 mg/mL and contains no preservatives. The ocrelizumab in the ocrelizumab SC formulation is co-formulated with rHuPH20 at a concentration of 1000 U/mL.

For information on the formulation of ocrelizumab SC co-formulated with rHuPH20, see the pharmacy manual and the Ocrelizumab Investigator's Brochure.

4.3.1.2 Ocrelizumab Intravenous

Ocrelizumab IV will be provided as a sterile, single-dose liquid at a concentration of 30 mg/mL and contains no preservatives. For information on the formulation of IV ocrelizumab, refer to the Ocrelizumab Investigator's Brochure, local prescribing information, and pharmacy manual.

4.3.1.3 Non-Investigational Medicinal Products

Specific premedications are required prior to the ocrelizumab infusion or injection. Table 1 shows the premedications that will be used prior to an IV infusion or SC injection of ocrelizumab.

Table 1 Premedications To Be Used Prior to IV Infusion or SC Injection

Prior to IV Administration of Ocrelizumab	Prior to SC Administration of Ocrelizumab
Mandatory methylprednisolone, given by slow IV infusion	Mandatory dexamethasone, given orally
Mandatory diphenhydramine, given orally or IV infusion	Mandatory desloratadine, given orally
Oral analgesic as needed and as tolerated (if using acetaminophen not to exceed 4g/daily per label).	Recommended oral analgesic/as needed/and as tolerated (if using acetaminophen, not to exceed 4g/day, per label)

IV=intravenous; SC=subcutaneous.

For further details on premedication administration, refer to Section 4.3.2.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.1.2.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

At participating sites only, *from* the third ocrelizumab dose *onwards* (i.e., *starting* at Week 48 visit), *study drug can* be administered by a healthcare professional at the patient's home or another suitable location (refer to Section 4.5.10).

Details on treatment administration (e.g., dose, actual date and time) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.

Guidelines for treatment modification, interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.4.

4.3.2.1 Subcutaneous Ocrelizumab

The 920 mg SC dose of ocrelizumab was determined based on data from the ongoing Phase Ib study (Ocarina I, Section 3.3.2). Detailed information on drug preparation and administration is provided in the pharmacy manual.

The injection of ocrelizumab SC should be administered by an experienced professional with access to appropriate medical support to manage severe injection reactions.

The study drug will be administered by a healthcare professional to patients subcutaneously with a manual syringe or syringe pump through a SC infusion set into the abdominal SC space, except for the 5 cm area directly around the navel (refer to the pharmacy manual) every 24 weeks. A minimum of 22 weeks should be maintained between the first and second SC doses, and between *the next* SC dose.

[redacted]

Site personnel will contact patients by telephone as indicated in Section 4.5.11 to record potential injection reactions.

Depending on the site and individual participant, some participants will have the option to receive *doses 3-5* of ocrelizumab at home by study staff (i.e., *Weeks 48-96* visits). The investigator will determine whether the participant is eligible for home administration, per Appendix 4, by appropriate study staff (according to local regulations) based on tolerability and suitability (refer to Section 4.3.2.3).

Rescue medications to treat anaphylactic and anaphylactoid reactions must be available at the site or at the dosing location for MN visit (see Appendix 11). [redacted] Participants will be alerted to watch for signs of anaphylactic

and anaphylactoid reactions and to contact the study center as soon as possible if any such signs are noted.

Premedication for Patients Treated with Ocrelizumab Subcutaneous

To reduce potential injection reactions, patients treated with ocrelizumab SC will be premedicated with 20 mg dexamethasone and 5 mg desloratadine given orally [redacted] In the rare case when the use of dexamethasone or desloratadine is contraindicated for the patient or is not available, an equivalent dose of an alternative steroid or antihistaminic should be used as premedication prior to the injection.

Corticosteroids and antihistamine medications are considered as equivalent in terms of anti-inflammatory potency to the premedication given to patients treated with ocrelizumab IV. If using acetaminophen, do not exceed the maximum daily dose or frequency in the label.

4.3.2.2 Intravenous Ocrelizumab

The infusion of ocrelizumab should be initiated and supervised by an experienced healthcare professional with access to appropriate medical support to manage severe reactions such as serious IRRs. The patient will need to remain at the clinic for at least 1 hour after the completion of infusion for observation.

Patients will receive the first dose of ocrelizumab IV as two 300 mg infusions (600 mg in total), each separated by 2 weeks, and from the Week 24 visit onwards patients will receive SC injections, every 24 weeks (refer to Section 4.3.2.1). A minimum interval of 20 weeks should be maintained between the second ocrelizumab infusion (ocrelizumab IV) of Dose 1 (i.e., infusion Day 14, Week 2) and the administration of Dose 2 (i.e., ocrelizumab SC dose on Week 24).

Table 2 Overview of Ocrelizumab IV Dosing and Schedule

Preparation of the Infusion for IV Administration		Infusion Instructions
Infusion 1 at Dose 1	300 mg IV in 250 mL of 0.9% sodium chloride	Initiate the infusion at a rate of 30 mL/hr for 30 minutes. The rate can be increased in 30-mL/hr increments every 30 minutes to a maximum of 180 mL/hr. Each infusion should be given over approximately 2.5 hours.
Infusion 2 (2 weeks later, Dose 1)	300 mg IV in 250 mL of 0.9% sodium chloride	

IV=intravenous.

Premedication for Patients Treated with Ocrelizumab Intravenous

To reduce potential IRRs, all patients who will receive ocrelizumab IV treatment must receive mandatory prophylactic treatment with 100 mg methylprednisolone administered by slow IV infusion to be completed approximately 30 minutes before the start of each ocrelizumab infusion. In the rare case when the use of methylprednisolone is contraindicated for the patient or not available, use of an equivalent dose of an alternative IV steroid should be used as premedication prior to the infusion.

Additionally, a mandatory oral or IV antihistaminic drug (such as 50 mg IV diphenhydramine or an equivalent dose of an alternative) must be administered approximately 30−60 minutes prior to the start of each ocrelizumab infusion.

Oral analgesic is recommended as needed and as tolerated. If using acetaminophen the 4g/day dose, per label, should not be exceed.

Hypotension, as a symptom of IRR, may occur during IV study drug infusions. Therefore, withholding antihypertensive treatments should be considered for 12 hours prior to and throughout each study drug infusion.

4.3.2.3 Retreatment Criteria for Ocrelizumab

A visit prior to any dosing visit will be required to collect blood samples to enable the study investigator to assess whether a patient meets retreatment criteria at the time of treatment with study drug.

The study investigator must ensure he or she has reviewed the central and local laboratory results of the patient prior to retreatment with ocrelizumab.

If study treatment will be administered at patient's home or another suitable location the retreatment criteria must be confirmed by site staff prior to the dose administration.

Prior to retreatment, the following conditions must be met:

- Absence of severe allergic or anaphylactic reaction to the previous ocrelizumab administration
- Absence of any significant or uncontrolled medical condition or treatment-emergent clinically significant laboratory abnormality
- Absence of active infection
- Absolute neutrophil count (ANC) $\geq 1.5 \times 10^3/\mu L$
- CD4 cell count $\geq 250/\mu L$
- IgG ≥ 3.3 g/L
- Negative pregnancy test
- Additional criteria for home administration*:* Absence of any local or systemic injection reaction of Grade ≥ 3 severity or meeting seriousness criteria that occurred during a previous ocrelizumab injection

If any of these criteria are not met prior to retreatment, further administration of ocrelizumab must be suspended until resolved or held indefinitely.

4.3.3 Investigational Medicinal Product Handling and Accountability

All IMPs required for completion of this study will be provided by the Sponsor (ocrelizumab IV and ocrelizumab SC). The study site (i.e., investigator or other authorized personnel [e.g., pharmacist or site personnel]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed

to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and the Ocrelizumab Investigator's Brochure for information on IMP handling, including preparation and storage, and accountability.

4.3.4 Continued Access to Ocrelizumab Subcutaneous

The Sponsor will offer continued access to Roche IMP (ocrelizumab SC or IV) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Roche IMP (ocrelizumab SC or IV) after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition (e.g., MS) and requires continued Roche IMP treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive Roche IMP (ocrelizumab SC or IV) after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for MS
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for MS
- Provision of the Roche IMP is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Treatment for Symptoms of Multiple Sclerosis

The investigator should attempt to maintain therapies (e.g., physiotherapy) or treatments for symptoms related to MS (e.g., walking ability, spasticity, incontinence, pain, fatigue) reasonably constant throughout the study. However, changes (including starting physiotherapy and/or symptomatic treatment) may be made if appropriate for a patient's well-being in the clinical judgment of the investigator. All such therapies or treatments should be recorded on a designated eCRF.

4.4.2 Therapy for Treatment of Relapses

Patients who experience a relapse during study may receive treatment with IV or oral corticosteroids, if judged to be clinically appropriate by the investigator. The following standardized treatment regimen may be used as warranted: 1 g/day IV methylprednisolone for a maximum of 5 consecutive days (or an equivalent oral dose of prednisolone or methylprednisolone). In addition, at the discretion of the investigator, corticosteroids may be stopped abruptly or tapered over a maximum of 10 days. Such patients should not discontinue the *study treatment solely based on the occurrence of a relapse, unless the patient or investigator deems they have met the criteria for treatment discontinuation (see Section 4.7.1).*

4.4.3 Prohibited Therapy and Alternative Treatments

The following therapies for MS are not permitted while under the study treatment phase: B cell–targeted therapies (e.g., rituximab, atacicept, belimumab, or ofatumumab), natalizumab, sphingosine-1-phosphate receptor modulators, alemtuzumab, cladribine, teriflunomide, dimethyl fumarate, interferons, glatiramer acetate, cyclophosphamide, mitoxantrone, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, total body irradiation, bone marrow transplantation, IV Ig, plasmapheresis, and other approved DMTs or investigational therapies for MS.

After patients have completed (or discontinued) treatment with ocrelizumab, they may receive an alternative treatment for their MS, as judged clinically appropriate by the investigator. However, as sufficient data are not available regarding the risks associated with switching to other products, the following recommendations are given:

- Caution is advised while patients remain B-cell depleted.
- Because of the unknown safety risk of administering DMTs for MS after discontinuation of ocrelizumab, certain treatments for MS, such as lymphocyte-depleting agents or lymphocyte-trafficking blockers (alemtuzumab,

natalizumab, sphingosine-1-phosphate receptor modulators , dimethyl fumarate, cyclophosphamide, azathioprine, cladribine, , etc.) are strongly discouraged for as long as the patient remains B-cell depleted because of unknown effects on the immune system (e.g., increased risk, incidence, or severity of infection).

4.4.4 Immunizations

Physicians are advised to review the immunization status of patients who are considered for treatment with ocrelizumab and follow local/national guidance for adult vaccination against infectious disease. Immunizations should be completed at least 6 weeks prior to first administration of ocrelizumab.

Immunization with any live or live-attenuated vaccine (i.e., measles, mumps, rubella, oral polio vaccine, bacille Calmette-Guérin, typhoid, yellow fever, vaccinia, cold-adapted live influenza strain vaccine, or any other vaccines not yet licensed but belonging to this category) is not recommended during ocrelizumab treatment and for as long as a patient is B cell depleted.

Data from the ocrelizumab IV Phase II and III program currently show that over 2 years after treatment with ocrelizumab, the proportion of patients with positive antibody titers against *Streptococcus pneumoniae*, influenza, mumps, rubella, *Varicella*, and tetanus toxoid was generally similar to the proportion at baseline.

For seasonal influenza vaccines, it is still recommended to vaccinate patients treated with ocrelizumab. Refer to the current version of the Ocrelizumab Investigator's Brochure for further guidance and updates on immunization.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1, Appendix 2, and Appendix 3. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

Patients will be followed using onsite visits, a mobile nursing visit (Section 4.5.10) and telephone calls (Section 4.5.11).

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening and baseline evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator may maintain a *detailed* record of all patients screened and to *document* eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including, but not limited to, clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures) and reproductive status will be recorded at screening and re-confirmed at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Any previous medications taken for the treatment of MS at any time since disease onset, including their start and end dates, and medications taken for the symptoms of MS in the 3-month period prior to the baseline visit will be recorded in the eCRF.

Demographic data will include age, sex, and self-reported race/ethnicity, if allowed per local regulations.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and baseline visits should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified post-baseline visits and as clinically indicated (refer to Appendix 1, Appendix 2, and Appendix 3). Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Limited, symptom-directed physical examinations may be performed by site personnel during MN visit (Appendix 4).

4.5.4 Vital Signs

Vital signs will be measured while the patient is in seated (preferred) or semi-seated position and will include temperature, systolic and diastolic blood pressure, pulse rate and pulse oximetry.

Baseline pulse oximetry should be performed for all patients as follows:

- For newly enrolled patients: Study Day 1 before premedication is given
- For already enrolled patients: At the next visit where vital signs are assessed per the schedule of assessments (Appendices 1, 2 and 3, i.e., Week 12 visit or at the next dosing visit before premedication is given).

Post-baseline pulse oximetry is only required in the event of severe systemic administration reactions including potential hypersensitivity/anaphylactic reaction (Section 5.1.4.4 and Appendix 11).

Blood pressure and pulse rate measurements will be recorded on the appropriate eCRF. Temperature should be measured and recorded in patient's notes only.

Vital sign measurement may be performed by site personnel during the MN visit (Appendix 4).

Clinically significant abnormalities observed at baseline will be recorded on the General Medical History and Baseline Conditions eCRF. At subsequent visits, new or worsened clinically significant abnormalities will be recorded on the Adverse Event eCRF.

4.5.4.1 Ocrelizumab Subcutaneous Administration

Vital signs should be measured prior to premedication (refer to Section 4.3.2.1) with dexamethasone (or an equivalent) and desloratadine (or an equivalent). .

Pulse oximetry should be performed as described above (Section 4.5.4).

On non-dosing days, vital signs should be taken at any time during the visit as indicated.

Additionally, unscheduled vital signs may be collected based on PK and safety data and at the discretion of the investigator at any time during the study as clinically indicated.

4.5.4.2 Ocrelizumab Intravenous Administration

Vital signs should be measured within 45 minutes prior to premedication with methylprednisolone (or an equivalent) infusion. In addition, vital signs should be recorded prior to the ocrelizumab infusion and one hour after the end of infusion.

Only in case of an IRR, vital signs should be recorded in the eCRF every 15 minutes ($\pm$5 minutes) in the first hour after the onset of the IRR, followed by every 30 minutes ($\pm$10 minutes) until 1 hour after the end of the infusion.

For patients randomly allocated to ocrelizumab IV treatment the baseline pulse oximetry should be performed as described in Section 4.5.4, and thereafter only in the event of severe systemic administration reactions including potential hypersensitivity/anaphylactic reactions (Section 5.1.4.4 and Appendix 11).

On non-dosing days, vital signs should be taken at any time during the visit.

4.5.5 Neurological Examination

A neurologic examination will be performed at the planned visit as indicated in the schedule of activities (Appendix 1, Appendix 2, and Appendix 3). During an unscheduled visit, the neurologic examination will be performed only if deemed necessary. A neurologic examination should include an assessment of mental status, level of consciousness, cranial nerve function, motor function, sensory function, reflexes, and coordination. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

In the presence of newly identified or worsening neurologic symptoms at any given time in the study, a neurologic evaluation should be scheduled promptly and performed within 7 days of onset of the new or worsening neurologic symptom(s).

Study investigators will screen patients for signs and symptoms of PML through evaluation of neurologic deficits localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, hemiparesis, and cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination). Refer to Appendix 12 for guidance on the diagnosis of PML.

Patients with suspected PML, defined as a new or worsening neurologic symptom that necessitates MRI and/or lumbar puncture and CSF analyses to rule out PML, should be withheld from study treatment until PML is ruled out by complete serial clinical evaluations and appropriate diagnostic testing (see Appendix 12). The Medical Monitor should be contacted by email as well as by telephone.

A patient with confirmed PML should be withdrawn from treatment. PML should be reported as a serious adverse event (with all available information) with immediate notification of the Medical Monitor (see also Section 5.1.1.2).

4.5.5.1 Assessment of Disability

Disability in MS is commonly measured by the EDSS (Section 4.5.9). EDSS will be administered at the timepoints indicated in the schedule of activities (see Appendix 1, Appendix 2, and Appendix 3). Additional EDSS assessments for individual patients may be requested between visits (i.e., during an MS relapse, neurological worsening, etc.). All functional system scores (FSS) and total EDSS scores will be captured electronically and completed in real-time *at the site*.

4.5.6 Assessment of Relapse

Patients will be evaluated for relapse by the study investigator at each visit throughout the study and, if necessary, at unscheduled visits to confirm relapse occurring between the visits.

All new or worsening neurological events compatible with MS representing a clinical relapse are to be reported in the appropriate eCRF. Patients with clinical relapses should be referred to the study investigator who will assess the EDSS/FSS independently to allow confirmation as to whether or not the clinical relapse(s) meet the criteria for protocol-defined relapse(s). EDSS should be performed within 7 days from the onset of the relapse.

For this study, a protocol-defined 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 least 30 days. Symptoms must persist for $>$24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reactions to concomitant medications). The new or worsening neurological symptoms must be accompanied by objective neurological worsening consistent with an increase of at least one of the following:

- Half a step (0.5 point) on the EDSS
- Two points on one of the selected FSS as listed below
- One point on two or more of the selected FSS as listed below

The change must affect the following selected FSS: pyramidal, ambulation, cerebellar, brainstem, sensory, or visual. Episodic spasms, sexual dysfunction, fatigue, mood change, or bladder or bowel urgency or incontinence will not suffice to establish a relapse. Note that the following items need not be scored: sexual dysfunction and fatigue.

It should be noted that all patients with new neurological symptoms defined at a visit should be referred to the study investigator considers the symptoms consistent with an intensification of neurological symptoms from a transient systemic infection.

Clinical relapses (i.e., regardless of whether they meet criteria for a protocol-defined relapse) will be recorded in the eCRF.

4.5.7 Brain Magnetic Resonance Imaging

MRI will be used to monitor CNS lesions in patients with MS and potentially other pathophysiology, such as inflammation and neurodegeneration. MRI scans of the brain will be obtained in all patients at study visits as indicated in Appendix 1, Appendix 2, and Appendix 3. The MRI sequences will be analyzed by a central reading facility ensuring the integrity and quality of the acquired data. The centralized reading center should be blinded to treatment assignment, and the reading will be performed in the absence of clinical information.

If during the screening phase, a MRI scan is required for MS diagnosis, then it can serve as a baseline scan. Note that this MRI scan should be obtained approximately 10 days

prior to performing the baseline visit to allow time for the centralized reading center to assess its quality and for potential re-scans if needed.

Patients who prematurely discontinue from study drug treatment during the controlled period will need to return to the clinic to perform the MRI scans required in this period (see Appendix 1 and Appendix 2 for additional details). In addition, MRI scans will be obtained at the Early Termination Visit if one was not performed during the prior 4 weeks.

MRI scans collected during the controlled period should occur within a window of ±2 weeks of the scheduled visit, as per the schedule of activities (see Appendix 1 and Appendix 2). The remaining MRI scans collected at the Week 48 *and 96* visits, should occur within a time ±4 weeks of the scheduled visit (see Appendix 1 and Appendix 2) or can occur 2 weeks of the scheduled MN visit (when patient comes for the Week 46 visit, see Appendix 3). If patients receive corticosteroids for a MS relapse, every effort should be made to obtain a scheduled MRI scan prior to the first corticosteroid dose, and there should be an interval of at least 3 weeks between the final dose of corticosteroids and the next scheduled MRI scan.

MRI scans will be read by a centralized reading center for secondary and exploratory endpoints. Further details on scanning acquisition sequences, methods, handling and transmission of the scans, certification of site MRI radiologist/technicians, and the procedures for the analysis of the scans at the central reading center are described in a separate MRI Acquisition Procedures Manual.

MRI assessments will include, but may not be limited to, T1-weighted scans before and after injection of Gd contrast, fluid-attenuated inversion recovery (FLAIR) and T2-weighted scans.

All MRI scans will also be reviewed locally by a radiologist for safety, and the MRI scan report will be provided to the study investigators who in turn will inform the patient about clinically relevant findings. The study investigator will have access to MRI scans.

Non-MS pathology should be reported on the corresponding eCRF, and an adverse event should be reported if clinically relevant.

4.5.8 Laboratory, Biomarker, and Other Biological Samples

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis, unless otherwise indicated, according to schedule of activities (Appendix 1, Appendix 2, and Appendix 3):

- **Hematology**: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count, WBC differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells), and quantitative platelet count

- **Blood chemistry**: creatinine, amylase, potassium, sodium, and liver function tests (ALT/SGPT, AST/SGOT, γ-glutamyl transferase, ALP, and total bilirubin)
- **Urinalysis:** A urine dipstick will be performed at the site (pH, specific gravity, glucose, protein, ketones, and blood), and a microscopic examination if abnormal and clinically significant
- **Anti-Drug Antibodies (ADA):** Plasma and serum samples will be collected for determination of antibodies against ocrelizumab or rHuPH20. Because ocrelizumab concentrations affect the ADA assay, the concentration of ocrelizumab will be measured as well at all timepoints with ADA assessment to enable interpretation of the results.
- **Quantitative Ig:** Ig levels (IgG, IgM, and IgA)
- **Pregnancy test**: All females of childbearing potential will have a serum pregnancy test at screening and urine pregnancy test *(performed at site)* prior to ocrelizumab administration.

  Females of childbearing potential must have regular pregnancy tests. A urine pregnancy test (sensitivity of at least 25 mU/mL on the β-hCG test) will be performed at the specific timepoints. On dosing visits, the urine pregnancy test should be performed prior to the premedication administration. A positive urine pregnancy test should be confirmed with a serum test prior to any further dosing with study drug. If a urine pregnancy test is positive, the patient will not receive the scheduled dose, and confirmatory serum pregnancy test will be performed by the central laboratory.
- **FSH level testing:** only applicable to female patients to confirm the post-menopausal status at screening.
- Serum samples to determine ocrelizumab serum concentration for PK analysis (see Appendix 5)
- **Viral serology and detection**: All patients must have negative hepatitis B surface antigen (HBsAg) test result at screening prior to enrollment. If total HBcAb is positive at screening, hepatitis B virus (HBV) DNA measured by polymerase chain reaction (PCR) must be negative to be eligible.

  For patients enrolled with negative HBsAg and positive total HBcAb, HBV DNA (PCR) must be repeated on a 24-week basis at pre-dosing visits as per the scheduled visits. Patients in whom the viral DNA becomes positive but in whom the quantity is at the lower limit of detection of the assay should have the test repeated as soon as possible. Patients found to have a confirmed viral DNA-positive test should be referred to a hepatologist for immediate assessment. These patients will not receive further doses of study drug; they will be however further followed up for safety (see Section 4.7.1).

  Liver function (i.e., ALT/SGPT, AST/SGOT, gamma-glutamyl transferase, total bilirubin) should be reviewed throughout the study. Patients who develop evidence of liver dysfunction should be assessed for viral hepatitis and, if necessary, referred to a hepatologist or other appropriately qualified expert. Study drug should be withheld until the diagnosis of viral hepatitis has been

excluded. Patients who develop hepatitis B should be discontinued from the treatment (see Section 4.7.1). Should treatment be prescribed, this will be recorded in the eCRF. Patients with viral hepatitis due to other agents, such as hepatitis A, may resume treatment after recovery.

- **Biomarker samples:** serum samples will be collected and analysis may include, but may not be limited to, NfL
- **Flow cytometry:** Analysis will include, but may not be limited to, the determination of the B-cell number (CD19+) and T-cell counts (CD3+, CD4+, CD8+). B-cell subsets including but not limited to B-cell memory, naïve, plasmablasts etc. may be measured (e.g., CD27 and CD38).
- Additional samples in the event of severe systemic administration reactions including potential hypersensitivity/anaphylactic reaction: serum samples will be taken for the assessment of tryptase, complement components (C3 and CH50), ADA and PK, as indicated in Section 5.1.4.1 and Appendix 11.

Blood and urine sample collection may be performed by site personnel at a MN visit (see Section 4.5.10).

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.14), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Plasma and serum samples collected for PK and immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood or serum samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or

patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.9 Expanded Disability Status Scale

The EDSS is the most commonly used clinician reported outcome (ClinRO) measure for quantifying changes in the disability level of patients with MS over time. The EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10.0 (death) (Kurtzke 1983; Kappos 2011). The EDSS is based on a standard neurological examination, incorporating functional systems (visual, brainstem, pyramidal, cerebellar< sensory, bowel and bladder, and cerebral [or mental]) that arerated and then scored as a FSS, and ambulation, which is scored as ambulation score. Each FSS is an ordinal clinical rating scale ranging from 0 to 5 or 6 and an ambulation score that is rated from 0 to 16. These ratings are then used in conjunction with observations, as well as information, concerning ambulation and use of assistive devices to determine the total EDSS score. All FSS, ambulation score, and total EDSS scores will be captured electronically and completed in real-time. Note that the following items do not need to be scored for this study: sexual dysfunction and fatigue.

In this study, Neurostatus-eEDSS definitions and calculating algorithms will be used (D'Souza et al. 2017).

4.5.10 Mobile Nursing Visit

At participating sites only, the administration of Dose*s* 3 *onwards* (i.e., the Week 48*, 72 and 96* visit*s*) *can* be performed by a healthcare professional from the study site (if local processes are in place) at the patient's home or another suitable location to improve access and convenience for patients participating in the study (Appendix 4).
A dedicated informed consent must be obtained and documented in written form (MN Informed Consent Form) before the optional home administration of ocrelizumab SC.

At the participating sites only, the investigator will determine whether the participant is eligible for home administration based on the retreatment criteria (refer to Section 4.3.2.3) and suitability. If at any time the investigator or patient determines that home administration by the site personnel is unsuitable, then study drug must be administered in the clinic. If during a visit the site personnel identifies any change in the patient's health status (e.g., new or worsening neurologic symptoms or any other situation that may warrant an unscheduled visit), an unscheduled visit will be scheduled as soon as possible with the site (i.e., within 7 days of symptom onset if possible).

4.5.11 Telephone Contact

After each ocrelizumab SC injection, site personnel will have a telephone conversation with the patient to elicit, in a non-leading way, information on adverse events that may have occurred after ocrelizumab SC treatment. On the day of first ocrelizumab SC dose (i.e. Dose 1 for ocrelizumab SC group and Dose 2 for ocrelizumab IV group) the site

personnel will contact the patient approximately 6 hours after the injection. On the second and subsequent doses of ocrelizumab SC the site personnel will contact the patient approximately 24 hours after injection. The site personnel should have more frequent calls with a particular patient if considered appropriate by the investigator (e.g. to follow up on potential injection reactions).

4.5.12 Dermatologist Evaluation of Injection Reactions

Any patient who experiences a skin or injection site reaction of Grade ≥3 severity or meeting seriousness criteria will undergo a dermatologist consultation.

4.5.13 Description of Patient-Reported Outcome Assessment Instruments

F*ive* PRO measures (will be included in this study, which include: Entry treatment experience questions, TASQ (IV infusion version and SC injection version), PPQ, an MS treatment preference questionnaire (MSTPQ) *and Patient global impression of satisfaction (PGI-SF).*

All patients will complete the following:

- Entry treatment experience questions at baseline, before their ocrelizumab treatment
- TASQ for SC injection at Weeks 24 and 48, 30-60 minutes after their SC injection
- MSTPQ at Week 48 prior to their ocrelizumab injection
- *PGI-SF at Week 96 prior to their ocrelizumab injection*

A subset of patients will complete the following:

- For patients whose first ocrelizumab treatment is a SC injection, they will complete:

  TASQ for SC at baseline 30-60 minutes after their first SC injection
- For patients whose first ocrelizumab treatment is an IV infusion they will complete:

  TASQ for IV at baseline 30-60 minutes after their first IV infusion of Dose 1

  PPQ at week 48 before their SC injection

4.5.13.1 Entry Treatment Experience Questions

The entry treatment experience questions are reported by the patients at baseline to understand their treatment experience related to the last DMT they were treated with prior to enrollment in this study (see Appendix 6). It consists of four items used to understand if patients took any previous DMT before starting the study and if so, when they stopped taking their most recent DMT, the reason for stopping this treatment, and how satisfied they were when taking it. Patients will be asked to respond on a 2-, 3-, 4- and 8-point scale, from which each item will be evaluated individually. Entry treatment experience questions will be administered at baseline, prior to ocrelizumab treatment and take approximately 30 seconds–1 minute to complete.

4.5.13.2 Treatment Administration Satisfaction Questionnaires (TASQ)

The TASQ is a patient-reported measure for which there are two versions; an IV Infusion version and a SC Injection version (see Appendix 7 and Appendix 8, respectively). These are adapted from the Rituximab Administration Satisfaction Questionnaire
(Theodore-Oklota et al. 2016) and will be used for the patient to evaluate and reflect on his or her last ocrelizumab administration experience. Each version consists of 13 items that are worded the same but include either an IV Infusion or SC Injection item. Items are rated on a 3- or 5-point Likert scale, for which a higher score corresponds to higher satisfaction and more positive experience. Individual items will be evaluated.

The TASQ will be completed by the patient after completion of their ocrelizumab treatment. Patients whose first ocrelizumab treatment was SC injection will complete the TASQ SC at baseline, whereas patients whose first ocrelizumab treatment was IV infusion will complete the TASQ IV at baseline. All patients will complete the TASQ SC at Weeks 24 and 48. It will take between 2–4 minutes to complete.

4.5.13.3 Patient Preference Questionnaire (PPQ)

The PPQ is a patient-reported measure that consists of three items, used to understand whether patients have a preference for SC administered ocrelizumab or IV administered ocrelizumab, the strength of their preference, and the main reasons for this (see Appendix 9). Patients are asked to respond on either 3- or 5- point scale, from which each item will be evaluated individually.

This measure will only be completed by the subset of patients whose first ocrelizumab treatment was administered as an IV infusion. It will be completed prior to the patient's ocrelizumab SC injection at week 48, and will take approximately 30 seconds–1 minute to complete.

4.5.13.4 MS Treatment Preference Questionnaire (MSTPQ)

The MSTPQ is completed by the patients to provide information about their overall level of satisfaction with ocrelizumab and whether they have a preference for ocrelizumab or the DMT they were most recently treated with prior to the study (see Appendix 10). It consists of three items and is rated on a 4- or 6- point scale, from which each item can be evaluated individually. The MSTPQ will be administered at Week 48 prior to ocrelizumab treatment and will take approximately 30 seconds–1 minute to complete.

4.5.13.5 *New PRO—Patient global impression of satisfaction (PGI-SF)*

The patient global impression is one item used to assess patient's overall satisfaction (PGI-SF) of ocrelizumab SC as a treatment for their MS symptoms (see Appendix 14). The PGI-SF is rated on a four point Likert scale ranging from Very satisfied (1) to Very dissatisfied (4). It is scored descriptively and takes approximately 30 seconds – 1 minute to complete. The PGI-SF will be administered at Week 96 prior to the patient's ocrelizumab treatment.

4.5.14 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.14.1 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.14.1) will not be applicable at that site.

4.5.14.2 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to ocrelizumab SC or IV, diseases, or drug safety:

- PAX gene samples for RNA and genomic DNA
- Whole blood samples for DNA
- Leftover blood, serum, plasma, and/or any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via whole genome sequencing (WGS), whole exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a

comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.14.3 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.14.4 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time

and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.14.5 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.14.6 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 OVERVIEW OF CLINICAL VISITS

After the screening, patients who fulfill the entry criteria will be scheduled for baseline assessments. Visits will take place as described in the schedule of assessments (see Appendix 1, Appendix 2, and Appendix 3).

Patients who cannot receive their study drug at the scheduled visit or within 24 hours of the visit should be rescheduled for a delayed dosing visit (see Section 4.6.1). Additional unscheduled visits for the assessment of disease worsening, new neurological symptoms, or safety events may occur at any time.

4.6.1 Delayed Dosing Visit

Delayed dosing visits may be scheduled only if the study drug cannot be administered (e.g., due to safety events) at the time points defined in the schedule of activities (see Appendix 1, Appendix 2, and Appendix 3). Thus, a patient who had all assessments of a dosing visit performed, but could not receive the study drug, should be rescheduled for the infusion or injection on another day, provided that they meet the retreatment criteria. At the delayed dosing visit, additional tests or assessments, such as routine safety laboratory tests, may be performed as clinically indicated. A minimum interval of 22 weeks should be maintained between the delayed dose and the subsequent dose. However, if the second ocrelizumab IV infusion of Dose 1 (i.e., infusion Day 14, Week 2) happens to be delayed, a minimum interval of 20 weeks should be kept between this infusion and the next administration of Dose 2 (i.e., ocrelizumab SC dose on Week 24 visit).

4.6.2 Unscheduled Visits

Patients who develop new or worsening neurological symptoms should be seen at the investigational site as soon as possible, regardless of the dates of their pre-planned, scheduled study visits and regardless of the study period. The EDSS assessment should be performed for any suspected neurological worsening. If an MS relapse (or any worsening neurological event) is diagnosed or suspected, EDSS assessment should be performed by site investigator (or designee, as applicable) within 7 days from the onset of a new or worsening neurological event (including relapses), in addition to completing the appropriate eCRF (see Section 4.5.5)

Other assessments performed at unscheduled (non-dosing) visits will depend on the clinical needs of the patient. The primary reason for performing an unscheduled visit will be reported in the eCRF.

4.7 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.7.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy: Ocrelizumab treatment will be discontinued for patients who become pregnant during the study. Patients will remain in the study and will have the opportunity to enter the safety follow-up phase.
- Life-threatening (NCI CTCAE Grade 4) infusion- or injection-related event that occurred during a previous ocrelizumab dose
- Develop active hepatitis B infection, either new onset or reactivation
- PML
- Patient's decision to discontinue the treatment

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment will not be replaced.

Patients who prematurely discontinue from study drug treatment will need to return to the clinic for a treatment discontinuation visit (see Appendix 1 and Appendix 2 for additional details) and to perform the MRI scans required in the controlled period (Section 4.5.7), if applicable; and are encouraged to enter and complete the safety follow-up phase (refer to Section 3.1.1.3).

After treatment discontinuation, every effort should be made to have the patient enter the safety follow-up phase of the study.

4.7.2 Patient Discontinuation from the Study

Patients will return to the clinic for a treatment discontinuation visit.

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up

- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

If a patient withdraws from the study, the patient should be asked if he or she can still be contacted for further information, unless otherwise specified by the local requirements. The outcome of that discussion should be documented in the medical record. If lost to follow-up, the investigator should contact the patient or a responsible relative by telephone followed by registered mail or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient withdrew from the study.

4.7.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.7.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with ocrelizumab IV and SC from clinical studies as well as post-marketing experience. The anticipated

important safety risks for both ocrelizumab formulations are outlined below. Refer to the ocrelizumab local label and the Ocrelizumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Ocrelizumab

Key information regarding risks is summarized below. For details, please refer to the current version of the Investigator Brochure.

5.1.1.1 Identified Risks and Adverse Drug Reactions

Infusion–Related Reactions

All CD20-depleting agents, including ocrelizumab, have been associated with acute IRRs. Symptoms of IRRs may occur during any ocrelizumab infusion but have been more frequently reported during the first IV infusion. Physicians should alert patients that IRRs can occur within 24 hours of the administration.

Across the RMS and PPMS trials, symptoms associated with IRRs included, but are not limited to pruritus, rash, urticaria, erythema, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, tachycardia, and anaphylaxis.

Patients who have received ocrelizumab IV should be observed for at least one hour after the completion of the infusion for observation of any symptom of IRR.

Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

Hypotension, as a symptom of IRR, may occur during IV ocrelizumab infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each study drug infusion.

Patients will be premedicated for ocrelizumab IV administration as described in Section 4.3.2 to minimize the risk of IRRs.

Injection-Site Reactions (subcutaneous formulation)

Injection site reactions (ISRs) were the most frequently reported adverse event in Study CN41144, occurring in 61.5% of the 96 patients who received at least one dose of ocrelizumab 1200 mg SC (CCOD 07 May 2021). All ISRs were Grade 1-2 in intensity,

non-serious, transient, and were not treatment- limiting. The majority of ISRs had resolved within 6 days and symptomatic treatment was provided for 10 out of the 96 patients. The most common ISR symptoms observed in patients who received 1200 mg SC were injection site erythema, pain, swelling, bruising, pruritus, hypersensitivity, and urticaria.

ISRs will continue to be further characterized during this study (e.g., by assessment of the reported ISR and dermatological assessment as indicated in Appendices 1-3 and Section 4.5.12).

The premedication regimen described in Section 4.3.2.1 is expected to minimize the risk of ISRs. See Section 5.3.5.1 for instructions on reporting ISRs.

Infections

Infection is an identified risk associated with ocrelizumab treatment, predominantly involving mild to moderate respiratory tract infections.

During the controlled period of the pivotal trials, the proportion of patients with serious infections in RMS was lower in the ocrelizumab group (1.3%) than in the interferon β-1a group (2.9%); in PPMS, the proportion of patients with serious infections, was similar in both groups: 6.7% in the placebo group compared with 6.2% in the ocrelizumab group.

No opportunistic infections were reported by any MS patient treated with ocrelizumab during the controlled period of the pivotal trials.

Non-disseminated herpes virus-associated infections, mostly mild to moderate, were also reported more frequently with ocrelizumab (approximately 5%–6%, simplex and zoster) than with comparators (approximately 3%).

In interventional clinical studies, there were no reports of hepatitis B reactivation in patients with MS treated with ocrelizumab, but one reported in a patient with RA treated with ocrelizumab. Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with ocrelizumab as per local guidelines. Patients with active HBV should not be treated with ocrelizumab. Patients with positive serology should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Delay ocrelizumab administration in patients with an active infection until the infection is resolved.

In the setting of a pandemic or epidemic, screening for active infections prior to and during study participation should be considered according to local/institutional guidelines or those of applicable professional societies (e.g., MS International Federation, European Academy of Neurology, American Academy of Neurology).

For PML see “Potential risks” below, Section 5.1.1.2.

Impaired Response to Vaccination

After treatment with ocrelizumab over 2 years in pivotal clinical trials, the proportion of patients with positive antibody titers against *Streptococcus pneumoniae*, mumps, rubella, and *Varicella* were generally similar to the proportions at baseline.

The results of the randomized, open-label Phase IIIb study (BN29739) that assessed if ocrelizumab recipients with RMS raise adequate humoral responses to selected vaccines indicate that patients treated with ocrelizumab were able to mount humoral responses, albeit decreased, to tetanus toxoid, 23-valent pneumococcal polysaccharide, keyhole limpet hemocyanin neoantigen, and seasonal influenza vaccines. The results are summarized in the current version of the Ocrelizumab Investigators Brochure.

Physicians should review the immunization status of patients being considered for treatment with ocrelizumab. Patients who require vaccination should complete it at least 6 weeks prior to initiation of ocrelizumab. For seasonal influenza vaccines, it is still recommended to vaccinate patients on ocrelizumab. Vaccination with live or live-attenuated vaccines are not recommended during the treatment with ocrelizumab and until B cells have returned to normal levels.

Due to the potential depletion of B-cells in neonates and infants of mothers, who have been exposed to ocrelizumab during pregnancy, it is recommended that vaccination with live or live-attenuated vaccines should be delayed until B-cells have recovered; therefore, measuring CD19-positive B cell level, in neonates and infants, prior to vaccination is recommended.

It is recommended that all vaccinations other than live or live-attenuated should follow the local immunization schedule and measurement of vaccine-induced response titers should be considered to check whether individuals can mount a protective immune response because the efficacy of the vaccination may be decreased (refer to Section 4.4.4).

Decrease in Immunoglobulins

Treatment with ocrelizumab resulted in a decrease in total immunoglobulins (Ig) over the controlled period of the studies, mainly driven by reduction in IgM. The proportion of patients with decrease in Igs below lower limit of normal (LLN) increased over time and with successive dosing. Based on additional patient exposure, in cases of continuous decrease over time, a higher risk of serious infection cannot be ruled out.

Serious Infections Related to Decrease in Immunoglobulins (Particularly in Patients Previously Exposed to Immunosuppressive/Immunomodulatory Drugs or with Pre-existing Hypogammaglobulinaemia)

The pooled data of the ocrelizumab pivotal clinical studies (RMS and PPMS) and their open-label extensions have shown an apparent association between decrease in

immunoglobulins and serious infections with ocrelizumab treatment and this was most apparent for IgG. There was no difference in the pattern (type, latency, duration, and outcome) of the serious infections reported in this subset of patients compared to the overall serious infections profile. In addition, risk factors for a subset of patients at higher risk of serious infections could not be identified.

Delayed Return of Peripheral B Cells

Treatment with ocrelizumab leads to rapid depletion of CD19+ B cells in blood by 14 days post treatment (first timepoint of assessment) as an expected pharmacologic effect. This was sustained throughout the treatment period. The longest follow-up time after the last ocrelizumab infusion from Phase II Study WA21493 in 51 patients of 600 mg ocrelizumab group indicates that the median time to repletion (returned to baseline/LLN, whichever occurred first) of B cells was 72 weeks (range 27–175 weeks).

5.1.1.2 Potential Risks

Systemic Injection Reactions (subcutaneous formulation)

Injection reactions with systemic symptoms may develop following SC administration of biological therapeutics. The majority of systemic injection reactions were of mild to moderate severity, with headache being the most commonly reported symptom. Details on management steps and assessments to be performed in the event of severe systemic injection reactions including potential hypersensitivity/anaphylactic reactions are provided in Section 5.1.4.4.

See Section 5.1.4.3 for instructions on reporting injection reactions.

Progressive Multifocal Leukoencephalopathy

JC virus infection, resulting in progressive multifocal leukoencephalopathy (PML) has been reported in patients treated with anti-CD20 antibodies, including ocrelizumab, and mostly associated with risk factors, such as patient population or polytherapy with immunosuppressants. The reporting rate with ocrelizumab has been approximately 1 case per 100,000 patients. Since a risk of PML cannot be ruled out, physicians should be vigilant for early signs and symptoms of PML, which can include any new onset, or worsening of neurological signs or symptoms as these can be similar to an MS relapse. If PML is suspected, dosing with ocrelizumab must be withheld. Evaluation of PML, including MRI scan, preferably with contrast (compared with pre-treatment MRI) confirmatory CSF testing for JC Viral DNA and repeat neurological assessments, should be considered. If PML is confirmed, ocrelizumab must be discontinued permanently. Refer to Appendix 12 for guidance for diagnosis of PML. Also refer to the Ocrelizumab Investigator's Brochure for more details.

Hypersensitivity Reactions

Hypersensitivity may be difficult to distinguish from IRRs or systemic injection reactions in terms of symptoms. A hypersensitivity reaction may present during any administration, although typically would not present during the first administration. For

subsequent administration, more severe symptoms than previously experienced, or new severe symptoms, should prompt consideration of a potential hypersensitivity reaction. If a hypersensitivity reaction is suspected during infusion, the administration must be stopped immediately and permanently. Patients with known IgE-mediated hypersensitivity to ocrelizumab must not be treated.

Precautions and procedures for anaphylaxis are described in Appendix 11. Section 5.1.4.3 details management steps and assessments to be performed in the event of severe systemic injection reactions including potential hypersensitivity/anaphylactic reactions.

Malignancies (Including Breast Cancer)

For US only: An increased risk of malignancy with ocrelizumab may exist. In controlled trials of MS, malignancies, including breast cancer, occurred more frequently in ocrelizumab-treated patients. Breast cancer occurred in 6 of 781 females treated with ocrelizumab and none of 668 females treated with interferon β-1A or placebo.

For all countries: Patients should follow standard breast cancer screening guidelines. Refer to the current Ocrelizumab Investigator's Brochure for more details.

Neutropenia

In the controlled treatment period of the pivotal Phase III studies WA21092, WA21093 and WA25046, decreased neutrophils were observed in 12% and 15% of patients with MS treated with ocrelizumab, in PPMS and RMS, respectively. Most were mild to moderate in severity, approximately 1% of the patients had Grade 3 or 4 neutropenia; and no temporal association with infections was identified. Based on additional patient exposure, an association between neutropenia and serious infections with ocrelizumab treatment was not observed. Refer to the Ocrelizumab Investigator's Brochure for more details.

5.1.2 Risks Associated with Corticosteroids

The adverse reactions of corticosteroids may result from unwanted glucocorticoid actions, or from inhibition of the hypothalamic-pituitary-adrenal axis. Refer to local prescribing information.

5.1.3 Risks Associated with Antihistamines

The adverse reactions depend on the sedating properties of the antihistamine and include but are not limited to nausea, drowsiness, headaches, dry mouth, and allergic reactions such as rash. Refer to local prescribing information.

5.1.4 Management of Patients Who Experience Adverse Events

5.1.4.1 Dose Modifications

Study drug dose modifications are not foreseen.

5.1.4.2 Treatment Interruption

During the study, ocrelizumab administration may be temporarily suspended in patients who experience relevant adverse events considered to be related to study drug and prevent the patient from retreatment with study drug during the study (see Section 4.3.2.3).

5.1.4.3 Management Guidelines for Injection Site Reactions

ISRs have been reported with other subcutaneously injected monoclonal antibodies, as well as with ocrelizumab SC. ISRs may occur rapidly or with a latency of a few days. Based on experience to date the reaction may manifest as local swelling, tenderness, pain and redness surrounding the injection site. If an ISR develops, patients should be monitored and observed closely, including the measurement of maximum diameter of the skin reaction at each subsequent visit. Symptomatic treatment depending on the severity (Table 3) should be provided as clinically indicated.

In case of a skin or injection reaction of Grade ≥3 severity or meeting seriousness criteria, patients will undergo a dermatologist consultation.

Table 3 Injection Site Reaction Grading

Grade	Description
1	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)
2	Pain; lipodystrophy; edema; phlebitis
3	Ulceration or necrosis; severe tissue damage; operative intervention indicated
4	Life-threatening consequences; urgent intervention indicated
5	Death

Note: Based on the NCI CTCAE (v5.0).

5.1.4.4 Management Guidelines for Severe Systemic Injection Reactions, including Potential Hypersensitivity/Anaphylactic Reactions

Precautions and procedures for anaphylaxis are described in Appendix 11. For cases of severe systemic injection reactions including potential hypersensitivity/anaphylactic reactions, the following should be implemented:

- Symptomatic treatment should be provided as clinically indicated
- Ensure that appropriate monitoring is in place, with continuous pulse oximetry monitoring until resolution of symptoms
- Collect serum tryptase, complement components (C3 and CH50), ADA and PK at the time points indicated in Table 4

Table *4* Samples To Be Collected in the Event of a Severe Systemic Injection Reaction Including Potential Hypersensitivity/Anaphylactic Reactions

Assessment	Timepoint related to event			
	As soon as possible but within 1 hour of event onset	3-4 hours post-event onset	24 hours post-event	Within 2 weeks post-event
Serum Tryptase	x	x		X
Serum C3	x	x	x	
Serum CH50	x	x	x	
ADA and PK	x			

ADA = anti-drug antibody; PK = pharmacokinetic

5.1.4.5 Management Guidelines for Infusion-Related Reactions

Slowing of the infusion rate or interruption of the infusion may be necessary in the event of an infusion reaction. In rare cases, study treatment may need to be discontinued. Refer to ocrelizumab local label for further guidelines.

Handling of IRRs will depend on the intensity of symptoms and shall not depend on the dose administered (see also Table 3 for grading of intensity of IRRs).

For a **mild to moderate (Grade 1 or 2)** non-allergic, infusion-related event, the infusion rate should be reduced to half the rate being given at the time of onset of the event (e.g., from 50 mL/hr to 25 mL/hr or from 100 mL/hr to 50 mL/hr). Once the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to the next closest rate on the patient's infusion schedule and the rate increments resumed.

For a **severe infusion-related event (Grade 3)** or a complex of flushing, fever, and throat pain symptoms, the infusion should be interrupted immediately and the patient should receive aggressive symptomatic treatment. The infusion should be restarted only after all the symptoms have disappeared. The initial infusion rate at restart should be half of the infusion rate that was in progress at the time of onset of the reaction.

For a **life-threatening infusion-related event (Grade 4)** during an infusion, the infusion should be immediately stopped, and the patient should receive appropriate treatment (including use of resuscitation medications and equipment that must be available and used as clinically indicated). The patient will be discontinued from study treatment.

The above examples of dose interruption and slowing (for mild/moderate and severe IRRs) will result in a change in the infusion rate and increase the total duration of the infusion but not the total dose.

Precautions and procedures for management of hypersensitivity and anaphylactic reactions are described in Appendix 11.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Section 5.3.5.9 and Section 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Grade 3 or higher injection site reactions
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.1.2 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

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 (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 48 weeks after the final dose of study drug.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 5 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 5 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 6):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 6 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions or Injection Reactions

Adverse events that occur **during or within 24 hours** after study drug administration and are judged to be related to study drug infusion or injection should be captured as a diagnosis [e.g., "infusion-related reaction", “injection reaction” (which is applicable for local or systemic injection reactions) or "anaphylactic reaction"] on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction or Injection-Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of MS.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to progression of MS, "Multiple Sclerosis progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When

recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Multiple Sclerosis

Medical occurrences or symptoms of deterioration that are anticipated as part of MS should not be recorded as adverse events. However, deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study should be recorded as an adverse event. When recording an unanticipated worsening of MS on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of multiple sclerosis").

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Elective hospitalizations or surgical procedures that are a result of a patient's preexisting condition(s) that have not worsened since receiving trial medication. Examples may include, but are not limited to, cholecystectomy for gallstones and diagnostic testing. Such events should still be recorded as medical procedures on the eCRF.
- Hospitalization to receive study drug unless this is prolonged (more than 24 hours).
- Hospitalization following an MS relapse as long as the reason for hospitalization is to receive standard treatment with IV methylprednisolone.

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria *or qualifies as an adverse event of special interest*, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For ocrelizumab, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with ocrelizumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.

  Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor. Sites are not expected to review the PRO data for adverse events.

5.3.5.14 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Medical Monitors and Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be provided separately. An Emergency Medical Call Center will *also* be available 24 hours per day, 7 days per week. *The* Emergency Medical Call Center will *connect the investigator with an Emergency Medical Contact,* provide medical translation service if necessary, , and track all calls. *Contact information including t*oll-free numbers for the *Emergency Medical Call Center* will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur Prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported.

The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 48 weeks after the final dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur more than 48 weeks after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the

child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. Information regarding infant health up to 1 year should be collected on the Infant Health Questionnaire (see Appendix 13).

5.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the adverse event reporting period (defined in Section 5.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until Pregnancy Outcome using the Infant Health Questionnaire (see Appendix 13) provided by the Sponsor.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 48 weeks after the last dose of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the Ocrelizumab Investigator's Brochure.

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An iDMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Full details of all statistical issues and planned statistical analyses will be specified in a separate Statistical Analysis Plan, which will be finalized prior to the locking of the study database.

6.1 DETERMINATION OF SAMPLE SIZE

PK data from the pivotal studies (WA21092, WA21093, and WA25046) showed a coefficient of variation (CV) for AUC of approximately 0.30 after the fourth dose of ocrelizumab administered at Week 72, following ocrelizumab IV 600 mg every 24 weeks, in both the RMS and PPMS population.

For treatment-naïve patients, the variability of AUC could be slightly higher during the first dosing cycle, when the patient's B cells have not been depleted. The variability of AUC following SC administration is expected to be higher compared to IV, with the estimated CV to be available following the ongoing Phase Ib study (OCARINA I).

Assuming the CV for the IV and SC administration are 0.50 and 0.75, respectively, an analysis of unequal variance is used, and the true GMR of AUC SC versus AUC IV is 1, 232 patients (116 per treatment arm) need to be enrolled in order to achieve 90% power with a one-sided α of 0.05 for the non-inferiority analysis. The non-inferiority would be established if the lower end of the two-sided 90% CI is $>$0.8. The non-inferiority limit of 0.8 corresponds to a maximum 20% loss in AUC for the SC administration compared with IV. The rationale for the 0.8 non-inferiority margin relies on the standard lower bound recommended in the regulatory guidance documents for demonstration of bioequivalence for PK bridging (EMA "Guideline on the Investigation of Bioequivalence" [2010]/FDA Draft Guidance for Industry, "Bioavailability Studies Submitted in NDAs or INDs—General Considerations" [2019]). If the observed CV in either the SC or IV arm of the CN41144 study at the time of the data snapshot is greater than these assumed values, then the sample size for this study may be increased to maintain the desired study power. In addition to the theoretical PK considerations described above, the proposed sample size also takes into account the adequacy of the safety database to demonstrate the safety profile of ocrelizumab SC in its intended use. The proposed estimated extent of exposure will allow for characterization of common AEs. Given the number of patients exposed and assuming 200 patients had at least one SC dose at the clinical cutoff date (CCOD), any risk of 1.49% or higher can be ruled out with 95% confidence if 0 events are observed in the study.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue treatment or study, or complete the study will be summarized. Reasons for premature treatment and study discontinuation will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, and stratification factors) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment group.

6.4 EFFICACY ANALYSES

6.4.1 Secondary Radiological Estimand

6.4.1.1 Main Estimand

The secondary efficacy analysis will be done separately for each MS subtype (RMS or PPMS), for specific visits, and each variable (T1Gd+ lesions or new and/or enlarging T2 lesions).

Patients will be grouped according to their actual treatment received and included if receiving, during the controlled period, at least one full or partial dose of either Reference or Experimental treatment.

T1 Gd+ lesions will be performed and analyzed on Week 8 and 24 visits while new and/or enlarging T2 lesions will be analyzed on Week 12 (relative to Week 8) and Week 24 (relative to Week 12).

The estimand for the secondary efficacy analysis follows a combination of while on study and treatment-policy and estimates the treatment effect on the considered MRI variable, regardless of adherence, on the basis of the following attributes:

a) Treatment: Ocrelizumab IV (Reference) versus ocrelizumab SC (Experimental).

b) Population: RMS or PPMS patients defined through the in/exclusion criteria reflecting the target population. The analysis population will consist of all randomized patients who performed a brain MRI scan.

c) Variable: total number of T1 Gd+ lesions (Week 8 or 24) or new and/or enlarging T2 lesions from all subjects at Week 12 or 24. New and/or enlarging T2 lesions are relative to the previous scan, i.e., relative to Week 8 at Week 12 and relative to Week 12 at Week 24.

d) Intercurrent events will be handled as follows:

- Withdrawal from treatment or incomplete dosing: MRI assessment will be collected in all patients. Data will be included with patients grouped according to their actual treatment.

e) Population-level-summary estimator

- The estimand variable will be modeled by a negative binomial regression that includes the treatment variable and is adjusted for covariates. Covariates for variable total number of T1 Gd+ lesions are: baseline T1 Gd+ lesion (present or not), and geographical region (U.S. vs. ROW). Covariates for variable new

and/or enlarging T2 lesions are baseline T2 lesion count and geographical region (U.S. vs. ROW). The adjusted Incidence Rates (for each treatment arm) estimated from such models will be reported along with the two-sided 95% CIs.

- If the negative binomial model fails to converge due to an extremely low number of patients with lesions, unadjusted rate and Poisson two-sided 95% CI will be reported instead.
- No formal statistical testing will be done. The estimated rates (adjusted or unadjusted) and two-sided 95% CI will be evaluated to confirm that SC and IV treatment result in similarly low rates of lesions.

f) Handling of missing data

- MRI performed but not possible to read the number of lesions: assessment will not be used in the estimand variable and the offset will not include the associated visit.
- MRI not performed: No data will be imputed.
- Withdrawal from study (missing data): No data will be imputed.

6.4.1.2 Supplementary Estimand Analysis Applying Hypothetical-Policy Strategy

Week 24 assessments should be performed during the controlled treatment period (i.e., before Week 24 SC dosing). It is not ruled out that some MRI assessments are collected after the Week 24 SC dosing has been given (i.e., during the ocrelizumab SC treatment period). This supplementary estimand will apply a hypothetical-policy strategy on such assessments. Hence this supplementary estimand will be performed as the main estimand excluding assessments performed during the ocrelizumab SC treatment period.

6.4.2 Exploratory Radiological and Clinical Endpoints

The parameters defined in Section 2 will be summarized by descriptive statistics by treatment in the RMS and PPMS patient populations and in the overall population.

MRI parameter Total number of new or enlarging T2 lesions as detected by brain MRI at Week 8 relative to the previous scan *(i.e., relative to Baseline)* will be analyzed as per secondary radiological main estimand.

6.4.3 Exploratory PRO Endpoints

The parameters defined in Section 2.3 will be summarized by descriptive statistics by treatment in the RMS and PPMS patient populations *where needed,* and in the overall population.

6.5 SAFETY ANALYSES

The safety analysis population and period of exposure will consist of all randomized patients who received at least one infusion (partial or complete) or injection (partial or complete) of study drug (ocrelizumab IV or ocrelizumab SC) with patients grouped

according to treatment received at first exposure or being ever exposed to ocrelizumab SC at the selected dose, until when patients receive any other DMTs including commercial ocrelizumab.

In an exploratory analysis, all safety analyses will be conducted on data collected from the first ocrelizumab dose until the end of the study.

Safety will be assessed through summaries of exposure to study treatment, AEs, changes in laboratory test results, and changes in vital signs.

6.5.1 Analyses of Adverse Events

All verbatim AE terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and AE severity will be graded according to CTCAE v5.0.

All AEs, SAEs, AEs leading to death, adverse event of special interest (AESI), and AEs leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent AEs) will be summarized by mapped term, appropriate thesaurus level, and severity grade.

For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

6.5.2 Analyses of Exposure, Laboratory, Vital Sign

Study treatment exposure (such as treatment duration, total dose received, and number of cycles) will be summarized with descriptive statistics.

Relevant laboratory and vital sign (pulse rate, blood pressure, pulse oximetry) data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum post-baseline severity grade.

Changes in vital signs will be summarized.

6.6 PHARMACOKINETIC ANALYSES

All patients who have measurable serum concentrations of ocrelizumab will be included in the PK analysis unless major protocol deviations or unavailability of information (e.g., exact blood sampling time, exact dosing information or incomplete dose administration, missing concentration data) occurred that may interfere with the PK evaluation. Non-linear mixed effects modeling or other appropriate methods, may be used to analyze the concentration versus time data of ocrelizumab derived from this study. The influence of covariates such as body weight, sex, and B-cell count will be taken into account.

Exposure (AUC) to ocrelizumab and C_{max} will be estimated for each patient. Estimates for these parameters will be tabulated and summarized (mean, standard deviation, coefficient of variation, median, minimum, and maximum).

Additional PK analyses may be conducted as appropriate.

6.6.1 Primary Analysis

The primary objective for this study is to establish the non-inferiority of ocrelizumab SC compared with ocrelizumab IV on the basis of serum ocrelizumab AUC up to Week 12 (AUC_{W1-12}).

The GMR of AUC SC versus AUC IV will be presented, together with the two-sided 90% confidence interval.

The non-inferiority will be established if the lower end of the two-sided 90% CI of the GMR of AUCs is $>$0.8. The non-inferiority limit of 0.8 corresponds to a maximal 20% loss in AUC for the SC administration compared with IV. All available results for PK samples obtained during the first 12 weeks will be included in the PK analysis.

The primary comparison between SC and IV administered ocrelizumab will be based on the AUC_{W1-12} (i.e., over the first 3 months of the 6 monthly dosing interval after first dose), as absorption is expected to be complete by Week 12.

6.6.1.1 Estimand for Primary Analysis

The estimand for the primary analysis is based on the following attributes:

a) Treatment: Ocrelizumab IV administered at Day 1 and Day 14, 300 mg each visit (Reference), versus ocrelizumab SC at the determined dose at Day 1 (Experimental).

b) Population: RMS and PPMS patients defined through the in/exclusion criteria reflecting the target population. The analysis population will consist of all randomized patients who have received the full assigned dose of ocrelizumab and have available PK data (and all necessary supporting information, i.e., exact dosing administration information, exact blood sampling times), with patients grouped according to their actual treatment. The number of randomized patients excluded from the analysis is expected to be small, falling under the following categories:

- Withdraw after randomization and prior to dosing. Every effort will be made to ensure all randomized patients will receive the treatment on Day 1. Treatment will start within 24 hours of randomization.
- Withdraw from treatment between Day 1 and Day 14 dosing for patients randomized to IV arm. These patients would have received 300 mg only from the Day 1 infusion. Their PK data cannot be compared with the patients who receive the full 600 mg dose. In the three Phase III IV studies, $<$3% patients did not receive the Day 14 dosing in each study. Reasons for treatment discontinuation will be documented.

- Incomplete dosing. A small number of patients may receive incomplete dosing. In the three Phase III IV studies, 0.6%–2% of the patients received <80% of the planned volume at the Day 1 infusion. No reliable PK comparison can be performed if the received dose is less than the full dose.
- Missing all PK data due to other reasons. Every effort will be made to ensure all PK samples with all supporting information are collected. Among these patients excluded from the analysis, systematic bias in potential exposure levels is not expected compared to all patients. All PK data from all patients in this study will be inspected visually. Samples and/or patients excluded from the analysis will be documented, together with the reason for exclusion.

c) Variable: estimated AUC_{W1-12}, using all available ocrelizumab serum concentrations from the PK samples.

d) Intercurrent events: they are handled within the population specification. Among the patients in the analysis population, there could be some missing individual PK samples due to missed visits, early withdrawal or other reasons. Every effort will be made to collect PK samples on schedule. The non-linear mixed effect model can estimate the AUC with limited PK data, assuming the data are missing at random.

e) Summary measure: GMR and two-sided 90% CI of SC versus IV of AUC between Week 1 and Week 12. Non-inferiority would be established if the lower end of the two-sided 90% CI is >0.8.

The primary analysis will occur once the last patient enrolled has completed the Week 12 visit, to ensure all PK samples in the first 12 weeks are included. A sensitivity analysis will be done using AUC from Week 1 to Week 24, using all available samples collected until CCOD (12 weeks after the last patient enrolled).

6.6.2 Secondary Analysis

The secondary PK objective of this study is to determine C_{max} of ocrelizumab SC in patients with MS.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity assessment will be conducted in all patients with at least one post-baseline ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (post-baseline incidence) will be summarized by treatment group. When determining post-baseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is at least 0.60 titer unit greater than the titer of

the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, pharmacokinetics, and biomarker endpoints will be analyzed and reported via descriptive statistics as appropriate.

6.8 BIOMARKER ANALYSES

Biomarkers will be assessed at baseline and subsequent timepoints following administration of ocrelizumab. Biomarkers will be presented as absolute value over time and/or percent change relative to baseline over time. Biomarker levels at baseline or over time may be compared with efficacy or safety measurements to assess prognostic or predictive properties. Descriptive or summary statistics will be used to describe biomarker assessments. *Baseline is defined as the latest assessment before first ocrelizumab exposure*.

6.9 INTERIM ANALYSES

No interim analyses are planned.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and IxRS data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

EDSS data will be collected through the use of an electronic device provided by a vendor (see Section 7.3 for details).

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 ELECTRONIC PATIENT- AND CLINICAL-REPORTED OUTCOME DATA

EDSS data will be collected electronically. An electronic device or web-based platform will be used to capture EDSS data. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

In the event that the vendor web-based platform or electronic device is unavailable, the paper EDSS should be completed. Once the vendor electronic device or web-based platform is available, all EDSS data must be carefully entered into web-based platform and store the paper version as source documentation.

The electronic data will be available for view access only, via a secure web server. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats that must be kept with the study records as source data. Acknowledgement of receipt of the data is required. In addition, the Sponsor will receive all data in a machine-readable format.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for

the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) *or Clinical Trials Regulation (536/2014)* and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor has implemented a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. The Sponsor identified potential risks associated with critical trial processes and data and implemented plans for evaluating and controlling these risks. Risk evaluation and control included the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits are provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will

permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 90 sites globally will participate to enroll approximately 232 patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, MRI, biomarker and PK analyses), as specified in Section 4.5.

An iDMC will be employed to monitor and evaluate patient safety throughout the study.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and/*or* other *summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and* reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical *Study Information* at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only.

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Appendix 1
Schedule of Activities–*Controlled Period* (Ocrelizumab IV Group)

	Screen.	BL	Controlled Period						Delayed Dosing Visit [b]	Unschd. Visit [c]	ET Visit [d]	SFU [e]
Dose		**1**						**2**				
Study week		**1**	**2**	**4**	**8**	**12**	**16**	**22**	**24**				
Study day	-42 to -1	1	14	28	56	84	112	154	168				
(Window in days)			±2	±7									
Informed consent [f]	x												
Review of eligibility criteria	x	x											
Demographic data	x												
Medical history and baseline conditions	x												
EDSS score [g]	x	x				x			x		x	x	
Neurological examination [h]	x	x				x			x		x	x	x
Vital signs [i]	x	x	x			x			x	x	x	x	x
Height (in cm) [j]		x	(x) [j]										
Weight		x											
Physical examination [k]	x	x							x	x	x	x	x
Entry treatment experience questions [l]		x											
Hematology, chemistry, urinalysis [m]	x	x				x		x			x	x	x
Flow cytometry (including CD3/4/8/19 count) [n]	x	x	x	x		x	x		x	x	x	x	x
CD4 flow cytometry [n]								x					
IgG, IgA, IgM	x	x						x			x	x	x
Hepatitis B screening [o]	x												
Hepatitis B virus DNA (if required) [o]								x					
Pregnancy test (females) [p]	x	x	x						x	x			
FSH level (if applicable) [q]	x												
Brain MRI [r]	(x)	x			x	x			x		x	x	

Appendix 1 Schedule of Activities—Controlled Period (Ocrelizumab IV Group)

	Screen.	BL	Controlled Period						Delayed Dosing Visit [b]	Unschd. Visit [c]	ET Visit [d]	SFU [e]
Dose		**1**						**2**				
Study week		**1**	**2**	**4**	**8**	**12**	**16**	**22**	**24**				
Study day	-42 to -1	1	14	28	56	84	112	154	168				
(Window in days)			±2	±7									
PPQ [s]													
MSPTQ [t]													
Ocrelizumab ADA sample (serum) [u]		x							x	x	x	x	x
rHuPH20 ADA sample (plasma) [u]									x	x	x	x	x
PK sample (serum) [v]		x	x	x	x	x	x		x	x	x	x	x
Biomarker sample (serum) [w]		x				x			x			x	x
RBR DNA collection (optional) [x]		x											
RBR Paxgene RNA collection (optional) [x]		x	x	x	x	x	x		x				
Review of retreatment criteria		x	x						x	x			
Premedication [y]		x	x						x	x			
Ocrelizumab IV administration [z]		x	x							x			
Ocrelizumab SC administration [aa]									x	x			
TASQ [bb]		x							x	x			
Telephone contact [cc]									x	x			
Concomitant medications [dd]		x	x	x	x	x	x		x	x	x	x	x
Adverse events [ee]		x	x	x	x	x	x		x	x	x	x	x
Dermatologist evaluation of injection site (for a skin or injection reaction of Grade ≥3 severity or meeting seriousness criteria)	Not Applicable								x				
Optional collection of Information on planned post-study MS treatment [ff]													*(x)*

Appendix 1 Schedule of Activities—Controlled Period (Ocrelizumab IV Group)

ADA=anti-drug antibody; BL=baseline; EDSS=Expanded Disability Status Scale; ET=early termination; FSH=follicle-stimulating hormone; IV=intravenous; MRI=magnetic resonance imaging; MS=multiple sclerosis; MSPTQ=MS treatment preference questionnaire; PK=pharmacokinetic; PPQ=Patient Preference Questionnaire; RBR=Roche Biosample Repository; SC=subcutaneous; Screen.=screening; SFU=safety follow-up; TASQ=Treatment Administration Satisfaction Questionnaire; Unschd.=unscheduled.

Notes: All assessments should be performed on the day of the scheduled visit, unless otherwise specified. On dosing day, all assessments should be performed prior to dosing, unless otherwise specified. Study drug will be administered to participants by IV infusion on Days 1 and 14 (i.e., Dose 1), and then by SC injection on Weeks 24*, 48, 72 and 96* (i.e., Doses 2 *to 5*).

[a] For the schedule of activities for the treatment period with optional home administration of ocrelizumab SC, see Appendix 4 and Section 4.5.10.

[b] A delayed dosing visit will be performed and recorded in the Delayed Dosing Visit eCRF when dosing cannot be administered at the scheduled dosing visit. Other tests or assessments may be performed as appropriate (refer to Section 4.6.1).

[c] Assessments at unscheduled (non-dosing) visits may be performed as clinically appropriate.

[d] Only for patients who decide to discontinue from study treatment. Patients should undergo an early termination (ET) visit, be discontinued from study drug, and enter the safety follow-up phase.

[e] The safety follow-up phase is defined as 24 weeks after the last dose.

[f] Must be obtained and documented in written form before any study-specific screening procedure and initiation of study treatment.

[g] EDSS including functional system scores will be assessed and collected. *All EDSS assessments should be performed at the site.*

[h] Neurological examination will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Potential relapses should be recorded throughout the treatment period.

[i] Vital signs will be measured while the patient is in seated (preferred) or semi-seated position and will include temperature, systolic and diastolic blood pressure, pulse rate, and pulse oximetry. Temperature should be measured and recorded in the patient's notes only. Baseline pulse oximetry should be performed for newly enrolled patients on study Day 1 before premedication is given and for already enrolled patients at the next visit where vital signs are assessed per the schedule of assessments. Post-baseline pulse oximetry is only required in the event of severe systemic administration reactions including potential hypersensitivity/anaphylactic reaction (Section 5.1.4.4 and Appendix 11). On ocrelizumab dosing visits, vital signs should be taken as indicated in Section 4.5.4.1 (ocrelizumab SC administration) or Section 4.5.4.2 (ocrelizumab IV administration). On visits without study drug administration, vital signs may be collected at any time. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF page. At subsequent visits, record new or worsened clinically significant abnormalities on the AE eCRF.

[j] Height will be only collected once during the study; either at baseline for newly enrolled patients or once during the study at the patient's next scheduled patient visit.

[k] At screening and baseline, perform a complete physical examination that should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary (if indicated), and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. During the study conduct, perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the AE eCRF.

[l] Entry treatment experience questions are reported by the patient to provide treatment experience questions related to the last DMT they were treated with prior to enrollment in this study. The entry treatment experience questions will be administered at baseline, prior to ocrelizumab treatment.

[m] Hematology includes hemoglobin, hematocrit, RBC, WBC (absolute and differential: neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells), and quantitative platelet count. Chemistry includes AST, ALT, gamma-glutamyl transferase, total bilirubin, creatinine, amylase, potassium, and sodium. Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, and blood), and a microscopic examination of abnormal and clinically significant abnormalities to be performed at the site.

[n] B-cells and other cell types will be assessed in fresh whole blood using flow cytometry, to be collected prior to the administration of premedication as indicated in Section 4.3.2. This tube will be assessed at the central laboratory for TBNK (B cell count), and B cell subset assays. On visits without study drug administration, sample may be collected at any time.

[o] All patients must have a negative HBsAg test result at screening prior to enrollment. If total HBcAb is positive at screening, HB virus DNA measured by PCR must be negative to be eligible. For those patients enrolled with negative HBsAg and positive total HBcAb, HB virus DNA (PCR) must be repeated every 24 weeks.

[p] All women of childbearing potential will have a serum pregnancy test at screening analyzed by the central laboratory. Urine pregnancy tests (Urine β–human chorionic gonadotropin sensitivity of at least 25 mU/mL) will be performed at the local laboratory at specified subsequent visits. If a urine pregnancy test is positive, the patient will not receive the scheduled dose, and a confirmatory serum pregnancy test will be performed at the central laboratory.

[q] Testing of the FSH level is only applicable to female patients to confirm the post-menopausal status at screening. The sample will be analyzed by the central laboratory.

[r] The baseline and post-baseline MRI scans will be obtained as indicated (refer to Section 4.5.7). If during the screening phase, a MRI scan is required for MS diagnosis then it can serve as a baseline scan. Note that this MRI scan should be obtained approximately 10 days prior to performing the baseline visit to allow time for the centralized reading center to assess its quality and for potential re-scans if needed. MRI scans collected during the controlled period should occur within a window of ±2 weeks of the scheduled visit, as per the schedule of activities. The MRI scan*s*, at the Week 48 *and 96* visit*s* should occur within a time ±4 weeks of the scheduled visit. For patients who discontinue from the study treatment during the controlled period, MRI scans should be still obtained as per the schedule of activities. In addition, MRI scans will be obtained in patients who discontinue from the study treatment (at ET visit) if one was not performed during the prior 4 weeks.

[s] Patient preference questionnaire will only be completed by a subset of patients whose first ocrelizumab treatment is administered as an IV infusion. It will be completed prior to the patient's ocrelizumab SC injection at Week 48, and take approximately 30 seconds–1 minute to complete.

[t] Patients will provide overall satisfaction information related ocrelizumab and whether they have a preference for ocrelizumab or the DMT they were most recently on prior to the study. The MSTPQ will be administered prior to ocrelizumab treatment as indicated.

[u] Serum and plasma samples, to be taken prior to the administration of premedication. On visits without study drug administration, sample may be collected at any time.

[v] On study drug infusion days, two serum samples (one prior to the IV methylprednisolone, or an equivalent dose of an alternative, infusion and one 30 minutes (±10 minutes) after completion of study drug infusion) will be collected. PK samples will be collected from the arm opposite to the infusion. On study drug injection days, one serum sample (prior to the oral premedication administration) will be collected (refer to Appendix 5).

[w] Serum samples for biomarkers will be collected prior to the administration of premedication as indicated. On visits without study drug administration, sample may be collected at any time.

[x] These sample types to be collected for research purposes if patient agrees to separate optional RBR consent—a single RBR DNA sample at baseline visit (or any subsequent visit if missed), and an RBR RNA (Paxgene) sample collected prior to the administration of premedication at all indicated visits (refer to Section 4.5.14.2).

[y] Patients will receive mandatory (corticosteroids and antihistamine) and optional (analgesic) prophylactic treatment before the start of each ocrelizumab infusion or injection as indicated in Section 4.3.2.2 or Section 4.3.2.1, respectively, to reduce potential IRR or injections reactions.

[z] Collect vital signs and blood samples (including an unscheduled ADA, PK, tryptase, C3 and CH50 samples), in the event of a severe systemic administration reaction including a potential hypersensitivity/anaphylactic reaction (refer to Appendix 11).

[aa] Record vital signs and collect blood samples (including an unscheduled ADA, PK, tryptase, C3 and CH50 samples), in the event of a severe systemic injection reaction including a potential hypersensitivity/anaphylactic reaction (refer to Section 5.1.4.4. These samples should be collected as soon as possible after the event and at the indicated timepoints in (Section 5.1.4.4; Table 4).

[bb] Patients will evaluate and provide their experience on their most recent ocrelizumab administration (TASQ, see Section 4.5.13.2). The TASQ will be completed after completion of their ocrelizumab treatment as indicated.

[cc] After each ocrelizumab SC injection, site personnel will have a telephone conversation with the patient to collect information on AEs that may have occurred after ocrelizumab SC treatment. On the day of first ocrelizumab SC dose (i.e., Dose 2 for ocrelizumab IV group), the site personnel will contact the patient approximately 6 hours after the injection. On the subsequent dose of ocrelizumab SC the site personnel will contact the patient approximately 24 hours after injection. The site personnel should have more frequent calls with a particular patient if considered appropriate by the investigator (e.g. to follow up on potential injection reactions).

[dd] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, and nutritional supplements) used by a patient in addition to protocol-mandated treatment.

[ee] All AEs will be reported for as long as the patient remains in the study. The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[ff] *The option to collect information about the patient's planned post-study MS treatment is provided at this visit.*

Appendix 2
Schedule of Activities–*Controlled Period* (Ocrelizumab SC Group)

	Screen.	BL	Controlled Period												Delayed Dosing Visit [b]	Unschd. Visit [c]	ET Visit [d]	SFU [e]
Dose		**1**												**2**				
Study week			**1**					**2**	**4**	**8**	**12**	**16**	**22**	**24**				
Study day	-42 to -1	1	2	3	5	7	10	14	28	56	84	112	154	168				
(Window in days)								±2	±7									
Informed consent [f]	x																	
Review of eligibility criteria	x	x																
Demographic data	x																	
Medical history and baseline conditions	x																	
EDSS score [g]	x	x									x			x		x	x	
Neurological examination [h]	x	x									x			x		x	x	x
Vital signs [i]	x	x									x			x	x	x	x	x
Height (in cm) [j]		x	(x)															
Weight		x																
Physical examination [k]	x	x												x	x	x	x	x
Entry treatment experience questions [l]		x																
Hematology, chemistry, urinalysis [m]	x	x									x		x			x	x	x
Flow cytometry (including CD3/4/8/19 count) [n]	x	x						x	x		x	x		x	x	x	x	x
CD4 flow cytometry [n]													x					
IgG, IgA, IgM	x	x											x			x	x	x
Hepatitis B screening [o]	x																	
Hepatitis B virus DNA (if required) [o]													x					

Appendix 2 Schedule of Activities—Controlled Period (Ocrelizumab SC Group)

	Screen.	BL	Controlled Period												Delayed Dosing Visit [b]	Unschd. Visit [c]	ET Visit [d]	SFU [e]
Dose		**1**												**2**				
Study week			**1**					**2**	**4**	**8**	**12**	**16**	**22**	**24**				
Study day	-42 to -1	1	2	3	5	7	10	14	28	56	84	112	154	168				
(Window in days)								±2	±7									
Pregnancy test (females) [p]	x	x												x	x			
FSH level (if applicable) [q]	x																	
Brain MRI [r]	(x)	x								x	x			x		x	x	
MSPTQ [s]																		
Ocrelizumab ADA sample (serum) [t]		x												x	x	x	x	x
rHuPH20 ADA sample (plasma) [t]		x												x	x	x	x	x
PK sample (serum) [u]		x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x
Biomarker samples (serum) [v]		x									x			x			x	x
RBR DNA collection (optional) [w]		x																
RBR Paxgene RNA collection (optional) [w]		x						x	x	x	x	x		x				
Review of retreatment criteria		x												x	x			
Premedication [x]		x												x	x			
Ocrelizumab SC administration y		x												x	x			
TASQ: SC injection [z]		x												x	x			
Telephone contact [aa]		x												x	x			
Concomitant medications [bb]		x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x
Adverse events [cc]		x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x

Appendix 2 Schedule of Activities—Controlled Period (Ocrelizumab SC Group)

	Screen.	BL	Controlled Period												Delayed Dosing Visit [b]	Unschd. Visit [c]	ET Visit [d]	SFU [e]
Dose		**1**												**2**				
Study week			**1**					**2**	**4**	**8**	**12**	**16**	**22**	**24**				
Study day	-42 to -1	1	2	3	5	7	10	14	28	56	84	112	154	168				
(Window in days)								±2	±7									
Dermatologist evaluation of injection site (for a skin or injection reaction of Grade ≥3 severity or meeting seriousness criteria)		x																
Optional: Information on planned post-study DMT																		*(x)*

ADA=anti-drug antibody; BL=baseline; EDSS=Expanded Disability Status Scale; ET=early termination; FSH=follicle-stimulating hormone; MRI=magnetic resonance imaging; MS=multiple sclerosis; MSPTQ=MS treatment preference questionnaire; PK=pharmacokinetic; PPQ=Patient Preference Questionnaire; RBR=Roche Biosample Repository; SC=subcutaneous; Screen.=screening; TASQ=Treatment Administration Satisfaction Questionnaire; Unschd.=unscheduled.

Note: All assessments should be performed on the day of the scheduled visit, unless otherwise specified. On dosing day, all assessments should be performed prior to dosing, unless otherwise specified. Study drug will be administered to participants by SC injection.

[a] For the schedule of activities for the treatment period with optional home administration of ocrelizumab SC, see Appendix 4.

[b] A delayed dosing visit will be performed and recorded in the Delayed Dosing Visit eCRF when dosing cannot be administered at the scheduled dosing visit. Other tests or assessments may be performed as appropriate (refer to Section 4.6.1).

[c] Assessments at unscheduled (non-dosing) visits may be performed as clinically appropriate.

[d] Only for patients who decide to discontinue from study treatment. Patients should undergo an ET visit, be discontinued from study drug, and enter the safety follow-up phase.

[e] The safety follow-up phase is defined as 24 weeks after the last dose.

[f] Must be obtained and documented in written form before any study-specific screening procedure and initiation of study treatment.

[g] EDSS including functional system scores will be assessed and collected. *All EDSS assessments should be performed at the site.*

[h] Neurological examination will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Potential relapses should be recorded throughout the treatment period.

[i] Vital signs will be measured while the patient is in seated (preferred) or semi-seated position and will include temperature, systolic and diastolic blood pressure, pulse rate, and pulse oximetry. Temperature should be measured and recorded in the patient's notes only. Baseline pulse oximetry should be performed for newly enrolled patients on study Day 1 before premedication is given and for already enrolled patients at the next visit where vital signs are assessed per the schedule of assessments. Post-baseline pulse oximetry is only required in the event of severe systemic administration reactions including potential hypersensitivity/anaphylactic reaction (Section 5.1.4.4 and Appendix 11). On ocrelizumab dosing visits, vital signs should be taken as indicated in Section 4.5.4.1 (ocrelizumab SC administration) or Section 4.5.4.2 (ocrelizumab IV administration). On visits without study drug administration, vital signs may be collected at any time. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF page. At subsequent visits, record new or worsened clinically significant abnormalities on the AE eCRF. On ocrelizumab dosing visits, vital signs should be taken as indicated in Section 4.5.4.1 (ocrelizumab SC administration). On visits without study drug administration vital signs may be collected at any time. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF page. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[j] Height will be only collected once throughout the study either at baseline for newly enrolled patients or once during the study at the patient's next scheduled patient visit.

[k] At screening and baseline, perform a complete physical examination that should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary (if indicated), and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. During the study conduct, perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[l] Entry treatment experience questions are reported by the patient to provide treatment experience questions related to the last DMT they were treated with prior to enrollment in this study. The entry treatment experience questions will be administered at baseline, prior to ocrelizumab treatment.

[m] Hematology includes hemoglobin, hematocrit, RBC, WBC (absolute and differential: neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells), and quantitative platelet count. Chemistry includes AST, ALT, gamma-glutamyl transferase, total bilirubin, creatinine, amylase, potassium, and sodium. Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, and blood), and a microscopic examination if abnormal and clinically significant abnormalities to be performed at the site.

[n] B-cells and other cell types will be assessed in fresh whole blood using flow cytometry, to be collected prior to the oral premedication as indicated in Section 4.3.2. This tube will be assessed at the central laboratory for TBNK (B cell count), and B cell subset assays. On visits without study drug administration sample may be collected at any time.

[o] All patients must have negative HBsAg test result at screening prior to enrollment. If total HBcAb is positive at screening, HB virus DNA measured by PCR must be negative to be eligible. For those patients enrolled with negative HBsAg and positive total HBcAb, HB virus DNA (PCR) must be repeated every 24 weeks.

[p] All women of childbearing potential will have a serum pregnancy test at screening analyzed by the central laboratory. Urine pregnancy tests (Urine β–human chorionic gonadotropin sensitivity of at least 25 mU/mL) will be performed at the local laboratory at specified subsequent visits. If a urine pregnancy test is positive, the patient will not receive the scheduled dose, and a confirmatory serum pregnancy test will be performed at the central laboratory.

[q] Testing of the FSH level is only applicable to female patients to confirm the post-menopausal status at screening. The sample will be analyzed by the central laboratory.

[r] The baseline and post-baseline MRI scans will be obtained as indicated (refer to Section 4.5.7). If during the screening phase, a MRI scan is required for MS diagnosis then it can serve as a baseline scan. Note that this MRI scan should be obtained approximately 10 days prior to performing the baseline visit to allow time for the centralized reading center to assess its quality and for potential re-scans if needed. MRI scans collected during the controlled period should occur within a window of ±2 weeks of the scheduled visit, as per the schedule of activities. For patients who discontinue from the study treatment during the controlled period, MRI scans should be still obtained as per the schedule of activities.

[s] Patients will provide overall satisfaction information related ocrelizumab and whether they have a preference for ocrelizumab or the DMT they were most recently on prior to the study. The MSTPQ will be administered prior to ocrelizumab treatment as indicated.

[t] Serum and plasma samples, to be taken prior to the oral premedication. On visits without study drug administration, sample may be collected at any time.

[u] On the first dosing day, two serum samples (one prior to the oral premedication administration and another 1 hour [±10 min] after end of injection) will be collected. On the subsequent dosing days, one serum sample (prior to the oral premedication administration) will be collected (see Appendix 5).

[v] Serum samples for biomarkers will be collected prior to the oral premedication as indicated. On visits without study drug administration, sample may be collected at any time.

[w] These sample types to be collected for research purposes if patient agrees to separate optional RBR consent—a single RBR DNA sample at baseline visit (or any subsequent visit if missed), and an RBR RNA (Paxgene) sample collected prior to the administration of premedication at all indicated visits (refer to Section 4.5.14.2).

[x] Patients will receive mandatory (corticosteroids and antihistamine) and optional (analgesic) prophylactic treatment [redacted] each ocrelizumab injection as indicated in Section 4.3.2.1 to reduce potential injections reactions.

[y] Record vital signs and collect blood samples (including an unscheduled ADA, PK, tryptase, C3 and CH50 samples), in the event of a severe systemic injection reaction including a potential hypersensitivity/anaphylactic reaction (refer to Section 5.1.4.4). These samples should be collected as soon as possible after the event and at the indicated timepoints in (Section 5.1.4.4; Table 4).

[z] Patients will evaluate and provide their experience on their most recent ocrelizumab administration (TASQ, see Section 4.5.13.2). The TASQ will be completed after completion of their ocrelizumab treatment as indicated.

[aa] After each ocrelizumab SC injection, site personnel will have a telephone conversation with the patient to collect information on AEs that may have occurred after ocrelizumab SC treatment. On the day of first ocrelizumab SC dose, the site personnel will contact the patient approximately 6 hours after the injection. On the second and subsequent doses of ocrelizumab SC the site personnel will contact the patient approximately 24 hours after injection. The site personnel should have more frequent calls with a particular patient if considered appropriate by the investigator (e.g., to follow up about potential injection reactions).

[bb] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment.

[cc] All AEs will be reported for as long as the patient remains in the study. The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all serious AEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

Appendix 3
Schedule of Activities— Ocrelizumab SC Treatment Period

	Ocrelizumab SC Treatment Period[a]						*Delayed Dosing Visit* [b]	*Unschd. Visit* [c]	*ET Visit* [d]	*SFU*[e]
Dose		**3**		**4**		**5**				
Study week	**46**	**48**	**70**	**72**	**94**	**96**				
Study day	**322**	**336**	**490**	**504**	**658**	**672**				
(Window in days)	**±7**									
EDSS score [f]		X		*x*		*x*		X	X	
Neurological examination [g]		X		X		X	X	X	X	*x*
Vital signs [h]		X		X		X	X	X	X	*x*
Physical examination [i]		X		X		X	X	X	X	*x*
Hematology, chemistry, urinalysis [j]	X		X		X			X	X	*x*
Flow cytometry (including CD3/4/8/19 count) [k]		X				*x*	X	X	X	
CD4 flow cytometry [k]	X		X		X					
IgG, IgA, IgM	X		X		X			X	X	*x*
Hepatitis B virus DNA (if required) [l]	X		X		X					
Pregnancy test (females) [m]		X		X		X	X			
Brain MRI [n]		X				*x*		X	X	
Ocrelizumab ADA sample (serum) [o]		X		X		X	X	X	X	
rHuPH20 ADA sample (plasma) [o]		X		X		X	X	X	X	*x*
PK sample (serum) [p]		X		X		X	X	X	X	*x*
Biomarker samples (serum) [q]		X				*x*			X	
RBR Paxgene RNA collection (optional) [r]		X								
Review of retreatment criteria		X		X		X	X			
Premedication [s]		X		X		X	X			
Ocrelizumab SC administration [t]		X		X		X	X			

Appendix 3 Schedule of Activities—Treatment Period (Ocrelizumab SC Group)

	Ocrelizumab SC Treatment Period[a]						*Delayed Dosing Visit* [b]	*Unschd. Visit* [c]	*ET Visit* [d]	*SFU*[e]
Dose		**3**		**4**		**5**				
Study week	**46**	**48**	**70**	**72**	**94**	**96**				
Study day	**322**	**336**	**490**	**504**	**658**	**672**				
(Window in days)	**±7**									
TASQ: SC injection [u]		X					X			
MSPTQ [v]		X								
PGI-SF [w]						X			*x*	
Telephone contact [x]		X		X		X	X			
Concomitant medications [y]		X		X		X	X	X	X	*x*
Adverse events [z]		X		X		X	X	X	X	*x*
Dermatologist evaluation of injection site (for a skin or injection reaction of Grade ≥3 severity or meeting seriousness criteria)	X									
Optional: Information on planned post-study MS treatment[aa]										*(x)*

Appendix 3 Schedule of Activities—Treatment Period (Ocrelizumab SC Group)

ADA = anti-drug antibody; BL = baseline; EDSS = Expanded Disability Status Scale; ET = early termination; FSH = follicle-stimulating hormone; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSPTQ = MS treatment preference questionnaire; PK = pharmacokinetic; PPQ = Patient Preference Questionnaire; RBR = Roche Biosample Repository; SC = subcutaneous; Screen. = screening; TASQ = Treatment Administration Satisfaction Questionnaire; Unschd. = unscheduled.

Note: All assessments should be performed on the day of the scheduled visit, unless otherwise specified. On dosing day, all assessments should be performed prior to dosing, unless otherwise specified. Study drug will be administered to participants by SC injection.

[a] For the schedule of activities for the treatment period with optional home administration of ocrelizumab SC, see Appendix 4.

[b] A delayed dosing visit will be performed and recorded in the Delayed Dosing Visit eCRF when dosing cannot be administered at the scheduled dosing visit. Other tests or assessments may be performed as appropriate (refer to Section 4.6.1).

[c] Assessments at unscheduled (non-dosing) visits may be performed as clinically appropriate.

[d] Only for patients who decide to discontinue from study treatment. Patients should undergo an ET visit, be discontinued from study drug, and enter the safety follow-up phase.

[e] The safety follow-up phase is defined as 24 weeks after the last dose.

[f] EDSS including functional system scores will be assessed and collected. All EDSS assessments should be performed at the site.

[g] Neurological examination will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Potential relapses should be recorded throughout the treatment period.

[h] Vital signs will be measured while the patient is in seated (preferred) or semi-seated position and will include temperature, systolic and diastolic blood pressure, pulse rate, and pulse oximetry. Temperature should be measured and recorded in the patient's notes only. Baseline pulse oximetry should be performed for newly enrolled patients on study Day 1 before premedication is given and for already enrolled patients at the next visit where vital signs are assessed per the schedule of assessments. Post-baseline pulse oximetry is only required in the event of severe systemic administration reactions including potential hypersensitivity/anaphylactic reaction (Section 5.1.4.4 and Appendix 11). On ocrelizumab dosing visits, vital signs should be taken as indicated in Section 4.5.4.1 (ocrelizumab SC administration) or Section 4.5.4.2 (ocrelizumab IV administration). On visits without study drug administration, vital signs may be collected at any time. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF page. At subsequent visits, record new or worsened clinically significant abnormalities on the AE eCRF. On ocrelizumab dosing visits, vital signs should be taken as indicated in Section 4.5.4.1 (ocrelizumab SC administration). On visits without study drug administration vital signs may be collected at any time. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF page. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] During the study conduct, perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[j] Hematology includes hemoglobin, hematocrit, RBC, WBC (absolute and differential: neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells), and quantitative platelet count. Chemistry includes AST, ALT, gamma-glutamyl transferase, total bilirubin, creatinine, amylase, potassium, and sodium. Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, and blood), and a microscopic examination if abnormal and clinically significant abnormalities to be performed at the site.

[k] B-cells and other cell types will be assessed in fresh whole blood using flow cytometry, to be collected prior to the oral premedication as indicated in Section 4.3.2. This tube will be assessed at the central laboratory for TBNK (B cell count), and B cell subset assays. On visits without study drug administration sample may be collected at any time.

[l] All patients must have negative HBsAg test result at screening prior to enrollment. If total HBcAb is positive at screening, HB virus DNA measured by PCR must be negative to be eligible. For those patients enrolled with negative HBsAg and positive total HBcAb, HB virus DNA (PCR) must be repeated every 24 weeks.

[m] Urine pregnancy tests (Urine β–human chorionic gonadotropin sensitivity of at least 25 mU/mL) will be performed at the local laboratory at specified visits. If a urine pregnancy test is positive, the patient will not receive the scheduled dose, and a confirmatory serum pregnancy test will be performed at the central laboratory.

[n] The MRI scans at Week 48 and Week 96 should occur within a time ±4 weeks of the scheduled visit. In addition, MRI scans will be obtained in patients who discontinue from the study treatment (at ET visit) if one was not performed during the prior 4 weeks.

[o] Serum and plasma samples, to be taken prior to the oral premedication. On visits without study drug administration, sample may be collected at any time.

[p] On study drug injection days, one serum sample (prior to the oral premedication administration) will be collected (refer to Appendix 5).

[q] Serum samples for biomarkers will be collected prior to the oral premedication as indicated. On visits without study drug administration, sample may be collected at any time.

[r] These sample types to be collected for research purposes if patient agrees to separate optional RBR consent—a single RBR DNA sample at baseline visit (or any subsequent visit if missed), and an RBR RNA (Paxgene) sample collected prior to the administration of premedication at all indicated visits (refer to Section 4.5.14.2).

[s] Patients will receive mandatory (corticosteroids and antihistamine) and optional (analgesic) prophylactic treatment [redacted] ach ocrelizumab injection as indicated in Section 4.3.2.1 to reduce potential injection reactions.

[t] Record vital signs and collect blood samples (including an unscheduled ADA, PK, tryptase, C3 and CH50 samples), in the event of a severe systemic injection reaction including a potential hypersensitivity/anaphylactic reaction (refer to Section 5.1.4.4). These samples should be collected as soon as possible after the event and at the indicated timepoints in (Section 5.1.4.4; Table 4).

[u] Patients will evaluate and provide their experience on their most recent ocrelizumab administration (TASQ, see Section 4.5.13.2). The TASQ will be completed after completion of their ocrelizumab treatment as indicated.

[v] Patients will provide overall satisfaction information related ocrelizumab and whether they have a preference for ocrelizumab or the DMT they were most recently on prior to the study. The MSTPQ will be administered prior to ocrelizumab treatment as indicated.

[w] *The patient global impression of satisfaction (PGI-SF) is completed by patients to assess their overall satisfaction of ocrelizumab SC as a treatment for their MS symptoms throughout the study. This will be administered prior to ocrelizumab treatment as indicated.*

[x] *After each ocrelizumab SC injection, site personnel will have a telephone conversation with the patient to collect information on AEs that may have occurred after ocrelizumab SC treatment. The site personnel will contact the patient approximately 24 hours after injection. The site personnel should have more frequent calls with a particular patient if considered appropriate by the investigator (e.g., to follow up about potential injection reactions).*

[y] *Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment.*

[z] *All AEs will be reported for as long as the patient remains in the study. The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all serious AEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.*

[aa] *The option to collect information about the patient's planned post-study MS treatment is provided at this visit.*

Appendix 4
Schedule of Activities—Treatment Period with Optional Home Administration of SC Ocrelizumab

	Ocrelizumab SC Treatment Period [a]					
Dose		**3**		**4**		**5**
Study week	**46**	**48**	**70**	**72**	**94**	**96**
Study day	322	336	490	504	658	672
(Window in days)	±7					
Visit type	Site	MN	Site	MN	Site	MN
MN Informed consent [b]	x		*x*		*x*	
EDSS score [c]		x [c]		*x* [c]		*x* [c]
Neurological examination [d]	x	(x)	*x*	(x)	*x*	(x)
Vital signs [e]		x		x		x
Physical examination [f]		x		x		x
Hematology, chemistry, urinalysis [g]	x		x		x	
Flow cytometry (including CD3/4/8/19 count) [h]		x				*x*
CD4	x		x		x	
IgG, IgA, IgM	x		x		x	
Hepatitis B virus DNA (if required) [i]	*x*		*x*		*x*	
Pregnancy test (females) [j]		x		x		x
Brain MRI [k]		x [k]				*x* [k]
PPQ [l]		x				
MSPTQ [m]		x				
PGI-*SF* [n]						x
Ocrelizumab ADA sample (serum) [o]		x		x		x
rHuPH20 ADA sample (plasma) [o]		x		x		x
PK sample (serum) [p]		x		x		x
Biomarker serum samples [q]		x				
RBR Paxgene RNA collection (optional) [r]		x				
Review of retreatment criteria		x		x		x
Premedication [s]		x		x		x
Ocrelizumab SC administration [t]		x		x		x
TASQ: SC injection [u]		x				
Telephone contact [v]		x		x		x
Concomitant medications [w]		x		x		x
Adverse events [x]		x		x		x
Dermatologist evaluation of injection site (for a skin or injection reaction of Grade ³3 severity or meeting seriousness criteria)	x					

Appendix 4 Schedule of Activities—Treatment Period with Optional Home Administration of SC Ocrelizumab

ADA=anti-drug antibody; EDSS=Expanded Disability Status Scale; MN=mobile nursing; MRI=magnetic resonance imaging; MS=multiple sclerosis; MSPTQ=MS treatment preference questionnaire; PK=pharmacokinetic; PPQ=Patient Preference Questionnaire; RBR=Roche Biosample Repository; SC=subcutaneous; TASQ=Treatment Administration Satisfaction Questionnaire.

Note: All assessments should be performed on the day of the scheduled visit, unless otherwise specified. On dosing day, all assessments should be performed prior to dosing, unless otherwise specified. Study drug will be administered to participants by SC injection.

[a] For the schedule of activities before and after the treatment period with optional home administration of ocrelizumab SC, see Appendix 1 and Appendix 2. *All EDSS assessments should be performed at the site.*

[b] Must be obtained and documented in written form before the optional home administration of ocrelizumab SC by a healthcare professional from the study site (if local processes are in place) at the patient's home or another suitable location (refer to Section 4.5.10). The investigator will determine whether the participant is eligible for home administration based on the eligibility criteria (i.e., absence of any local or systemic injection reaction of Grade ≥3 severity or meeting seriousness criteria that occurred during a previous ocrelizumab injection and suitability).

[c] EDSS including functional system scores will be assessed and collected. The EDSS collected at the Week 48*/72/96* MN visit *should* be performed at site when *the* patient comes for the Week 46*/70/94* visit*, respectively*.

[d] Neurological examination will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Potential relapses should be recorded throughout the treatment period. The neurological examination can be alternatively performed at the Week 48*/72/96* MN visit*s*.

[e] Vital signs will be measured while the patient is in seated (preferred) or semi-seated position and will include temperature, systolic and diastolic blood pressure, pulse rate, and pulse oximetry. Temperature should be measured and recorded in the patient's notes only. Baseline pulse oximetry should be performed for newly enrolled patients on study Day 1 before premedication is given and for already enrolled patients at the next visit where vital signs are assessed per the schedule of assessments. Post-baseline pulse oximetry is only required in the event of severe systemic administration reactions including potential hypersensitivity/anaphylactic reaction (Section 5.1.4.4 and Appendix 11) On ocrelizumab dosing visits, vital signs should be taken as indicated in Section 4.5.4.1 (ocrelizumab SC administration).

[f] During the study conduct, perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[g] Hematology includes hemoglobin, hematocrit, RBC, WBC (absolute and differential: neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells), and quantitative platelet count. Chemistry includes AST, ALT, gamma-glutamyl transferase, total bilirubin, creatinine, amylase, potassium, and sodium. Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, and blood), and a microscopic examination if abnormal and clinically significant to be performed at the site.

[h] B-cells and other cell types will be assessed in fresh whole blood using flow cytometry, to be collected prior to the oral premedication as indicated in Section 4.3.2. This tube will be assessed at the central laboratory for TBNK (B cell count), and B cell subset assays. On visits without study drug administration, sample may be collected at any time.

[i] All patients must have negative HBsAg test result at screening prior to enrollment. If total HBcAb is positive at screening, HB virus DNA measured by PCR must be negative to be eligible. For those patients enrolled with negative HBsAg and positive total HBcAb, HB virus DNA (PCR) must be repeated every 24 weeks.

[j] If a urine pregnancy test is positive, the patient will not receive the scheduled dose, and a confirmatory serum pregnancy test will be performed at the central laboratory.

[k] The MRI scan will be obtained as indicated (refer to Section 4.5.6). The MRI scan collected at the Week 48 visit can be performed at site when patient comes for the Week 46 visit, if needed.

[l] Patient preference questionnaire will only be completed by a subset of patients whose first ocrelizumab treatment is administered as an IV infusion. It will be completed prior to the patient's ocrelizumab SC injection at the Week 48 MN visit, and take approximately 30 seconds–1 minute to complete.

[m] Patients will provide overall satisfaction information related ocrelizumab and whether they have a preference for ocrelizumab or the DMT they were most recently on prior to the study. The MSTPQ will be administered prior to ocrelizumab treatment as indicated.

[n] *The patient global impression of satisfaction (PGI-SF) is completed by patients to assess their overall satisfaction of ocrelizumab SC as a treatment for their MS symptoms throughout the study. This will be administered prior to ocrelizumab treatment as indicated.*

[o] Serum and plasma samples, to be taken prior to the oral premedication.

[p] On the dosing day, one serum sample (prior to the oral premedication administration) will be collected.

[q] Serum sample for biomarkers will be collected prior to the oral premedication as indicated.

[r] This sample to be collected for research purposes if patient agrees to separate optional RBR consent—an RBR RNA (Paxgene) sample collected prior to the administration of premedication (refer to Section 4.5.14.2).

[s] Patients will receive mandatory (corticosteroids and antihistamine) and optional (analgesic) prophylactic treatment before the start of injection as indicated in Section 4.3.2.2 to reduce potential injections reactions.

[t] Record vital signs and collect blood samples (including an unscheduled ADA, PK, tryptase, C3 and CH50 samples), in the event of a severe systemic injection reaction including a potential hypersensitivity/anaphylactic reaction (refer to Section 5.1.4.4). These samples should be collected as soon as possible after the event and at the indicated timepoints in (Section 5.1.4.4; Table 4).

[u] Patients will evaluate and provide their experience on their most recent ocrelizumab administration (TASQ, see Section 4.5.13.2). The TASQ will be completed after completion of their ocrelizumab treatment as indicated.

[v] Approximately 24 hours after ocrelizumab SC injection, site personnel will have a telephone conversation with the patient to collect information on adverse events that may have occurred after ocrelizumab SC treatment. The site personnel should have more frequent calls with a particular patient if considered appropriate by the investigator (e.g., to follow up about injection reactions).

[w] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment.

[x] All AEs will be reported for as long as the patient remains in the study. The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all serious AEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

Appendix 5
Schedule of Pharmacokinetic Samples at Dosing Visits

Scheduled Timepoint	Ocrelizumab SC Injection	Ocrelizumab IV Infusion
Day 1/Baseline	Before premedication prior to the ocrelizumab injection 1 hour (±10 minutes) postdose after completion of the ocrelizumab injection	Before premedication prior to the ocrelizumab infusion 30 minutes (±10 minutes) postdose after completion of the ocrelizumab infusion
Day 14/Week 2	At any time	Before premedication prior to the ocrelizumab infusion 30 minutes (±10 minutes) postdose after completion of the ocrelizumab infusion
Subsequent visits	Prior to premedication (refer to Appendix 1, Appendix 2, and Appendix 3)	NA

IV=intravenous; SC=subcutaneous; NA=not applicable.

Appendix 6
Sample Entry Treatment Experience Questions

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Entry Treatment Experience Questions

Instructions: Please complete the following questions based on the most recent MS treatment you took before starting this study

1. Did you receive any MS treatment before starting this study?

☐ Yes ☐ No

If you responded 'No' then this is the end of the questionnaire.
If you responded 'Yes' then please continue to questions 2, 3 and 4.

2. When did you stop taking your most recent MS treatment?

☐ 0-3 months ago ☐ 4-12 months ago ☐ More than 12 months ago

3. What was the main reason(s) for stopping your most recent MS treatment? Select up to TWO responses

☐ I stopped treatment so I could enroll in this study

☐ MS symptoms were worsening

☐ MS symptoms were not improving as expected

☐ Side effects bothered me

☐ Treatment administration was too frequent

☐ All things considered, it took too much of my time

☐ Treatment administration was uncomfortable

☐ Other

4. Taking all things into consideration, how satisfied or dissatisfied were you with the most recent MS treatment you received to treat your MS symptoms?

☐	☐	☐	☐
Very satisfied	Satisfied	Dissatisfied	Very dissatisfied

Appendix 7
Sample Treatment Administration Satisfaction Questionnaire—IV

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Treatment administration satisfaction questionnaire - Intravenous infusion

Instructions: Please complete the following questions based on your last ocrelizumab treatment. Your treatment was given through a thin plastic tube and a needle that was put directly into a vein in your arm, called an intravenous or IV infusion. Please answer the questions **based on your most recent IV infusion**.

1. Thinking about the ocrelizumab IV infusion, how **satisfied** or **dissatisfied** are you with the **IV infusion** procedure?

☐	☐	☐	☐	☐
Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied

2. Thinking about the ocrelizumab IV infusion, how do you rate the **pain** you experienced **during** the **IV infusion process?**

☐	☐	☐	☐	☐
None	Mild	Moderate	Severe	Very Severe

3. Thinking about the ocrelizumab IV infusion, how do you rate the **pain** you experienced at the **site of the drug infusion?**

☐	☐	☐	☐	☐
None	Mild	Moderate	Severe	Very Severe

4. Thinking about the ocrelizumab IV infusion, how do you rate the **swelling** you experienced **at the site of the drug infusion?**

☐	☐	☐	☐	☐
None	Mild	Moderate	Severe	Very Severe

5. Thinking about the ocrelizumab IV infusion, how do you rate the **redness** you experienced at **the site of the drug infusion?**

☐	☐	☐	☐	☐
None	Mild	Moderate	Severe	Very Severe

6. Thinking about the ocrelizumab IV infusion, are the **side effects** of the **IV infusion** as you expected?

☐	☐	☐	☐	☐
Much less than expected	Somewhat less than expected	Met my expectations	Somewhat worse than my expectations	Much worse than my expectations

7. Thinking about the ocrelizumab IV infusion, how do you feel about the **amount of time** it takes for you to get your IV infusion?

☐	☐	☐
Too short	Just right	Too long

8. Thinking about the ocrelizumab IV infusion, do you feel that the **length of time** to get your IV infusion was **as you expected?**

☐	☐	☐	☐	☐
Much shorter than expected	Somewhat shorter than expected	As expected	Somewhat longer than expected	Much longer than expected

9. Thinking about your last ocrelizumab IV infusion, how **bothered** are you by the **amount of time** it takes to get the infusion?

☐	☐	☐	☐	☐
Not at all bothered	A little bothered	Moderately bothered	Quite bothered	Very bothered

10. After receiving the ocrelizumab IV infusion, do you feel **physically restricted** by any side effects at the site of drug infusion?

☐	☐	☐	☐	☐
Not at all	A little bit	Somewhat	Quite a bit	Very much

11. How **convenient** was it for you to **get your IV infusion**?

☐	☐	☐	☐	☐
Very convenient	Convenient	Neither convenient nor inconvenient	Inconvenient	Very inconvenient

12. When you received the ocrelizumab infusion, were you able to **talk** to your **nurse and/or doctor as much as** you would **like** about your illness? (please only select ONE answer)

☐ Yes, I had more than enough time to talk to my nurse and/or doctor.

☐ Yes, but I would have liked more time to talk to my nurse and/or doctor.

☐ It does not matter to me if I have time to talk to my nurse and/or doctor during my treatment.

☐ No, I did not have enough time to talk to my nurse and/or doctor.

☐ No, I did not talk to my nurse and/or doctor at all.

13. Thinking about the ocrelizumab treatment, would you **recommend** the way you received the treatment (**IV infusion**) to another patient?

☐	☐	☐	☐	☐
Definitely yes	Probably yes	I don't know	Probably not	Definitely not

Appendix 8
Sample Treatment Administration Satisfaction Questionnaire—SC

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Treatment administration satisfaction questionnaire - Subcutaneous injection

Instructions: Please complete the following questions based on your last ocrelizumab treatment. Your treatment was given through a needle injected into your abdomen (or belly) area called a subcutaneous or SC injection. Please answer the questions **based on your most recent SC injection.**

1. Thinking about your last ocrelizumab SC injection, how **satisfied** or **dissatisfied** are you with the **SC injection** procedure?

☐	☐	☐	☐	☐
Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied

2. Thinking about your last ocrelizumab SC injection, how do you rate the **pain** you experienced **during the SC injection process?**

☐	☐	☐	☐	☐
None	Mild	Moderate	Severe	Very Severe

3. Thinking about your last ocrelizumab SC injection, how do you rate the **pain** you experienced at the **site of the drug injection?**

☐	☐	☐	☐	☐
None	Mild	Moderate	Severe	Very Severe

4. Thinking about your last ocrelizumab SC injection, how do you rate the **swelling** you experienced **at the site of the drug injection?**

☐	☐	☐	☐	☐
None	Mild	Moderate	Severe	Very Severe

5. Thinking about your last ocrelizumab SC injection, how do you rate the **redness** you experienced at **the site of the drug injection?**

☐	☐	☐	☐	☐
None	Mild	Moderate	Severe	Very Severe

6. Thinking about your last ocrelizumab SC injection, are the **side effects** of the **SC injection** as you expected?

☐	☐	☐	☐	☐
Much less than expected	Somewhat less than expected	Met my expectations	Somewhat worse than my expectations	Much worse than my expectations

7. Thinking about your last ocrelizumab SC injection, how do you feel about the **amount of time** it takes for you to get your SC injection?

☐	☐	☐
Too short	Just right	Too long

8. Thinking about your last ocrelizumab SC injection, do you feel that the **length of time** to get your SC injection was **as you expected**?

☐	☐	☐	☐	☐
Much shorter than expected	Somewhat shorter than expected	As expected	Somewhat longer than expected	Much longer than expected

9. Thinking about your last ocrelizumab SC injection, **how bothered** are you by the **amount of time** it took to get the injection?

☐	☐	☐	☐	☐
Not at all bothered	A little bothered	Moderately bothered	Quite bothered	Very bothered

10. After receiving your last ocrelizumab SC injection, do you feel **physically restricted** by any side effects at the site of drug injection?

☐	☐	☐	☐	☐
Not at all	A little bit	Somewhat	Quite a bit	Very much

Appendix 8 Sample Treatment Administration Satisfaction Questionnaire – SC

11. How **convenient** was it for you to get your most recent SC injection?

☐	☐	☐	☐	☐
Very convenient	Convenient	Neither convenient nor inconvenient	Inconvenient	Very inconvenient

12. When you received your last ocrelizumab treatment, were you able to **talk** to your **nurse and/or doctor as much as** you would **like** about your illness? (Please select only ONE answer.)

☐ Yes, I had more than enough time to talk to my nurse and/or doctor.

☐ Yes, but I would have liked more time to talk to my nurse and/or doctor.

☐ It does not matter to me if I have time to talk to my nurse and/or doctor during my treatment.

☐ No, I did not have enough time to talk to my nurse and/or doctor.

☐ No, I did not talk to my nurse and/or doctor at all.

13. Thinking about your last ocrelizumab treatment, **would you recommend** the way you received the SC treatment to another patient?

☐	☐	☐	☐	☐
Definitely yes	Probably yes	I don't know	Probably not	Definitely not

Appendix 9
Sample Patient Preference Questionnaire

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

PATIENT PREFERENCE QUESTIONNAIRE

You have now received the drug ocrelizumab in two different ways:

- through a thin plastic tube and a needle that was put directly into a vein in your arm, called an intravenous or IV infusion
- given through a needle injected into your abdomen (or stomach) area, called a subcutaneous or SC injection

Please answer the following questions about your experiences and your preferences. There are not any right or wrong answers.

1) All things considered which method of administration did you prefer?

☐ IV ☐ SC ☐ No preference

If you have responded 'No preference,' this is the end of the questionnaire.
If you have a preference, please respond to questions 2 and 3.

2) If you have a preference for one of the administration routes, how strong is this preference?

☐ Very strong ☐ Fairly strong ☐ Not very strong

3) If you have a preference for one of the administration routes, what are the main reasons for your preference? Select up to TWO responses

☐ Feels less emotionally distressing

☐ Requires less time in the clinic

☐ Lower level of injection-site pain

☐ Feels more comfortable during administration

☐ Other reason

Appendix 10
Sample MS Treatment Preference Questionnaire

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MS treatment preference questionnaire

Instructions: Please complete the following questions based on your experience with ocrelizumab and the most recent MS treatment you received prior to enrolling in this study

1. **Taking all things into consideration, how satisfied or dissatisfied are you with ocrelizumab as a treatment for your MS symptoms?**

☐ Very satisfied ☐ Satisfied ☐ Dissatisfied ☐ Very dissatisfied

2. **All things considered, based on your experience with ocrelizumab and the most recent MS treatment you took prior to the study, which did you prefer?**

☐ I had not taken any MS treatment prior to this study

☐ Preference for ocrelizumab

☐ Preference for MS treatment I had taken prior to the study

☐ No preference

3. **What is the reason for your preference? (Select all responses that apply)**

☐ It treats my MS symptoms more effectively

☐ Less side effects

☐ All things considered, it takes less of my time

☐ It is administered less frequently

☐ Treatment administration is more comfortable

☐ Other

Appendix 11
Precautions and Procedures For Severe Systemic Administration Reactions Including Hypersensitivity/Anaphylactic Reactions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion:

- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Monitoring devices: electrocardiogram (ECG) monitor, blood pressure monitor, pulse oximeter monitor (record values in the eCRF), and thermometer
- Oxygen
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment administration, the following procedures should be performed:

1. Stop the study treatment administration, if applicable.
2. Call for additional medical assistance, as required.
3. Maintain an adequate airway.
4. Administer epinephrine if anaphylaxis is suspected.
5. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
6. Administer antihistamines, corticosteroids, IV fluids or other medications as required by patient status and as directed by the physician in charge.
7. Continue to observe the patient and document observations until resolution.
8. Collect serum tryptase, complement components (C3 and CH50), ADA and PK at the time points indicated in Table 1.

Table 1 Samples to be Collected in the Event of a Severe Systemic Administration Reactions Including Potential Hypersensitivity/Anaphylactic Reactions

Assessment	Timepoint related to event			
	As soon as possible but within 1 hour of event onset	3–4 hours post-event onset	24 hours post-event	Within 2 weeks post-event
Serum Tryptase	x	x		x
Serum C3	x	x	x	
Serum CH50	x	x	x	
ADA and PK	x			

ADA = anti-drug antibody; PK = pharmacokinetic

Appendix 12
Progressive Multifocal Leukoencephalopathy: Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy

Action Steps if PML Is Suspected

- If the clinical presentation is suggestive of progressive multifocal leukoencephalopathy (PML) further investigations should include brain magnetic resonance imaging (MRI) evaluation as soon as possible (see Table 1). If MRI evaluation reveals lesions suspicious for PML (Berger et al. 2013; see Figure 1), a lumbar puncture with evaluation of the cerebrospinal fluid (CSF) should be undertaken for the detection of JC virus (JCV) DNA by polymerase chain reaction using a validated sensitive assay. A diagnosis of PML can potentially be made by evaluating clinical and MRI findings plus the identification of JCV in the CSF.
- For details, please refer to the most up-to-date laboratory manual providing sample handling and shipment instructions.
- There is no known treatment or cure for PML. Treatment considerations are discussed in the medical literature (Calabrese et al. 2007).

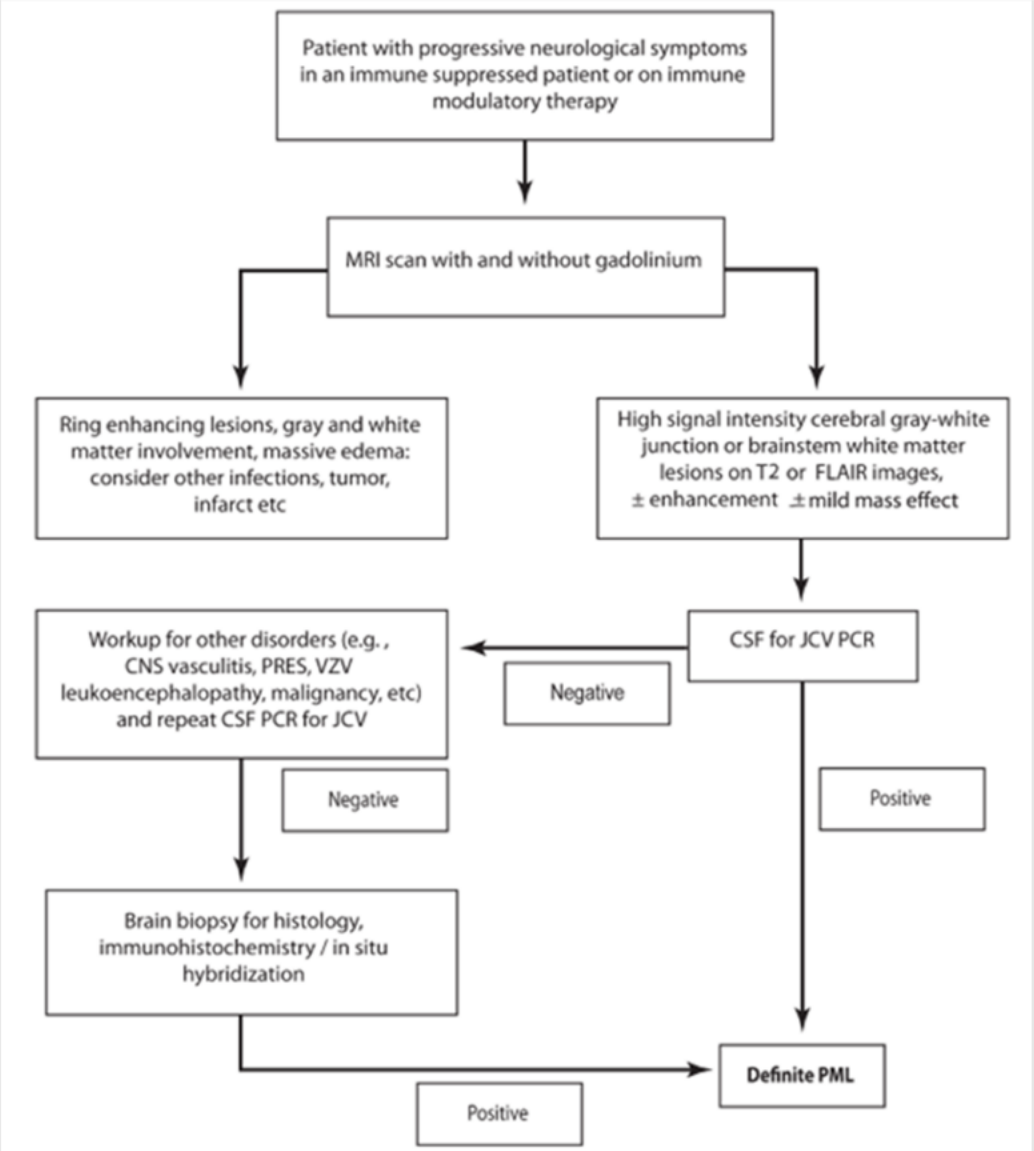
Magnetic Resonance Imaging Assessment

- Although there are no pathognomonic findings that differentiate PML from multiple sclerosis (MS), a brain MRI scan that includes fluid-attenuated inversion recovery and T2-weighted and T1-weighted sequences, with and without gadolinium, should be performed to assess patients with neurologic changes suggestive of PML (see Figure 1).
- Comparison with baseline scan may assist with interpretation of the findings on the newly acquired MRI for differences in lesion characteristics that may help differentiate between PML and MS (see Table 2).

Cerebrospinal Fluid Assessment

- The detection of JCV DNA in the CSF of a patient with clinical and MRI features suggestive of PML establishes the diagnosis of PML.
- If JCV DNA is not detected in CSF and if clinical suspicion of PML remains high, a repeat lumbar puncture should be performed.
- If diagnosis remains uncertain and suspicion of PML remains high, a brain biopsy may be considered to establish a definitive diagnosis.

Figure 1 Diagnostic Algorithm Framework for PML



FLAIR = fluid-attenuated inversion recovery; JCV = JC virus; PML = progressive multifocal leukoencephalopathy; PRES = posterior reversible encephalopathy syndrome; VZV = varicella-zoster virus.

Source: Berger et al. 2013.

Table 1 Clinical Signs and Symptoms Typical of Multiple Sclerosis and Progressive Multifocal Leukoencephalopathy

Onset	MS Acute	PML Subacute
Evolution	• Over hours to days • Normally stabilized • Resolve spontaneously even without therapy	• Over weeks • Progressive
Clinical presentation	• Diplopia • Paresthesia • Paraparesis • Optic neuritis • Myelopathy	• Cortical symptoms/signs • Behavioral and neuropsychological alteration • Retrochiasmal visual defects • Hemiparesis • Cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination)

MS=multiple sclerosis; PML=progressive multifocal leukoencephalopathy.
Adapted from: Kappos et al. 2007.

Table 2 MRI Lesion Characteristics Typical of PML and MS

Feature	Multiple Sclerosis	PML
Location of new lesions	Mostly focal; may affect entire brain and spinal cord, in white and possibly gray matter; posterior cranial fossa lesions are rarely seen	Diffuse lesions, mainly subcortical and rarely periventricular, located almost exclusively in white matter, although occasional extension to gray matter has been seen; posterior fossa frequently involved (cerebellum)
Borders	Sharp edges; mostly round or finger-like in shape (especially periventricular lesions), confluent with other lesions; U-fibers may be involved	Ill-defined edges; infiltrating; irregular in shape; confined to white matter, sparing gray matter; pushing against the cerebral cortex; U-fibers destroyed
Mode of extension	Initially focal, lesions enlarge within days or weeks and later decrease in size within months	Lesions are diffuse and asymmetric, extending homogeneously; no confluence with other lesions; confined to white matter tracks, sparing the cortex; continuous progression
Mass effect	Acute lesions show some mass effect	No mass effect even in large lesions (but lesion slightly abuts cerebral cortex)
On T_2-weighted sequence	• Acute lesions: hyperintense center, isointense ring, discrete hyperintensity outside the ring structure • Subacute and chronic lesions: hyperintense, with no ring structure	Diffuse hyperintensity, slightly increased intensity of newly involved areas compared with old areas, little irregular signal intensity of lesions
On T_1-weighted sequence	Acute lesions: densely hypointense (large lesions) or isointense (small lesions); increasing signal intensity over time in 80%; decreasing signal intensity (axonal loss) in about 20%	Slightly hypointense at onset, with signal intensity decreasing over time and along the affected area; no reversion of signal intensity
On FLAIR sequence	Hyperintense, sharply delineated	Hyperintensity more obvious, true extension of abnormality more clearly visible than in T_2-weighted images
With enhancement	• Acute lesions: dense homogeneous enhancement, sharp edges • Subacute lesions: ring enhancement • Chronic lesions: no enhancement	Usually no enhancement even in large lesions; in patients with HIV, some peripheral enhancement is possible, especially under therapy
Atrophy	Focal atrophy possible, due to focal white matter degeneration; no progression	No focal atrophy

FLAIR = fluid-attenuated inversion recovery; MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy.

Adapted from: Yousry et al. 2006.

Appendix 13
Pregnancy Outcome and Infant Health Information on First Year of Life

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Pregnancy Outcome and Infant Health Information on First Year of Life

If twin or multi-gestational pregnancy, this questionnaire has to be filled out separately for each baby born in the multi-gestational pregnancy.

Please check all that apply and provide detailed information on complications in infant on last page.

Table 1: Parent's (or Person with Parental Responsibility in Law) Consent to Data Collection

Has parent's (or person's with parental responsibility in law) data authorization form been signed?	☐Yes ☐No	Date signed _____	Other – comment _____
	Date consent withdrawn: (if applicable)		

Table 2: Information on Birth

Mode of birth	☐Vaginal delivery Forceps / vacuum: - Yes ☐ - No ☐ ☐Cesarean section (CS) - scheduled CS ☐ - emergency CS ☐	Reason for assisted delivery/Cesarean section_____
Gestational age at birth	_____ weeks - since conception ☐ - since LMP ☐	Induced labor - Yes ☐ - No ☐

Table 3: Growth Alteration, Congenital Anomalies and Functional Deficits

Date of Assessment			
Growth alteration - Yes ☐ - No ☐	☐Small for gestational age (SGA) ☐Low birth weight ☐Short birth length	If Growth alteration present: Specify weight:_____ Specify length: _____	Contributing factors:
Congenital anomalies - Yes ☐ - No ☐	☐ Major structural malformation A defect that has either cosmetic or functional significance to the child	Specify: _____ _____	Contributing factors:
	☐ Minor structural malformation A defect that occurs infrequently but has neither cosmetic nor functional significance to the child	Specify: _____ _____	Contributing factors:
	☐ Deformation A defect attributable to deformation of a structure, which had previously formed normally (usually due to mechanical force)	Specify: _____ _____	Contributing factors:
	☐ Disruption A defect due to destruction of a structure, which has previously formed normally (may be of vascular, infectious, or mechanical origin)	Specify: _____ _____	Contributing factors:
Functional deficit (except for infections, which should be described in separate table below) - Yes ☐ - No ☐	☐Functional deficit	Specify: _____ _____ _____	Contributing factors: _____ _____

Infant status at the time of latest follow-up (at birth, 3 months, 6 months, 12 months)

Table 4: Status of Infant

Date of Assessment		Contributing factors/ Comments
Status of infant	☐Normal ☐Abnormal, specify abnormality: _____ ☐Neonatal/infant death, specify cause and date of death: _____	_____ _____
Nursing status	☐Exclusive breastfeeding ☐Mixed feeding (partial breastfeeding along with infant formula and/or baby food), specify date since when: _____ ☐Fully weaned, specify date since when: _____	_____

Infections in neonate and infant during first year of life

Any infection detected at birth?

☐ Yes

☐ No

☐ Unknown

If available, please provide CD19 count (B cell values) at birth (regardless of infection). Are the results (select one option below)____?

☐ Normal

☐ Abnormal

☐ Unknown

If abnormal, specify test result:

If abnormal, date of test:

If infection detected at birth then Tables 5 and 6 should to be filled out and additional detailed information may be provided on last page.

If no infection detected at birth, however an infection developed later during the first year of live, please move directly to Table 7.

If no infection detected at birth, and if also no infection developed during the first 12 months then move directly to Table 8.

Table 5: Information on Infection in Neonate at Birth

Specify the event term:	**Event number**		
Location of infection present in neonate at birth? Site of infection (specify):		**Outcome of infection?**	**Duration of infection?**
		☐Resolved ☐Improving ☐Fatal ☐Persisting ☐Unknown	**Duration**:_____
Intensity of infection (Grade 1-5 NCI CTCAE)?	**Seriousness of infection?**	**Treatment with anti-infective?**	**Pathogen causing infection known?**
Severity: ☐Mild (Grade 1) ☐Moderate (Grade 2) ☐Severe (Grade 3) ☐Life-threatening (Grade 4) ☐Death (Grade 5)	Serious: ☐Yes ☐No	☐Yes, specify: _____ ☐No ☐Unknown	☐Yes, specify: _____ ☐No ☐Unknown
Relevant laboratory test results (in newborn infant):			
CD19 count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
IgG levels	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
White blood cell count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Neutrophil count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Lymphocyte count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Other, specify:	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____

Table 6: Maternal risk factors for neonatal infection (during most recent pregnancy, if infant developed neonatal infection at birth)

Maternal risk factors for neonatal infection	**Date of diagnosis**	If **diagnosed, was pregnant mother treated with anti-infective prior to delivery?**
☐Maternal intrapartum colonization or infection with group B streptococcus (GBS) ☐Maternal listeriosis ☐Premature rupture of membranes (PROM) ☐Meconium in amniotic fluid (meconium-stained liquid) ☐Active genital herpes infection ☐CMV ☐HPV (papilloma virus) Other, specify	_____ _____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____ _____

Relevant laboratory test results in pregnant mother:			
CD19 count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
IgG levels	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
White blood cell count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Neutrophil count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Lymphocyte count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Other, specify: (e.g., any specific antibodies and their titers)	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____

Any infection detected during first year of infant's life?

☐ Yes

☐ No

☐ Unknown

If infection detected during first year of infant's life, then Table 7 should to be filled out and additional detailed information may be provided on last page. If no infection developed during first 12 months of life, then please move directly to Table 8.

Table 7: Information on infection detected during first year of infant's life

Specify the event term:	**Event number (automatically populated by the system?)**		
Location of infection?	**Infant's age on day of onset of infection?**	**Outcome of infection?**	**Duration of infection?**
Site of infection (specify): _____ _____	**Age:** _____	☐Resolved ☐Improving ☐Fatal ☐Persisting ☐Unknown	**Duration:**_____
Intensity of infection (Grade 1-5 NCI CTCAE)?	**Seriousness of infection?**	**Treatment with anti- infective?**	**Pathogen causing infection known?**
Severity: ☐Mild (Grade 1) ☐Moderate (Grade 2) ☐Severe (Grade 3) ☐Life-threatening (Grade 4) ☐Death (Grade 5)	Serious: ☐Yes ☐No	☐Yes, specify: _____ ☐No ☐Unknown	☐Yes (specify): _____ ☐No ☐Unknown
Relevant laboratory test results (in infant):			
CD19 count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
IgG levels	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
White blood cell count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Neutrophil count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Lymphocyte count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Other, specify:	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____

Table 8: Vaccinations administered to infant at birth and during first year of age

Vaccinations administered at birth and during first year of age	Date administered	Infant's age on day of vaccination	Comments (abnormal outcome, reason for postponing vaccination, etc.)
☐Hepatitis B			
☐Rotavirus			
☐Diphtheria, tetanus, and pertussis			
☐Hemophilus influenza type b			
☐Pneumococcal			
☐Poliovirus ☐Attenuated oral polio vaccine ☐Inactivated polio vaccine			
☐Meningococcal group B bacteria			
☐Tuberculosis (Bacille Calmette Guérin, BCG) bacteria			
☐Other vaccination, specify: _____			

Table 9: Fetal/neonatal abnormalities in previous pregnancies

Fetal/neonatal abnormalities (in previous pregnancies)			Please, provide specifics including contributing factors
None ☐	Yes ☐	Unknown ☐	
Infection; if yes, specify			
Death in utero; if yes, specify reason			
Birth defects; if yes, specify			
Family history of birth defects; if yes, specify			
Small for gestational age at birth (or Intrauterine growth retardation)			
Premature delivery (before 37 weeks)			
Other; specify			

Detailed information on health-related findings in infant during first year of life

Please enter text in the free text box below.

Appendix 14
Sample: Patient Global Impression of Satisfaction

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Taking all things into consideration, how satisfied or dissatisfied are you with ocrelizumab SC as a treatment for your MS symptoms?

☐	☐	☐	☐
Very satisfied	Satisfied	Dissatisfied	Very dissatisfied

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