

Official Title: A Single Arm, Open Label Multicentre Extension Study to Evaluate the Effectiveness and Safety of Ocrelizumab in Patients with Multiple Sclerosis Previously Enrolled in a F. Hoffmann-La Roche Sponsored Ocrelizumab Phase IIIb/IV Clinical Trials

NCT Number: NCT03599245

Document Date: Protocol Amendment Version 7: 11-Oct-2023

PROTOCOL

TITLE: A SINGLE ARM, OPEN LABEL MULTICENTRE
EXTENSION STUDY TO EVALUATE THE
EFFECTIVENESS AND SAFETY OF OCRELIZUMAB IN
PATIENTS WITH MULTIPLE SCLEROSIS PREVIOUSLY
ENROLLED IN A F. HOFFMANN-LA ROCHE
SPONSORED OCRELIZUMAB PHASE IIIb/IV CLINICAL
TRIAL

PROTOCOL NUMBER: MN39158
VERSION NUMBER: 7.0
EUDRACT NUMBER: 2017-004886-29
IND NUMBER: 100,593
NCT NUMBER: NCT03599245
TEST PRODUCT: Ocrelizumab (RO4964913)
MEDICAL MONITOR: 
SPONSOR: F. Hoffmann-La Roche Ltd
DATE FINAL: Version 1.0: 28 Feb 2018
DATE AMENDED Version 2.0: 30 August 2018
Version 3.0: 28 March 2019
Version 4.0: 10 August 2020
Version 5.0: 24 March 2021
Version 6.0: 6 January 2022
Version 7.0: See electronic date stamp on the final
page of this document

PROTOCOL AMENDMENT, VERSION 7.0: RATIONALE

Per the requirements set forth under the Clinical Trials Regulation (CTR) for switching over from the Clinical Trial Directive (CTD), Protocol MN39158 has been amended solely to consolidate Protocol MN39158, Version 6 (Poland) into Protocol Version 6 (Global), resulting in Protocol Version 7 (Global). The following Poland-specific requirements have been incorporated into the protocol:

- Benefit-Risk Assessment of the Conduct of the Study During the COVID-19 Pandemic (Appendix 8 – For Poland only)

TABLE OF CONTENTS

PROTOCOL AMENDMENT ACCEPTANCE FORM	9
PROTOCOL SYNOPSIS	10
1. BACKGROUND	19
1.1 Background on Multiple sclerosis	19
1.2 Background on ocrelizumab	20
1.3 Study Rationale and Benefit-Risk Assessment.....	23
1.3.1 Risk assessment for concomitant use of a COVID-19 vaccine	24
2. OBJECTIVES AND ENDPOINTS	25
3. STUDY DESIGN	27
3.1 Description of the Study.....	27
3.1.1 Overview of Study Design.....	28
3.1.2 Screening.....	28
3.1.3 Treatment Period	29
3.1.4 Safety Follow up Period	30
3.2 End of Study and Length of Study	31
3.3 Rationale for Study Design	31
3.3.1 Rationale for ocrelizumab Dose and Schedule	33
3.3.2 Rationale for Patient Population	33
3.3.3 Rationale for NfL Biomarker assessments in plasma: CASTING/MA30005 study patients only	33
4. MATERIALS AND METHODS	34
4.1 Patients.....	34
4.1.1 Inclusion Criteria	34
4.1.2 Exclusion Criteria	35
4.2 Method of Treatment Assignment and Blinding	35
4.3 Study Treatment and Other Treatments Relevant to the Study Design	35
4.3.1 Study Treatment Formulation and Packaging.....	35
4.3.1.1 Ocrelizumab.....	35
4.3.2 Study Treatment Dosage, Administration, and Compliance	36

4.3.2.1	Ocrelizumab.....	36
4.3.3	Prophylactic Medication	38
4.3.4	Investigational Medicinal Product Handling and Accountability.....	38
4.3.5	Continued Access to Ocrelizumab	39
4.4	Concomitant Therapy	40
4.4.1	Prohibited Therapy	40
4.5	Study Assessments	40
4.5.1	Informed Consent Forms and Screening Log	41
4.5.2	Medical History, Concomitant Medication, and Demographic Data	41
4.5.3	Physical Examinations	41
4.5.4	Vital Signs.....	41
4.5.5	Neurological Examinations	41
4.5.6	Assessment of Disability	43
4.5.7	Brain Magnetic Resonance Imaging	43
4.5.8	Laboratory, Biomarker, and Other Biological Samples	44
4.5.9	Optional Samples for Research Biosample Repository	45
4.5.9.1	Overview of the Research Biosample Repository	45
4.5.9.2	Approval by the Institutional Review Board or Ethics Committee	46
4.5.9.3	Sample Collection	46
4.5.9.4	Confidentiality	46
4.5.9.5	Consent to Participate in the Research Biosample Repository.....	47
4.5.9.6	Withdrawal from the Research Biosample Repository	47
4.5.9.7	Monitoring and Oversight.....	48
4.5.10	Patient-Reported Outcomes	48
4.5.11	SDMT	49
4.5.12	Patient Diary (optional)	49
4.5.13	Analysis of immune responses following SARS-CoV-2 vaccination (optional procedure).....	49
4.6	Treatment, Patient, Study, and Site Discontinuation.....	50
4.6.1	Study Treatment Discontinuation.....	50

4.6.2	Patient Discontinuation from Study	52
4.6.3	Study Discontinuation	52
4.6.4	Site Discontinuation	52
5.	ASSESSMENT OF SAFETY	53
5.1	Safety Plan	53
5.1.1	Risks Associated with corticosteroids	54
5.1.2	Risks associated with antihistamines.....	54
5.1.3	Risks Associated with Ocrelizumab	54
5.1.3.1	Identified Risks and Adverse Drug Reactions.....	54
5.1.3.2	Potential Risks	57
5.1.4	Management of Patients Who Experience Specific Adverse Events.....	58
5.2	Safety Parameters and Definitions	59
5.2.1	Adverse Events.....	59
5.2.2	Serious Adverse Events (Immediately Reportable to the Sponsor)	60
5.2.3	Adverse Events of Special Interest (Immediately Reportable to the Sponsor).....	60
5.3	Methods and Timing for Capturing and Assessing Safety Parameters	61
5.3.1	Adverse Event Reporting Period.....	61
5.3.2	Eliciting Adverse Event Information	61
5.3.3	Assessment of Severity of Adverse Events	61
5.3.4	Assessment of Causality of Adverse Events.....	62
5.3.5	Procedures for Recording Adverse Events	63
5.3.5.1	Infusion-Related Reactions.....	63
5.3.5.2	Diagnosis versus Signs and Symptoms.....	63
5.3.5.3	Adverse Events That Are Secondary to Other Events	64
5.3.5.4	Persistent or Recurrent Adverse Events	64
5.3.5.5	Abnormal Laboratory Values	65
5.3.5.6	Abnormal Vital Sign Values	65
5.3.5.7	Abnormal Liver Function Tests	66
5.3.5.8	Deaths	66
5.3.5.9	Preexisting Medical Conditions.....	67

5.3.5.10	Lack of Efficacy or Worsening of Multiple Sclerosis.....	67
5.3.5.11	Hospitalization or Prolonged Hospitalization.....	67
5.3.5.12	Cases of Accidental Overdose or Medication Error	68
5.3.5.13	Patient-Reported Outcome Data.....	69
5.4	Immediate Reporting Requirements from Investigator to Sponsor	69
5.4.1	Medical Monitors and Emergency Medical Contacts	70
5.4.2	Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest	70
5.4.2.1	Events That Occur prior to Study Drug Initiation.....	70
5.4.2.2	Events That Occur after Study Drug Initiation.....	71
5.4.3	Reporting Requirements for Pregnancies	71
5.4.3.1	Pregnancies in Female Patients	71
5.4.3.2	Abortions.....	72
5.4.3.3	Congenital Anomalies/Birth Defects	72
5.5	Follow-Up of Patients after Adverse Events.....	72
5.5.1	Investigator Follow-Up	72
5.5.2	Sponsor Follow-Up	73
5.6	Adverse Events That Occur after the Adverse Event Reporting Period.....	73
5.7	Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees.....	73
6.	STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN.....	74
6.1	Determination of Sample Size	74
6.2	Summaries of Conduct of Study	74
6.3	Summaries of Demographic and Baseline Characteristics	74
6.4	Effectiveness Analyses	75
6.4.1	Effectiveness Endpoints	75
6.5	Safety Analyses	76
6.5.1	Safety Outcome Measures	76
6.5.2	Safety Analyses	76
6.6	OTHER ANALYSES	76
6.7	Subgroup analysis	76
6.8	Handling Of Missing Data	76

6.9	Interim Analysis	76
7.	DATA COLLECTION AND MANAGEMENT	76
7.1	Data Quality Assurance	76
7.2	Electronic Case Report Forms.....	77
7.3	Source Data Documentation.....	77
7.4	Use of Computerized Systems	78
7.5	Retention of Records	78
8.	ETHICAL CONSIDERATIONS.....	79
8.1	Compliance with Laws and Regulations	79
8.2	Informed Consent	79
8.3	Institutional Review Board or Ethics Committee	80
8.4	Confidentiality	81
8.5	Financial Disclosure.....	81
9.	STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION	81
9.1	Study Documentation	81
9.2	Protocol Deviations.....	82
9.3	Management of Study Quality.....	82
9.4	Site Inspections	82
9.5	Administrative Structure.....	82
9.6	Dissemination of Data and Protection of Trade Secrets	83
9.7	Protocol Amendments	84
10.	REFERENCES.....	85

LIST OF TABLES

Table 1 Objectives and Corresponding Endpoints.....	25
Table 2 Guidelines for Management of Specific Adverse Events	58
Table 3 Adverse Event Severity Grading Scale for IRRs and Other Events Not Specifically Listed in NCI CTCAE.....	62
Table 4 Causal Attribution Guidance	63

LIST OF FIGURES

Figure 1	Study schema.....	28
Figure 2	Overview of End of Treatment Period.....	30
Figure 3	Overview of Sample Collection for SARS-CoV-2 Vaccine Immunological Assessments for Optional Procedure.....	50

LIST OF APPENDICES

Appendix 1	Schedule of Assessments.....	89
Appendix 2	Safety Follow-Up Schedule of Assessments.....	94
Appendix 3	Expanded Disability Status Scale (EDSS)	95
Appendix 4	Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy	99
Appendix 5	Patient-Reported Outcomes.....	104
Appendix 6	Pregnancy Outcome and Infant Health Information on First Year of Life.....	109
Appendix 7	Patient Diary (OPTIONAL).....	117
Appendix 8	<i>Benefit-Risk Assessment of the Conduct of the Study During the COVID-19 Pandemic</i>	118

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE: A SINGLE ARM, OPEN LABEL MULTICENTRE
EXTENSION STUDY TO EVALUATE THE
EFFECTIVENESS AND SAFETY OF OCRELIZUMAB
IN PATIENTS WITH MULTIPLE SCLEROSIS
PREVIOUSLY ENROLLED IN A F. HOFFMANN-LA
ROCHE SPONSORED OCRELIZUMAB PHASE
IIIb/IV CLINICAL TRIAL

PROTOCOL NUMBER: MN39158

VERSION NUMBER: 7.0

EUDRACT NUMBER: 2017-004886-29

IND NUMBER: 100,593

NCT NUMBER: NCT03599245

TEST PRODUCT: Ocrelizumab (RO4964913)

MEDICAL MONITOR: [REDACTED]

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 the CRO.

{Name}
{Address}

PROTOCOL SYNOPSIS

TITLE: A SINGLE ARM, OPEN LABEL MULTICENTRE EXTENSION STUDY TO EVALUATE THE EFFECTIVENESS AND SAFETY OF OCRELIZUMAB IN PATIENTS WITH MULTIPLE SCLEROSIS PREVIOUSLY ENROLLED IN A F. HOFFMANN-LA ROCHE SPONSORED OCRELIZUMAB PHASE IIIb/IV CLINICAL TRIAL

PROTOCOL NUMBER: MN39158
VERSION NUMBER: 7.0
EUDRACT NUMBER: 2017-004886-29
IND NUMBER: 100,593
NCT NUMBER: NCT03599245
TEST PRODUCT: Ocrelizumab (RO4964913)
PHASE: Phase IIIb/IV
INDICATION: Multiple sclerosis
SPONSOR: F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

This extension study will evaluate the effectiveness and safety of ocrelizumab in multiple sclerosis (MS) patients who were previously enrolled in a F. Hoffmann-La Roche (Roche) sponsored ocrelizumab phase IIIb/IV trial (i.e. the Parent, P-trial). Specific objectives and corresponding endpoints for the study are outlined in the table below.

Objectives	Corresponding Endpoints
Primary Objective:	
To evaluate the effectiveness of ocrelizumab therapy in MS patients who were previously enrolled in a Roche sponsored phase IIIb/IV-trial	Evaluate clinical measures related to disease progression over the duration of treatment in MS patients
Overview of the effectiveness measures:	
Different effectiveness measures evaluated for ocrelizumab in MS patients who were previously enrolled in a Roche sponsored phase IIIb/IV-trial	Related to disability progression: - Time to onset of confirmed disability progression (CDP) sustained for at least 24 weeks and for at least 48 weeks - Proportion of patients who have confirmed disability improvement (CDI), CDP for at least 24 weeks and for at least 48 weeks yearly and over the duration of treatment - Proportion of patients who have improved, stable or worsened disability compared with baseline (inclusion in Extension study) measured by expanded disability status scale (EDSS) (annually/by epoch and over

Objectives	Corresponding Endpoints
	duration of treatment) Stable EDSS is defined as EDSS change +/- 0.5. Worsening is > 0.5 increase of EDSS, Improvement is >0.5 decrease of EDSS. • Mean change from inclusion in the parent study in EDSS score over the course of treatment • Time to 20% increase in timed 25-foot walk test (T25FWT); time to 20% increase in timed nine-hole peg test (9HPT) sustained for at least 24 weeks and for at least 48 weeks, and proportion of patients achieving a sustained increase assessed yearly and over the duration of treatment Other clinical measures and composite endpoints: • Time to first protocol-defined event of disease activity • Time to first relapse • Annualized relapse rate • Proportion of patient relapse free, yearly and over the course of treatment • Proportion of patients with no evidence of protocol-defined disease activity (NEDA) yearly and over the duration of the treatment where disease activity is defined as at least one the following events: protocol-defined relapse; 24 weeks CDP based on increases in EDSS; a T1 Gadolinium (Gd)-enhanced lesion; or a new and/or enlarging T2 hyperintense lesion on magnetic resonance imaging (MRI). • Proportion of patients with no evidence of progression (NEP) defined as no progression sustained for at least 24 weeks on all of the following three components (CDP; 20% increase in timed T25FWT; 20% increase in timed 9HPT) yearly and over the course of treatment • Proportion of patients with no evidence of progression sustained for at least 24 weeks and no active disease (NEPAD) defined as no progression on all of the three components of NEP (CDP, T25FWT, 9HPT), no new relapse and no enlarging or new T2 or T1 Gd-enhancing lesion yearly and over the course of treatment • Change from baseline (parent trial) in cognitive performance as measured by the Symbol digit modalities test (SDMT) Related to MRI • Total number of T1 Gd-enhancing lesions as detected by brain MRI over time • Total number of new and/or enlarging T2 lesion as detected by brain MRI over time • Change in total T1 hypointense lesion volume over time • Total number of fluid-attenuated inversion-recovery (FLAIR) late enhancing lesions as detected by brain MRI over time (pertinent to CASTING /MA30005 patients only)

Objectives	Corresponding Endpoints
	- Total number of FLAIR late enhancing lesions as detected by brain MRI at the end of the treatment period - Change in brain volume (including white and grey matter fractions) as detected by brain MRI over time - Presence and evolution of leptomeningeal follicles (pertinent to ENSEMBLE/MA30143 patients with identified FLAIR late enhancing lesions and CASTING/MA30005 patients) Other measures related to MS disease: - Time to treatment discontinuation/switch Patient reported outcomes (PROs) - Employment status (Work Productivity and Activity Impairment Questionnaire [WPAI]) - SymptoMScreen - Quality of life (QoL) (Multiple Sclerosis Impact Scale [MSIS]-29)
Exploratory Objective:	
To investigate the effect of ocrelizumab on antibody and T cell responses in patients administered an approved severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine	Analysis of immune response (SARS-CoV-2 antibody titers and SARS-CoV-2 T cell responses) to SARS-CoV-2 vaccine
Safety Objective:	
To evaluate the safety and tolerability of ocrelizumab therapy in MS patients who were previously enrolled in a Roche sponsored phase IIIb/IV-trial	- Rate and nature of adverse events - Changes in vital signs, neurological examinations, clinical laboratory results, locally reviewed MRI for safety (non-MS central nervous system [CNS] pathology) and concomitant medications (including pre-medications and medications used during and following ocrelizumab administration)

STUDY DESIGN

DESCRIPTION OF STUDY

This is a single arm, open label, multicenter Extension study in patients on ocrelizumab therapy who are eligible for roll over based on the investigator decision in the Roche Parent trial. Patients will receive treatment with ocrelizumab as single 600 mg infusions in 500 mL 0.9% sodium chloride every 24 weeks up to Week 72 of this study. In patients who did not experience a serious infusion-related reaction (IRR) with any previous conventional ocrelizumab infusion (~3.5 hours), the next 600 mg infusion can be administered as a shorter (~2 hours) infusion for subsequent doses, after providing written informed consent. If patients develop a serious IRR while on the shorter infusion, they will be switched to the conventional infusion and should not be restarted on the shorter infusion at any following infusion visit.

The study will consist of the following periods:

- Screening period: The screening visit should be scheduled up to two weeks prior to the first infusion of ocrelizumab. This period of time should not be exceeded.
- Treatment period: The first visit of the Treatment period (first infusion of ocrelizumab) should be 24 weeks (± 14 days) after the last infusion of ocrelizumab in the P-trial. Ocrelizumab will

be administered every 24 weeks up to Week 72 of this study and the last visit in the treatment period will be conducted 24 weeks after the last dose of ocrelizumab.

- A safety follow-up period of 48 weeks after the last infusion of the study drug, as explained below

Safety follow-up period:

The safety follow-up period is of 48 weeks after the last infusion of study drug (Section 3.1.4 for details). When patients begin an alternative treatment for MS (see Section 4.4.1 “Prohibited Therapy”), they will be discontinued from the study.

Patients who decide to leave the study and switch to ocrelizumab outside of the study, either after completion of the 96-week Treatment Period or after early discontinuation from the 96-week Treatment Period, will not enter the safety follow-up period.

NUMBER OF PATIENTS

Any patients with MS who were previously enrolled in a Roche sponsored P-trial, and with a positive benefit risk ratio as determined by treating neurologist can be enrolled in this study.

TARGET POPULATION

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Able to comply with the study protocol, in the investigator's judgment
- Eligible for roll-over into the MN39158/LIBERTO study (including the female patients who were pregnant during the parent studies and are still in the safety follow up period) based on the investigator decision in a Roche sponsored ocrelizumab P-trial upon risk/benefit assessment for continuous treatment with ocrelizumab
- Meet re-treatment criteria with ocrelizumab (Please see Section 3.1.3)
- Patients who became pregnant by chance between the last visit of the parent study and screening of this study, as confirmed by pregnancy tests at screening, will enter the safety follow-up immediately and re-start the treatment after birth and breastfeeding are over, as per re-treatment criteria in Section 3.1.3
- For women of childbearing potential:

Agreement to remain abstinent or use an acceptable birth control method during the treatment period and for at least 6 months or longer after the final dose of ocrelizumab, as applicable in the ocrelizumab package leaflet.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

- The following contraceptive methods are considered acceptable (failure rate $>1\%$ [Clinical Trial Facilitation Group (CTFG)]): (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 $<1\%$ [CTFG]) 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) vasectomised partner; (7) sexual abstinence.

Exclusion Criteria

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

- Hypersensitivity to ocrelizumab or to any of its excipients.
- Patients in a severely immunocompromised state until the condition resolves.
- Evidence of any adverse event potentially attributable to ocrelizumab, for which the summary of product characteristics (SmPC) recommends permanent discontinuation
- Existence of a contra-indication as per SmPC
- Prohibited concomitant medication as specified in Section 4.4.1.
- Patients intending to become pregnant during the study or within 6 months after the last dose of the study drug in the parent study.
- Patients who discontinued ocrelizumab in the P-trial (exemption made for treatment discontinuation due to unplanned pregnancy and breastfeeding for patients who continued clinical study assessments in the safety follow-up of the parent study).

END OF STUDY

The end of the study is defined as the last patient last visit (LPLV) in the Safety Follow-up Period or the last patient completing the week 96 visit whichever comes later. Patients who decide to leave the study and switch to ocrelizumab outside of the study or an alternative disease modifying therapy (DMT), either after completion of the 96-week Treatment Period or after early discontinuation from the 96-week Treatment Period, will not enter the safety follow-up period.

LENGTH OF STUDY

The total length of the study is expected to be dependent on the end of treatment of the last patient rolling over from the last parent study. For each patient, the treatment period is two years.

INVESTIGATIONAL MEDICINAL PRODUCTS

TEST PRODUCT (INVESTIGATIONAL DRUG)

Ocrelizumab will be administered as one 600-mg infusion in 500 mL 0.9% sodium chloride every 24 weeks for the duration of the study.

NON-INVESTIGATIONAL MEDICINAL PRODUCTS

The following premedications must be administered prior to each infusion of ocrelizumab to reduce the frequency and severity of IRRs:

- 100 mg intravenous methylprednisolone (or an equivalent) administered by slow IV infusion, to be completed approximately 30 minutes and not less than 25 minutes prior to each ocrelizumab infusion.
- Antihistamine, via oral, intramuscular or IV route to be completed approximately 30–60 minutes and not less than 25 minutes prior to each ocrelizumab infusion (the antihistamine should be the first premedication to be administered).
- The addition of an antipyretic (e.g., acetaminophen/ paracetamol) may also be considered.

STATISTICAL METHODS

The analysis of this study will be exploratory and primarily make use of descriptive statistical methods.

The intent-to-treat (ITT) population will include all enrolled patients who received any dose of ocrelizumab and will be used for the primary analyses of effectiveness and safety. The last 48-

week and 24-week CDP / CDI confirmatory assessment will be performed at the End of Treatment visit (week 96).

Effectiveness of ocrelizumab will be evaluated by means of a set of endpoints addressing different facets of MS. There is no primary endpoint defined in this study. The effectiveness endpoints include time to onset of confirmed CDP sustained for at least 24 and for at least 48 weeks, proportion of patients who have CDI, CDP for at least 24 and for at least 48 weeks, change from baseline in EDSS score over time of the parent study and this extension study, relapse rates, MRI-based measures of disease activity and progression or degeneration, measures of cognition, and patient reported outcomes. For a full list of effectiveness endpoints refer to Section 2.

The primary study analysis will be performed in subpopulations of the P-trials after the last patient from the corresponding P-trial completes the last (End of Treatment) visit in this MN39158/LIBERTO study. The evaluation of the clinical effectiveness of ocrelizumab will be based upon the events and assessments in-between the baseline (start of parent study) and end of Treatment period visit. A descriptive analysis based on the Kaplan-Meier method will be performed for the time to CDP and other time-to-event endpoints, such as the time to first relapse or to first event of disease activity. Change of EDSS from baseline till end of treatment will be analyzed based on statistical models such as mixed models for repeated measures. Details will be specified in the statistical analysis plan (SAP).

DETERMINATION OF SAMPLE SIZE

This is an extension study of ocrelizumab where patients will be enrolled from qualifying P-trials. A formal determination of sample size was therefore not performed.

INTERIM ANALYSES

No formal confirmatory effectiveness or safety interim analyses are planned. Exploratory interim analyses of selected endpoints, and in particular periodic analyses of safety data are planned to be performed during the course of the study.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADR	Adverse drug reaction
AEs	Adverse events
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ARR	Annual relapse rate
AST	Aspartate aminotransferase
CCOD	Clinical cut-off date
CDP	Confirmed disability progression
CDI	Confirmed disability improvement
CI	Confidence interval
CNS	Central nervous system
CRO	Contract research organization
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
DNA	Deoxyribonucleic acid
DMT	Disease modifying therapy
DWI	Diffusion Weighted Imaging
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EDSS	Expanded Disability Status Scale
FDA	Food and Drug Administration
FLAIR	Fluid-attenuated inversion-recovery
FSH	Follicle-stimulating hormone
FSS	Functional Systems Score
Gd	Gadolinium
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HEENT	Head, eye, ear, nose, and throat
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
IB	Investigator's brochure
ICH	International Conference on Harmonisation
IFN- β	Interferon beta

Abbreviation	Definition
Ig	Immunoglobulin
IMP	Investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IRR	Infusion-related reaction
ITT	intent-to-treat
IV	Intravenous
IxRS	Interactive voice/Web response system
JCV	John Cunningham virus
LLN	Lower limit of normal
LPLV	Last patient, last visit
MMRM	Mixed model with repeated measure
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSFC	Multiple sclerosis functional composite
MSIS-29	Multiple sclerosis impact scale (29-item scale)
NCI	National Cancer Institute
NEDA	No evidence of disease activity
NEP	No evidence of progression
NEPAD	No evidence of progression or active disease
NfL	Neurofilament light chain
9HPT	Nine Hole peg test
NMIP	Non-investigational medicinal product
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PML	Progressive multifocal leukoencephalopathy
PMS	Progressive multiple sclerosis
PP	Per-protocol
PPMS	Primary progressive multiple sclerosis
P-trial	Parent trial
PRMS	Progressive relapsing multiple sclerosis
PRO	Patient-reported outcome
PY	Patient years
QoL	Quality of life
RA	Rheumatoid arthritis
RCT	Randomized clinical trial
RBC	Red blood cell
RBR	Research Biosample Repository
RMS	Relapsing multiple sclerosis

Abbreviation	Definition
RNA	Ribonucleic acid
RRMS	Relapsing-remitting multiple sclerosis
SAEs	Serious adverse events
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SDMT	Symbol digit modalities test
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SIs	Serious infections
SmPC	Summary of product characteristics
SPMS	Secondary progressive multiple sclerosis
T25FWT	Timed 25-foot walk test
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopeia
WBC	White blood cell
WPAI	Work productivity and activity impairment questionnaire

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 400,000 people in the United States (US) and 2.3 million worldwide ([Tullman et al. 2013](#)). MS primarily affects young adults, with 70–80% of patients having an age of onset (i.e., initial visit to a physician) between 20 and 40 years ([Anderson et al. 1992](#); [Noonan et al. 2002](#)), and has a strong gender bias, with approximately 64–70% of diagnosed patients being women ([Goodin 2014](#)).

MS was historically clinically subcategorized into four phenotypic disease patterns distinguished by the occurrence and timing of relapses relative to disease onset and disability progression. These include relapsing-remitting MS (RRMS), primary progressive MS (PPMS), progressive relapsing MS (PRMS), and secondary progressive MS (SPMS) ([Lublin et al. 1996](#)); where RRMS and SPMS represent relapsing-onset MS disease whereas PPMS and PRMS represent progressive-onset MS disease forms. The PRMS entity is no longer to be identified as a separate phenotype and represents a subgroup of the PPMS population according to recently revised disease course definitions ([Lublin et al. 2014](#)).

The most frequent disease course of MS begins with a relapsing-onset presentation in approximately 85% patients developing the so-called relapsing-remitting form of MS ([Confavreux et al. 2000](#); [Leray et al. 2015](#)). In half of such patients, the disease advances to a secondary progressive stage within approximately 10 years ([Weinshenker et al. 1989](#)). However, the onset of secondary progressive disease course as per physician's diagnosis is dependent on age, rather than on disease duration, and appears to be the strongest determinant of poor long-term disease prognosis ([Confavreux and Vukusic 2006](#); [Confavreux et al. 2003](#); [Koch et al. 2007](#); [Scalfari et al. 2011](#); [Tutuncu et al. 2013](#)). Clinically active RRMS is defined by the occurrence of relapses, acute or subacute episodes of new or increasing neurologic dysfunction followed by full or partial recovery in the absence of fever or infection ([Lublin et al. 2014](#)). In contrast, SPMS following a relapsing-remitting disease course is characterized by progression of variable rate with or without occasional relapses, minor remissions, and plateaus ([Lublin et al. 1996](#)), where "progression" is defined as the accumulation of disability unrelated to relapse activity ([Lublin et al. 2014](#)).

The clinical signs in MS can occur in isolation or in combination, and can include motor weakness, spasticity, gait and coordination imbalances, sensory dysfunction, vision loss, cognitive impairment, sexual dysfunction, fatigue, depression, chronic pain, and sleep disorders ([Tanasescu et al. 2014](#)). Current diagnosis of definite MS involves both clinical (history and neurological exam) and paraclinical (for example, magnetic resonance imaging [MRI], cerebrospinal fluid oligoclonal bands and/or elevated immunoglobulin (Ig) G index, evoked potentials) evidence.

MS treatments tackle separately the acute exacerbations and their prevention. Management of relapses involves the use of corticosteroids, while disease-modifying therapies (DMTs) aim to decrease the clinical relapse rate and concomitant inflammation within the CNS ([Tanasescu et al. 2014](#)). DMTs, which include immunomodulatory, anti-inflammatory, and immunosuppressive drugs, are used to slow the development of MS-related neurological damage and disability progression. Although there are now several approved therapies for RMS, some lack sufficient efficacy to quell progression of disability, while more effective therapies are often reserved for later use because of serious risks. Thus, there remains a need for highly effective therapies with a benefit-risk profile that supports its expeditious use at any time during the course of disease to preserve CNS tissue and neurological function, stem accrual of irreversible disability, and improve the quality of life (QoL) for people living with MS.

1.2 BACKGROUND ON OCRELIZUMAB

Ocrelizumab is a recombinant humanized anti-human monoclonal antibody that selectively targets and eliminates CD20-expressing B-cells ([Klein et al. 2013](#)), which are believed to play a critical role in MS. CD20 is a cell surface antigen found on pre-B-cells, mature B-cells, and memory B-cells, but it is not expressed on lymphoid stem cells and plasma cells ([Stashenko et al. 1980](#); [Loken et al. 1987](#); [Tedder and Engel 1994](#)). While ocrelizumab selectively depletes CD20-expressing B-cells ([Kappos et al. 2011](#)), the capacity of B-cell reconstitution and pre-existing humoral immunity are preserved ([Martin and Chan 2006](#); [DiLillo et al. 2008](#)). In addition, innate immunity and total T-cell numbers do not appear to be significantly affected ([WA21493 Clinical Study Report](#)).

Please see the ocrelizumab Investigator's Brochure (IB) for additional details on nonclinical and clinical studies.

Summary of Clinical Studies of Ocrelizumab in MS

In two double-blind, double-dummy Phase III global relapsing multiple sclerosis (RMS) trials (Studies WA21092 and WA21093 OPERA I [[NCT01247324](#)] and OPERA II [[NCT01412333](#)]), ocrelizumab 600 mg demonstrated superior efficacy over subcutaneous interferon beta (IFN β)-1a 44 μ g ([Hauser et al. 2015](#)). Efficacy outcomes were consistent between trials and across the primary and key clinical and imaging secondary endpoints. Ocrelizumab 600 mg demonstrated statistically significant superiority compared with IFN β -1a on each of the following major efficacy endpoints:

- Relative reductions of 46% and 47% (both $p < 0.0001$) in the protocol-defined annual relapse rate (ARR) in Studies WA21092 and WA21093, respectively (primary endpoint).
- A 40% relative reduction in both the 12-week confirmed disability progression [CDP] (Hazard ratio [HR] 0.60 [95% confidence interval [CI]: 0.45, 0.81], $p=0.0006$) and 24-week CDP (HR 0.60 [95% CI: 0.43, 0.84], $p=0.0025$) in the pooled analysis of Studies WA21092 and WA21093. Each individual trial also demonstrated a

significant relative risk reduction of 12-week CDP and 24-week CDP (43% reduction for both 12- and 24-week CDP in Study WA21092 and 37% reduction for both 12- and 24-week CDP in Study WA21093).

- Relative reductions of 94% and 95% (both $p < 0.0001$) in the number of T1- gadolinium (Gd)-enhancing lesions per scan at Weeks 24, 48 and 96 in Study WA21092 and Study WA21093, respectively.
- Relative reductions of 77% and 83% (both $p < 0.0001$) in the total number of new and/or enlarging T2 hyperintense lesions per scan at Weeks 24, 48 and 96 in Study WA21092 and Study WA21093, respectively.

In a Phase III global PPMS trial (ORATORIO Study WA25046, [NCT01194570](#)), ocrelizumab 600 mg demonstrated statistically significant superiority compared with placebo on each of the following major efficacy endpoints ([Montalban et al. 2015](#)).

- A 24% relative risk reduction in 12-week CDP, the primary endpoint (HR=0.76 [95% CI: 0.59, 0.98], $p = 0.0321$).
- A 25% relative risk reduction in 24-week CDP (HR=0.75 [95% CI: 0.58, 0.98], $p = 0.0365$).
- Relative reduction of 29% in the progression rate of timed 25-foot walk from baseline to Week 120 ($p = 0.0404$).
- A decrease in the volume of T2 lesions by 3.4% over 120 weeks, compared with the placebo group in which the T2 lesion volume increased by 7.4% ($p < 0.0001$).
- Relative reduction of 17.5% in whole brain volume loss from Week 24 to Week 120 ($p=0.0206$).

Clinical Safety

The safety data included are from five studies in MS: two Phase III studies in RMS (Studies WA21092 and WA21093), one Phase III study in PPMS (Study WA25046), one Phase II study in RRMS (Study WA21493) and one substudy (shorter infusion substudy) of the Phase IIIb study in early stage RRMS (Study MA30143).

The four studies WA21092, WA21093, WA25046, and WA21493 have completed the controlled treatment period and are in the open label extension phase. In the two double-blind, double-dummy RMS Phase III studies (pooled data of Studies WA21092 and WA21093) during the 96-week controlled treatment period, the rates of treatment discontinuations for adverse events (AEs) were lower in patients treated with ocrelizumab 600 mg (3.5%) than in patients receiving IFN β -1a (6.2%). The proportion of patients with adverse events (83.3% in both groups) as well as the total number of

adverse events were similar in the ocrelizumab and the IFN β -1a treatment groups over the 96-week treatment period. The proportion of patients reporting infections was higher in the ocrelizumab group compared with the IFN β -1a group, (58.4% vs. 52.4%, respectively). In addition, there were more events of infection in the ocrelizumab group (1224 events) compared with the IFN β -1a group (948 events) and these were primarily upper respiratory tract infections of Grade 1 or 2 intensity. The proportion of patients with serious adverse events (SAEs) was lower in the ocrelizumab treatment group than in the IFN β -1a treatment group (6.9% in the ocrelizumab treatment group versus 8.7% in the IFN β -1a treatment group). Overall, the proportion of patients with serious infections (SIs) was lower in the ocrelizumab group (1.3%) than in the IFN β -1a group (2.9%).

Two serious infusion-related reactions (IRRs) were reported; one in the IFN β -1a group (severe balance disorder and other symptoms; Grade 3) and one in the ocrelizumab group (life-threatening bronchospasm; Grade 4). As expected, the proportion of patients experiencing IRRs were increased in the ocrelizumab group (34.3%) compared with the active control group (9.7%) who received dummy infusions. During the 96-week-controlled treatment period, a total of six malignancies were reported, two events (one mantle cell lymphoma and one squamous cell carcinoma) occurred in two patients (0.2%) in the IFN β -1a treatment group and four events (two invasive ductal breast carcinomas, one renal cancer and one malignant melanoma) occurred in four patients (0.5%) in the ocrelizumab treatment group. During the 96-week-controlled treatment period, three deaths occurred in Studies WA21092 and WA21093; two patients (suicide and mechanical ileus) in the IFN β -1a treatment group and one patient (suicide) in the ocrelizumab treatment group.

In the PPMS Phase III double-blind placebo-controlled Study WA25046, the proportion of patients with adverse events leading to discontinuation from treatment was similar in ocrelizumab (4.1%) and placebo (3.3%) groups. The proportion of patients who experienced at least one adverse event was 90% in the placebo group compared with 95% in the ocrelizumab group. Taking into account that twice as many patients were randomized to ocrelizumab than placebo, the number of adverse events experienced by patients with an adverse event was similar (1762 events in the placebo group and 3690 events in the ocrelizumab group). The proportion of patients who experienced an infection was 69.8% in the ocrelizumab group compared with 67.8% in the placebo group. The proportion of patients with SIs was similar in both groups: 5.9% in the placebo group compared with 6.2% in the ocrelizumab group. As expected, the proportion of patients who reported IRRs was higher in the ocrelizumab group (39.9%) compared with placebo (25.5%). Overall, 5 patients (1.0%) experienced a serious IRR in the ocrelizumab group. During the controlled treatment period, a total of 15 malignancies in 13 patients were reported: two events (basal cell carcinoma and adenocarcinoma of the cervix) occurred in two patients (0.8%) in the placebo group and 13 events (five basal cell carcinoma, two invasive ductal breast carcinoma, one anaplastic large-cell lymphoma, one breast cancer, one endometrial cancer, one invasive breast carcinoma, one malignant fibrous histiocytoma, one pancreatic

carcinoma metastatic) occurred in 11 patients (2.3%) in the ocrelizumab group. The proportion of patients with serious adverse events (22.2% in the placebo group compared with 20.4% in the ocrelizumab group), was similar in both groups. There were five deaths during the controlled treatment period, one in the placebo group (road traffic accident) and four in the ocrelizumab group (pulmonary embolism, pneumonia, pancreatic carcinoma, pneumonia aspiration).

All Exposure Population

The safety data from controlled periods of Studies WA21092 (Phase III, RMS), WA21093 (Phase III, RMS), WA25046 (Phase III, PPMS), and Study WA21493 (Phase II, RRMS) as well as BN29739, MA30005, MA30143, ML29966, MN30035, MN39158 and MN39159 are included up to a clinical cut-off date (CCOD) of January 2020. A total of 5,680 patients exposed to ocrelizumab, accounting for 18,218 patient years (PY), are included in this section (MS All Exposure Population).

The most common adverse events were IRRs which were manageable using appropriate measures, and infections, mostly Grade 1 or Grade 2 in intensity. The overall rate of SIs remains low and stable. Urinary tract infection and pneumonia remained the SIs events reported with the highest rates per 100PY. The event rate per 100PY of SIs appears to increase numerically with fluctuation over time driven solely by the PPMS population subset. The majority of SIs were of Grade 3 intensity or below, resolved without sequelae, within ≤ 2 weeks and were not treatment limiting. Though malignancy remains a potential risk and needs to be further characterized, the incidence rate of malignancy in ocrelizumab treated patients remained consistent with that of the general MS population. For more detailed information on safety from clinical trials and post-marketing settings, please refer to the most recent version of the IB.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Multiple sclerosis is a chronic disease that requires lifelong treatment in order to reduce frequency of relapse and accumulation of disability. Once a patient is diagnosed with definite MS, accepted treatment guidelines propose that he/she be offered lifelong treatment, as there is no evidence to suggest that MS spontaneously remits ([Rio et al. 2011](#)). Results of long-term, follow-up studies suggest that exposure to DMT for more than 2 years improves outcomes by delaying the time to disability progression. Moreover, a majority of MS patients treated with a DMT, who discontinued therapy, had a return of their baseline disease activity after approximately 2 years ([Siger et al. 2011](#)).

The phase III randomized clinical trials (RCTs) have demonstrated a favorable benefit-risk ratio of ocrelizumab in RMS and PPMS patients. These studies have completed the controlled treatment period and are in the open label extension phase. The ongoing/planned phase IIb/IV trials (the Parent, P-trial) will further evaluate the effectiveness and safety of ocrelizumab in MS patients. At their completion or closure some patients might still be on treatment with ocrelizumab and may benefit from the

continuation of the therapy with ocrelizumab. Based on the favorable profile of ocrelizumab, it is justified to offer ocrelizumab to these patients in order to reduce the frequency of relapses and delay disability progression. Furthermore, F. Hoffmann-La Roche (Roche) had committed to provide treatment for above mentioned patients in the P-trial. Thus, patients who complete the treatment period of the P-trials will be offered participation in this Extension study. Providing patients with the opportunity to prolong treatment with ocrelizumab will provide more information on the long-term safety of ocrelizumab in MS, as well as further collection of tolerability and effectiveness information from patients with long-term exposure. Analyzing the long-term safety, tolerability, and effectiveness of ocrelizumab is of critical importance to eventually help clinicians make informed decisions on therapy for patients.

1.3.1 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 impact is anticipated to affect the efficacy and safety in patients enrolled in ocrelizumab clinical trials. Existing information on identified risks, safety monitoring, and risk mitigation measures related to administration of vaccines (including those for SARS-CoV-2) provided in the study protocol (namely immunization concomitant therapy and impaired response to vaccination sections) are considered adequate.

As described in ‘impaired response to vaccination’ protocol Section [5.1.3.1](#), 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. The vaccination study (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 this 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). Boosters 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 Concomitant Therapy Section [4.4](#)).

2. OBJECTIVES AND ENDPOINTS

This Extension study will evaluate the effectiveness and safety of ocrelizumab in MS patients who were previously enrolled in a Roche sponsored ocrelizumab phase IIIb/IV P-trial. Specific objectives and corresponding endpoints for the study are outlined in the [Table 1](#) below.

Table 1 Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Objective:	
To evaluate the effectiveness of ocrelizumab therapy in MS patients who were previously enrolled in a Roche sponsored phase IIIb/IV-trial	Evaluate clinical measures related to disease progression over the duration of treatment in MS patients
Overview of the effectiveness measures:	
Different effectiveness measures evaluated for ocrelizumab in MS patients who were previously enrolled in a Roche sponsored phase IIIb/IV-trial	Related to disability progression: - Time to onset of CDP sustained for at least 24 weeks and for at least 48 weeks - Proportion of patients who have confirmed disability improvement (CDI), CDP for at least 24 weeks and for at least 48 weeks yearly and over the duration of treatment - Proportion of patients who have improved, stable or worsened disability compared with baseline (inclusion in Extension study) measured by expanded disability status scale (EDSS) (annually/ by epoch and over duration of treatment) Stable EDSS is defined as EDSS change +/- 0.5. Worsening is > 0.5 increase of EDSS, Improvement is > 0.5 decrease of EDSS. - Mean change from inclusion in the parent study in EDSS score over the course of treatment - Time to 20% increase in timed 25-foot walk test (T25FWT); time to 20% increase in timed nine-hole peg test (9HPT) sustained for at least 24 weeks and for at least 48 weeks, and proportion of patients achieving a sustained increase assessed yearly and over the duration of treatment Other clinical measures and composite endpoints: - Time to first protocol-defined event of disease activity - Time to first relapse - Annualized relapse rate - Proportion of patient relapse free, yearly and over the course of treatment - Proportion of patients with no evidence of protocol-defined disease activity (NEDA) yearly and over the duration of the treatment where disease activity is defined as at least one the following events: protocol-defined relapse; 24 weeks CDP based on increases in EDSS; a T1 Gd-enhanced lesion; or a new and/or enlarging T2 hyperintense lesion on MRI.

Objectives	Corresponding Endpoints
	• Proportion of patients with no evidence of progression (NEP) defined as no progression sustained for at least 24 weeks on all of the following three components (CDP; 20% increase in timed T25FWT; 20% increase in timed 9HPT yearly and over the course of treatment) • Proportion of patients with no evidence of progression sustained for at least 24 weeks and no active disease (NEPAD) defined as no progression on all of the three components of NEP (CDP, T25FWT, 9HPT), no new relapse and no enlarging or new T2 or T1 Gd-enhancing lesion yearly and over the course of treatment • Change from baseline (parent trial) in cognitive performance as measured by the Symbol digit modalities test (SDMT) Related to MRI • Total number of T1 Gd-enhancing lesions as detected by brain MRI over time • Total number of new and/or enlarging T2 lesion as detected by brain MRI over time • Change in total T1 hypointense lesion volume over time • Total number of fluid-attenuated inversion-recovery (FLAIR) late enhancing lesions as detected by brain MRI over time (pertinent to CASTING/MA30005 patients only) • Total number of FLAIR late enhancing lesions as detected by brain MRI at the end of the treatment period • Change in brain volume (including white and grey matter fractions) as detected by brain MRI over time • Presence and evolution of leptomeningeal follicles (pertinent to ENSEMBLE/MA30143 patients with identified FLAIR late enhancing lesions and CASTING/MA30005 patients) Other measures related to MS disease: • Time to treatment discontinuation/switch Patient reported outcomes (PROs) • Employment status (Work Productivity and Activity Impairment Questionnaire [WPAI]) • SymptoMScreen • QoL (Multiple Sclerosis Impact Scale [MSIS]-29)
Exploratory Objective:	
• To investigate the effect of ocrelizumab on antibody and T cell responses in patients administered an approved severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine	• Analysis of immune response (SARS-CoV-2 antibody titers and SARS-CoV-2 T cell responses) to SARS-CoV-2 vaccine

Objectives	Corresponding Endpoints
Safety Objective:	
To evaluate the safety and tolerability of ocrelizumab therapy in MS patients who were previously enrolled in a Roche sponsored phase IIIb/IV-trial	- Rate and nature of adverse events - Changes in vital signs, neurological examinations, clinical laboratory results, locally reviewed MRI for safety (non-MS CNS pathology) and concomitant medications (including pre-medications and medications used during and following ocrelizumab administration)

The definition of a protocol-defined event of disease activity is the occurrence of any of the following while on treatment with ocrelizumab:

- a protocol-defined relapse as defined in Section 4.5.5
- 24 weeks CDP based on increases in EDSS (see Section 4.5.6)
- a new T1 Gd-enhanced lesion
- a new and/or enlarging T2 hyperintense lesion on MRI

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a single arm, open label, multicenter Extension study in patients on ocrelizumab therapy who are eligible for roll over based on the investigator decision in the Roche Parent trial. Patients will receive treatment with ocrelizumab as single 600 mg infusions in 500 mL 0.9% sodium chloride every 24 weeks up to Week 72 of this study.

The study will consist of the following periods:

- Screening period: The screening visit should be scheduled up to two weeks prior to the first infusion of ocrelizumab. This period of time should not be exceeded.
- Treatment period: The first visit of the Treatment period (first infusion of ocrelizumab) should be 24 weeks (± 14 days) after the last infusion of ocrelizumab in the P-trial. Also, in case of pregnancy / breastfeeding the Enrolment visit would be done at the same time as the last visit of the P-trial.
Ocrelizumab will be administered every 24 weeks up to Week 72 of this study and the last visit in the treatment period will be conducted 24 weeks after the last dose of ocrelizumab.
- A safety follow-up period of 48 weeks after the last infusion of the study drug, as explained below.

Safety Follow-up Period:

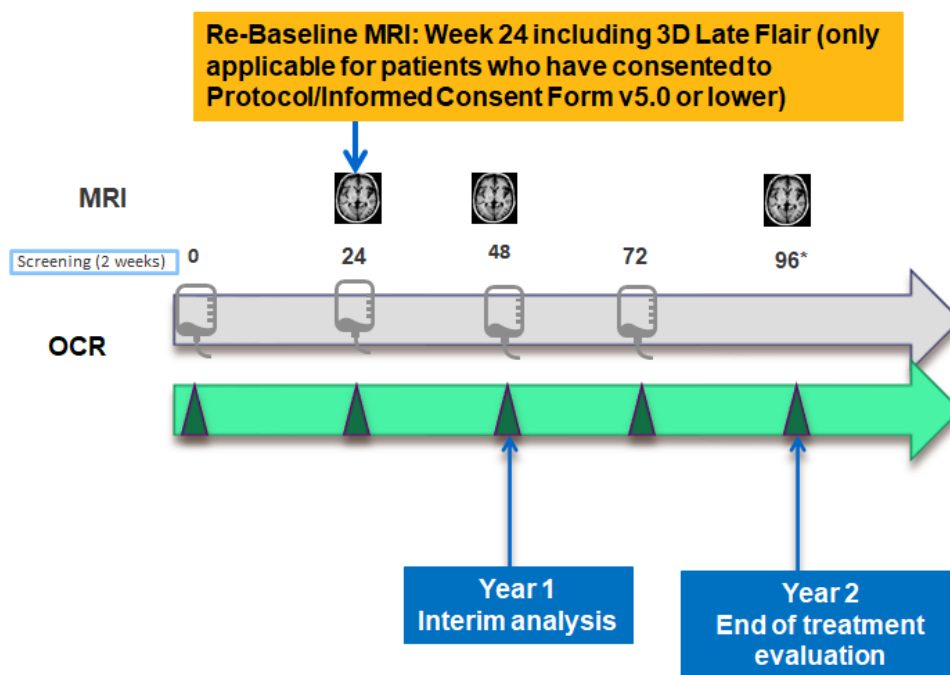
The safety follow-up period is of 48 weeks after the last infusion of study drug (Section 3.1.4 for details). When patients begin an alternative treatment for MS (see section 4.4.1 “Prohibited Therapy”), they will be discontinued from the study.

Patients who decide to leave the study and switch to ocrelizumab outside of the study, either after completion of the 96-week Treatment Period or after early discontinuation from the 96-week Treatment Period, will not enter the safety follow-up period.

3.1.1 Overview of Study Design

Figure 1 presents an overview of the study procedures. A schedule of assessments is provided in Appendix 1.

Figure 1 Study schema



FLAIR = Fluid-attenuated inversion-recovery; MRI = Magnetic resonance imaging; OCR = Ocrelizumab

* For patients who complete the study treatment period, the week 96 visit will include the 24-week safety follow-up assessments.

3.1.2 Screening

After providing written informed consent, patients will enter a screening period for evaluation of eligibility. The screening visit should be scheduled up to two weeks prior to the first infusion of ocrelizumab. This period of time should not be exceeded.

3.1.3 Treatment Period

The first visit of the Treatment period (first infusion of ocrelizumab) should be 24 weeks (± 14 days) after the last infusion of ocrelizumab in the P-trial. Patients will be treated with single 600-mg infusions in 500 mL 0.9% sodium chloride every 24 weeks up to Week 72 of this study and the last visit in the treatment period will be conducted 24 weeks after the last dose of ocrelizumab. In patients who did not experience a serious IRR with any previous conventional ocrelizumab infusion (~ 3.5 hours), the next 600 mg infusion can be administered as a shorter (~ 2 hours) infusion for subsequent doses, after providing written informed consent; see Section 4.3.2.1 for the details on infusion rates for the conventional and shorter infusion of ocrelizumab. If patients develop a serious IRR while on the shorter infusion, they will be switched to the conventional infusion and should not be restarted on the shorter infusion at any following infusion visit.

The last 48-week and 24-week CDP / CDI confirmatory assessments will be performed at the End of Treatment visit (week 96). For patients who discontinue the study (e.g., switch to ocrelizumab outside of the study, or start treatment with another DMT), the EDSS CDP confirmatory assessments will not be performed.

Criteria for Re-Treatment with Ocrelizumab

All laboratory samples can be taken up to 2 weeks prior to the scheduled study visit. If laboratory results are required to confirm re-treatment criteria, these need to be available prior to dosing.

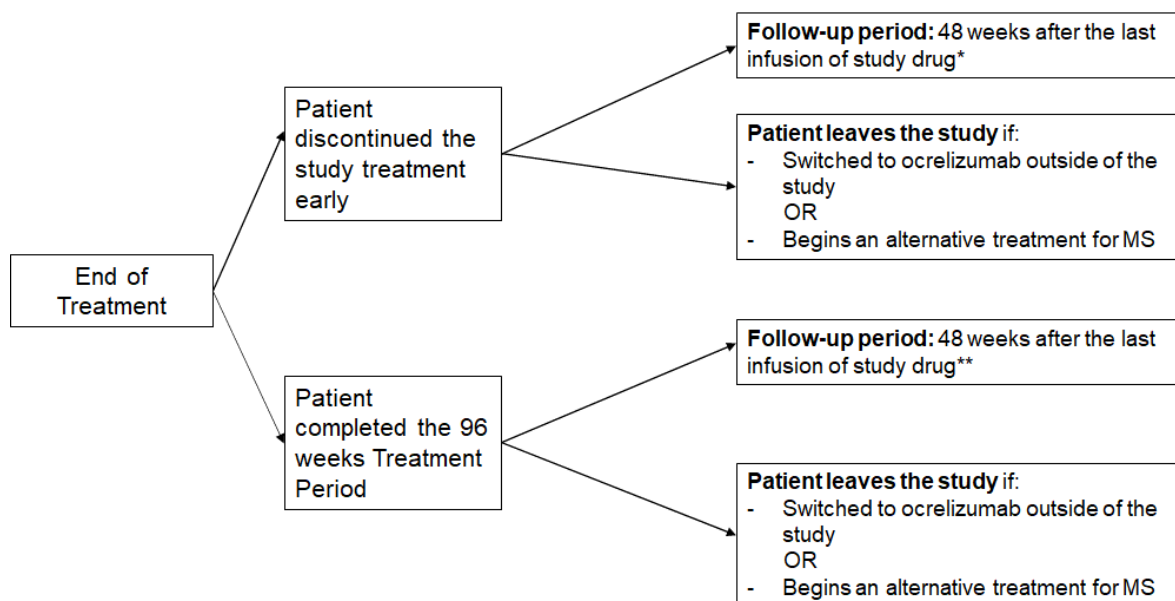
Decision on re-treatment criteria will be made in accordance with standard of care and the local ocrelizumab label.

Ongoing pregnancy or breastfeeding: In case of unplanned pregnancy, treatment should be interrupted, and the patient should be monitored for safety; however, the patient will remain in the trial and will have the opportunity to re-start the treatment after birth and breastfeeding are over. The total duration of treatment period will be 96 weeks from enrollment, irrespective of how long the treatment was interrupted due to pregnancy. For patients who had treatment interrupted due to pregnancy at the time of their rollover from the parent study, the total duration on treatment will not extend the total duration in the parent study and this extension study. During pregnancy and breastfeeding, the patient will continue to come for the regular scheduled visits [whenever possible, adhering to the time of scheduled visits as per protocol] and will perform all assessments except MRI.

Patients will be followed up for 48 weeks after the last infusion of study drug. When patients begin an alternative treatment for MS (see Section 4.4.1 “Prohibited Therapy”), they will be discontinued from the study (See Figure 2 and Section 3.1.4). Patients who decide to leave the study and switch to ocrelizumab outside of the study,

either after completion of the 96-week Treatment Period or after early discontinuation from the 96-week Treatment Period, will not enter the safety follow-up period.

Figure 2 Overview of End of Treatment Period



*Safety follow-up at Week 24 and Week 48 after the last infusion of the study drug

**Safety follow-up period starts from Week 72 and continues up to 24 weeks after the Week 96 visit, having up to 48 weeks total duration.

3.1.4 Safety Follow up Period

The safety follow-up period is of 48 weeks after the last infusion of the study drug. When patients begin an alternative treatment for MS (see Section 4.4.1 "Prohibited Therapy"), they will be discontinued from the study". Patients who decide to leave the study and switch to ocrelizumab outside of the study, either after completion of the 96-week Treatment Period or after early discontinuation from the 96-week Treatment Period, will not enter the safety follow-up period.

A schedule of assessments for the Follow-up Period is presented in [Appendix 2](#).

During the Safety Follow-up Period, patients will be formally assessed at clinical visits every 24 weeks (± 14 days). For patients who complete the study treatment period, the week 96 visit will include the 24-week safety follow-up assessment followed by a 48-week safety follow-up assessment after the last dose of ocrelizumab. For patients discontinuing the treatment early, there will be two safety follow-up assessment visits (at week 24 and week 48 after the last dose of ocrelizumab). See [Appendix 2](#) for further details.

For patients withdrawing from treatment early, every effort should be made to complete the Safety Follow-up Period and all related assessments as applicable.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study is defined as the last patient last visit (LPLV) in the Safety Follow-up Period or as the last patient completing the week 96 visit whichever comes later. Patients who decide to leave the study and switch to ocrelizumab outside of the study or an alternative DMT, either after completion of the 96-week Treatment Period or after early discontinuation from the 96-week Treatment Period, will not enter the safety follow-up period.

The total length of the study is expected to be dependent on the end of treatment of the last patient rolling over from the last parent study. For each patient, the treatment period is 2 years.

3.3 RATIONALE FOR STUDY DESIGN

The primary aim of this Extension study is to evaluate the long-term effectiveness and safety of ocrelizumab and provide continued ocrelizumab therapy to patients who were administered ocrelizumab therapy in the phase IIIb/IV P-trial and found to benefit from continuation of ocrelizumab treatment. Given the potentially long-term use of ocrelizumab in MS, this study of up to 2.5 years duration for an individual patient will provide additional safety data in MS patients to be contextualized with the population studied in the pivotal phase III and phase IIIb/IV trials.

The effectiveness of ocrelizumab will be evaluated based on various clinical outcomes related to disease progression over a period of two years.

One of the key outcome measures is time to onset of CDP sustained for at least 24 weeks and 48 weeks with CDP defined as in the parent (feeding) studies.

An increase of 1 point on the EDSS above baseline, subsequently confirmed at repeat assessment 24 weeks later (24 weeks CDP) is the most commonly used measure in MS clinical trials ([Gray and Butzkueven 2008](#)). To ensure that worsening in EDSS score represents permanent physical disability rather than an exacerbation-related temporary fluctuation in neurological status, a worsening EDSS score has to be sustained for at least 24 weeks for a patient to be considered a treatment failure. Previous studies have shown that spontaneous recovery from sustained progression of 1.0 EDSS point of this duration is most unusual ([Jacobs et al. 1996](#)). CDP is therefore a robust measure when performed over a 6-month interval, and reduction in the risk of 24 weeks CDP provides good evidence for the beneficial effects on disability ([Wiendl et al. 2015](#)).

EDSS is the most widely used and well-known scale to assess changes in disability in MS. Evaluation of change from start of Extension study in EDSS score over the course of the study will provide an overall estimate of the dysfunction that was experienced by the patient during the study period. Other key end-points such as MRI variables

(for example, lesion count, lesion volume, and brain volume) are commonly used in clinical trials to assess treatment efficacy and disease progression ([Lavery et al. 2014](#)).

Prevention of disability progression as measured by the different elements: CDP but also upper limb function (9HP) and lower limb function (T25FW) are important for the patient to allow optimal functioning. In addition to disability, clinical and subclinical elements of disease activity (relapses, T1 Gd+ and new/enlarging T2 lesions) remain of importance since these elements can contribute to the progression of the disability or the MS disease in general.

NEDA is considered a measurement of better disease control. The evaluation of proportion of patients reaching or maintaining the NEDA status could be considered beneficial on long term evolution of the MS disease.

As the burden of cognitive impairment in MS is considerable and is of crucial significance in employment outcomes and social disability ([Gray and Butzkueven. 2008](#)), the SDMT, a validated test to detect impairment of key neurocognitive functions that underlie many substitution tasks, including sustained attention, visual scanning, and recent memory ([SDMT manual](#)) will be used to assess the changes in cognitive performances. MS is a chronic, disabling condition having a significant impact on patients' QoL and therefore MSIS-29, a clinically useful and scientifically-sound patient-based outcome measure of the impact of MS in clinical trials ([Hobart et al. 2001](#)) will be used to assess the physical and psychological impact of MS from the patient's perspective. Additionally, 'SymptoMScreen' score, which is a PRO based upon a battery of seven-point Likert scales for 12 distinct domains commonly affected by MS will also be used in this study ([Green et al. 2017](#)). Finally, the WPAI questionnaire will be used to assess the impact of MS on employment and the ability to perform regular activities.

A 3D late FLAIR sequence will be added to the MRI assessments. This will allow the visualization of the meningeal follicular structures (gadolinium enhancement) which are known to appear usually at a later stage of the disease. This additional assessment should allow to understand better the presence or absence of meningeal follicular structures in patients in this early stage of RRMS disease.

Rationale for measuring impact of ocrelizumab on response to SARS-CoV-2 vaccines

The results of the randomized, open-label Phase IIIb study (VELOCE), which assessed if ocrelizumab recipients with RMS raise adequate humoral responses to selected vaccines, indicate that patients with RMS who are peripherally B-cell depleted after treatment with ocrelizumab can mount humoral responses, albeit attenuated, to tetanus toxoid, 23-valent pneumococcal polysaccharide, keyhole limpet hemocyanin neoantigen, and seasonal influenza vaccines. The immune response of other components of the immune system (e.g., T cell response), known to confer immunological protection in addition to antibodies, were not evaluated.

Recently, vaccines against the SARS-CoV-2 virus have received authorizations for use from regulatory agencies. Vaccine efficacy data, and vaccine effectiveness from real world settings have shown that the available vaccines lead to a significant reduction in the number of COVID-19 infections and the number of severe cases that require hospitalization or result in fatal outcomes. Available data from the vaccine trials demonstrate that these vaccines can induce an antibody response as well as T cell responses. While not fully understood, accruing evidence suggests that both antibodies and T cell-mediated immunity have a protective role against future SARS-CoV-2 infection and severe clinical presentations. Currently, evidence on the SARS-CoV-2 vaccine response in persons taking immunomodulatory treatments is lacking, including in patients with MS treated with ocrelizumab.

Humoral immunity, including antibody titers, will be assessed by validated assays including the Elecsys SARS-CoV-2 Spike antibody test. SARS-CoV-2-specific T cell responses will be measured using a well-validated assay such as interferon gamma (IFN γ) ELISpot (enzyme-linked immunospot). Immunophenotyping outcomes are to be assessed by flow cytometry. Other exploratory assays for humoral and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data.

Responses will be measured within a few weeks post-immunization and up to 18 months after the vaccination to evaluate the impact of ocrelizumab on the vaccine immune response over time.

3.3.1 Rationale for ocrelizumab Dose and Schedule

The dose level of ocrelizumab administered in this study is 600 mg every 24 weeks. This dosing regimen is anticipated to be well-tolerated and is consistent with the dosing regimen used in Phase III, Phase IIIb/IV studies and the summary of product characteristics (SmPC).

3.3.2 Rationale for Patient Population

This is an ocrelizumab extension study and therefore will include MS patients who were previously enrolled in a Roche sponsored ocrelizumab phase IIIb/IV P-trial.

3.3.3 Rationale for NfL Biomarker assessments in plasma: CASTING/MA30005 study patients only

The biomarker of neuroinflammation, neurofilament light (NfL) chain, an acute neuronal injury marker, has been correlated with gadolinium (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 CSF level, making NfL an attractive non-invasive biomarker to assess neuronal injury in MS ([DiSanto et al. 2017](#)).

The plasma samples collected in CASTING/MA30005 study will be reassigned to the analysis of NfL in those patients from CASTING/ MA30005 study who sign the Informed Consent Form for NfL testing.

4. MATERIALS AND METHODS

4.1 PATIENTS

Patients with MS who were previously enrolled in a Roche sponsored phase IIIb/IV P-trial with ocrelizumab and having a positive benefit risk ratio as determined by the treating neurologist, can roll over from one of the below listed studies:

- MA30005 study – for patients with RRMS who have a suboptimal response to an adequate course of DMT.
- MA30143 study – for patients with early stage RRMS.

The presented list is not limited but can be extended to ongoing/planned phase IIIb/IV qualifying P-trials in later time.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Able to comply with the study protocol, in the investigator's judgment
- Eligible for roll-over into the MN39158/LIBERTO study (including the female patients who were pregnant during the parent studies and are still in the safety follow up period) based on the investigator decision in a Roche sponsored ocrelizumab P-trial upon risk/benefit assessment for continuous treatment with ocrelizumab
- Meet re-treatment criteria with ocrelizumab (Please see Section 3.1.3)
- Patients who became pregnant by chance between the last visit of the parent study and screening of this study, as confirmed by pregnancy tests at screening, will enter the safety follow-up immediately and re-start the treatment after birth and breastfeeding are over, as per re-treatment criteria in Section 3.1.3
- For women of childbearing potential:

Agreement to remain abstinent or use an acceptable birth control method during the treatment period and for at least 6 months or longer after the final dose of ocrelizumab, as applicable in the ocrelizumab package leaflet.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

- The following contraceptive methods are considered acceptable (failure rate $>1\%$ [Clinical Trial Facilitation Group (CTFG)]): (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% [CTFG]) 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) vasectomised partner; (7) sexual abstinence.

4.1.2 Exclusion Criteria

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

- Hypersensitivity to ocrelizumab or to any of its excipients.
- Patients in a severely immunocompromised state until the condition resolves.
- Evidence of any adverse event potentially attributable to ocrelizumab, for which the local label recommends permanent discontinuation.
- Existence of a contra-indication as per SmPC
- Prohibited concomitant medication as specified in Section 4.4.1.
- Patients intending to become pregnant during the study or within 6 months after the last dose of the study drug in the parent study
- Patients who discontinued ocrelizumab in the P-trial (exemption made for treatment discontinuation due to unplanned pregnancy and breastfeeding for patients who continued clinical study assessments in the safety follow-up of the parent study).

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study in which all patients will receive single 600 mg infusions of ocrelizumab every 24 weeks. Therefore, no randomization or blinding will be used in this study.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is ocrelizumab. Premedications are considered non-investigational medicinal products (NIMPs).

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Ocrelizumab

Ocrelizumab will be supplied by the Sponsor as a liquid formulation containing 30-mg/mL ocrelizumab in 20 mM sodium acetate at pH 5.3, with 4% trehalose and 0.02% polysorbate 20. The drug product is provided as a single-use liquid formulation in a 15-cc, type I United States Pharmacopeia (USP), glass vial fitted with a 20-mm, fluoro-

resin, laminated stopper and an aluminum seal with a flip-off plastic cap. The vial contains 300 mg ocrelizumab. No preservative is used as each vial is designed for single use, thus the vials should be handled aseptically.

The ocrelizumab drug product in vials should be stored at 2-8 degrees Celsius and protected from light, should not be frozen and not be shaken.

The ocrelizumab drug product must be diluted before administration. Solutions of ocrelizumab for intravenous (IV) administration are prepared by dilution of the drug product into an infusion bag containing 0.9% sodium chloride to a final drug concentration of 1 to 2 mg/mL.

Ocrelizumab may contain fine translucent and/or reflective particles associated with enhanced opalescence. Do not use the solution if discolored or if the solution contains discrete foreign particulate matter. The infusion solution must be administered using an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of up to 0.2 µm).

The prepared infusion solution of ocrelizumab is physically and chemically stable for 24 hours at 2–8 °C and subsequently 8 hours at room temperature. The prepared infusion solution should be used immediately. If not used immediately, it can be stored up to 24 hours at 2 to 8 °C. Infusion solution must be completely administered to the patient within 32 hours of preparation (not exceeding 24 hours at 2 to 8 °C and 8 hours at room temperature). In the event an IV infusion cannot be completed the same day, the remaining solution should be discarded.

For information on the formulation and handling of ocrelizumab, see the Ocrelizumab IB and Drug Preparation Guidelines.

4.3.2 Study Treatment Dosage, Administration, and Compliance

4.3.2.1 Ocrelizumab

Ocrelizumab will be administered as single 600-mg infusions in 500 mL 0.9% sodium chloride every 24 weeks ($\pm$ 14 days) up to Week 72 of this study. As a conventional infusion, a 600-mg dose ocrelizumab infusion should be given as a slow IV infusion over approximately 215 minutes (3.5 hours) and in accordance with the local label as applicable. In patients who did not experience a serious infusion-related reaction (IRR) with any previous conventional ocrelizumab infusion (~3.5 hours), the next 600 mg infusion can be administered as a shorter (~2 hours) infusion for subsequent doses, after providing written informed consent. The shorter infusion of 600mg ocrelizumab in 500ml 0.9% sodium chloride should be administered as follows: the infusion should be initiated at a rate of 100ml/hour for the first 15 minutes. The infusion rate can then be increased to 200ml/hour for the next 15 minutes and to 250ml/hour for the 30 minutes thereafter. The remainder of the infusion can be delivered at a rate of 300ml/hour for the remaining 60 minutes. The infusion should be completed in approximately 2 hours. See the most

recent version of the Ocrelizumab IB addendum and Drug Preparation Guidelines for detailed instructions on drug preparation, storage, and administration.

If patients develop a serious IRR while on the shorter infusion, they will be switched to the conventional infusion and should not be restarted on the shorter infusion at any following infusion visit.

Although ocrelizumab may be administered on an outpatient basis, patients may be hospitalized for observation at the discretion of the Investigator. Ocrelizumab infusions should be initiated and supervised by an experienced professional with access to appropriate medical support to manage severe reactions such as serious IRRs.

To reduce potential IRRs, all patients will receive prophylactic treatment with 100 mg intravenous methylprednisolone, or equivalent, administered by slow IV infusion, to be completed approximately 30 minutes and not less than 25 minutes prior to each ocrelizumab infusion and antihistamine, via oral, intramuscular or IV route to be completed approximately 30- 60 minutes and not less than 25 minutes prior to each infusion of ocrelizumab (the antihistamine should be the first premedication to be administered). The addition of an antipyretic (e.g., acetaminophen/paracetamol) may also be considered. Hypotension, as a symptom of IRR, may occur during ocrelizumab IV infusions. Therefore, withholding antihypertensive treatments should be considered for 12 hours prior to and throughout each ocrelizumab infusion.

Ocrelizumab must not be administered as an IV push or bolus. Well-adjusted infusion pumps should be used to control the infusion rate, and ocrelizumab should be infused through a dedicated line. It is important not to use evacuated glass containers, which require vented administration sets, to prepare the infusion because this causes foaming as air bubbles pass through the solution.

It is anticipated that the patient will need to stay at the hospital or clinic for a full day for the infusion visits. After completion of the infusion, the patient must be kept under observation for at least 1 hour. After completion of the infusion, the IV cannula should remain in situ for at least 1 hour to allow for administration of drugs intravenously, if necessary, in the event of a delayed reaction. If no adverse events occur during this period, the IV cannula may be removed, and the patient may be discharged.

See the Ocrelizumab IB and Drug Preparation Guidelines for detailed instructions on drug preparation, storage, and administration.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section [5.1.4](#).

An overdose or incorrect administration of ocrelizumab should be noted on the Study Drug Administration electronic case report form (eCRF). Adverse events

associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF.

4.3.3 Prophylactic Medication

The following premedications must be administered prior to each infusion of ocrelizumab to reduce the frequency and severity of IRRs:

- 100 mg intravenous methylprednisolone (or an equivalent), administered by slow IV infusion, to be completed approximately 30 minutes and not less than 25 minutes prior to each ocrelizumab infusion
- Antihistamine, via oral, intramuscular or IV route to be completed approximately 30–60 minutes and not less than 25 minutes prior to each ocrelizumab infusion (the antihistamine should be the first premedication to be administered)
- The addition of an antipyretic (e.g., acetaminophen/paracetamol) may also be considered.

Any overdose or incorrect administration of methylprednisolone should be noted on the Pre-Infusion Prophylactic Treatment eCRF. Adverse events associated with an overdose or incorrect administration of methylprednisolone should be recorded on the Adverse Event eCRF.

Patients administered a sedating antihistamine for the treatment or prevention of IRRs should be given appropriate warnings concerning drowsiness and potential impairment of ability to drive or operate machinery.

4.3.4 Investigational Medicinal Product Handling and Accountability

The IMP required for completion of this study (ocrelizumab) will be provided by the Sponsor where required by local health authority regulations. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) 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 interactive voice/web response system (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, either by time monitoring (shipment arrival date and time) or temperature monitoring, 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 will 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/or the ocrelizumab IB for information on IMP handling, including preparation and storage, and accountability.

4.3.5 Continued Access to Ocrelizumab

The Sponsor will offer continued access to Roche IMP (ocrelizumab) 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) after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition 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) 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 would not 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 RMS and PPMS
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for RMS and PPMS
- 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 Web site:

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 within 6 weeks prior to the screening visit to the study completion/ discontinuation visit. All such medications should be reported to the Investigator and recorded on the Previous and Concomitant Medications eCRF.

For this study ongoing concomitant medication from the parent study data is collected and to be reported on the Previous and Concomitant medications eCRF.

4.4.1 Prohibited Therapy

No formal drug-drug interaction studies have been conducted with ocrelizumab, as no drug-drug interactions are expected via the Cytochromes P450, other metabolizing enzymes or transporters.

Ocrelizumab is a monotherapy and has not been studied in combination with other DMTs. As with other immunomodulatory therapies, exercise caution when initiating ocrelizumab after an immunosuppressive therapy, and when initiating another therapy after ocrelizumab, taking into consideration the potential for overlapping pharmacodynamic effects.

Immunosuppressants, lymphocyte-depleting agents, or lymphocyte-trafficking blockers should NOT be administered while patient is B-cell depleted.

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

See the ocrelizumab IB for a more detailed safety profile. In addition, the Investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in [Appendix 1](#). All activities must be performed and documented for each patient.

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. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria and none of the exclusion criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Patients' demographics (age, gender, self-reported race, and educational level) will be collected. As medical history will be collected in the P-trial, it will not be recorded again.

4.5.3 Physical Examinations

A complete physical examination should include an evaluation of head, eye, ear, nose, and throat (HEENT), cardiovascular, dermatological, musculoskeletal, respiratory, and gastrointestinal systems. The following assessments will also be conducted: neurological examination (see Section 4.5.5), relapse description, EDSS (see Section 4.5.6), and MRI (see Section 4.5.7). Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities not related to MS should be recorded as adverse events on the Adverse Event eCRF. See [Appendix 1](#) (Schedule of Assessments) for the timing of these assessments.

4.5.4 Vital Signs

Vital signs will include measurements of heart rate, systolic and diastolic blood pressures, and temperature.

Vital signs should be taken within 45 minutes prior to the premedication methylprednisolone (or an equivalent) infusion and administration of antihistaminics. In addition, vital signs should be measured prior to the ocrelizumab infusion then every 15 minutes (± 5 minutes) for the first hour, followed by every 30 minutes (± 10 minutes) until 1 hour after the end of the infusion.

Vital sign measurements will be performed as outlined in the schedule of assessments (see [Appendix 1](#)). Record new or worsened clinically significant abnormalities on the adverse event eCRF (as presented in Section 5.3.5).

4.5.5 Neurological Examinations

Neurological examinations will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Potential relapses should be recorded throughout the treatment period. See [Appendix 1](#) (Schedule of Assessments) for the timing of these assessments.

A protocol-defined MS relapse is an occurrence of new or worsening neurological symptoms attributable to MS that meets the following criteria:

- Symptoms must persist for >24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reactions to medications).
- Symptoms should be preceded by neurological stability for at least 30 days.
- Symptoms should be accompanied by new objective neurological worsening determined with a timely EDSS/ Functional Systems Score (FSS) assessment, consistent with an increase of at least:
 - ≥ 0.5 points on EDSS scale.
 - or ≥ 2 points on one of the following FSS scales: pyramidal, ambulation, cerebellar, brainstem, sensory, or visual.
 - or ≥ 1 point on two or more of the following FSS scales: 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 (Please note: Sexual dysfunction and fatigue need not be scored).

All patients with new neurological symptoms suggestive of a relapse should have an EDSS/FSS assessment performed as soon as possible, ideally within 7 days of the onset of symptoms. EDSS/FSS data is needed to allow the sponsor to confirm whether the reported clinical relapse meets the criteria for a protocol-defined relapse.

Please note: All MS relapses (i.e., regardless of whether they may meet criteria for a protocol-defined relapse which will be adjudicated by the Sponsor based on the above criteria) will be recorded on a pre-specified eCRF “MS relapse” form. MS relapses should not be reported on Adverse Event eCRF, unless they are serious.

As infection is a potentially serious complication of B cell-depleting therapy, investigators will also screen patients for signs and symptoms of any CNS infections and specifically progressive multifocal leukoencephalopathy (PML) by evaluating neurological deficits localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, hemiparesis, cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination). Patients with suspected PML should be withheld from ocrelizumab treatment until PML is ruled out by complete clinical evaluation and appropriate diagnostic testing. A patient with confirmed PML should be withdrawn from the study. PML should be reported as a serious adverse event (with all available information) with immediate notification of the Medical Monitor. Please refer to [Appendix 4](#) for guidance for diagnosis of PML.

Cognitive status: The cognitive status of the patient will be evaluated at baseline, and further yearly for the full duration of the trial with the use of SDMT.

4.5.6 Assessment of Disability

Disability in MS will be measured by the EDSS. See [Appendix 1](#) (Schedule of Assessments) for the timing of these assessments.

The EDSS is based on a standard neurological examination, incorporating seven functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral) rated and scored as FSSs. Each FSS is an ordinal clinical rating scale ranging from 0 to 5 or 6. These ratings are then used in conjunction with observations and information concerning ambulation and use of assistive devices to determine the EDSS score (i.e., ambulation score 0 to 12). When determining the EDSS step, the Visual and the Bowel and Bladder FSS will be converted to a lower score as per the Neurostatus instructions. The original unconverted score should be recorded in the respective eCRF page. The EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10 (death) (see [Appendix 3](#)).

Disability progression has been defined as an increase of ≥ 1.0 point from the baseline EDSS score that is not attributable to another etiology (e.g., fever, concurrent illness, or concomitant medication) when the baseline score is 5.5 or less, and ≥ 0.5 when the baseline score is above 5.5. For patients with an EDSS of 0, progression is defined as a change ≥ 1.5 points. Disability progression is considered confirmed when the increase in the EDSS is confirmed at a regularly scheduled visit at least 24 weeks after the initial documentation of neurological worsening.

CDI is defined as an improvement of ≥ 1 point on the EDSS score confirmed at a regular scheduled visit at least 24 weeks after the initial documentation of neurological status when the baseline score is 5.5 or less, and ≥ 0.5 when the baseline score is above 5.5. The CDI is measured only patients with a baseline EDSS of ≥ 2.0). Stable disability is defined as a difference in EDSS score of no greater than ± 0.5 at the end of each year compared with baseline scores, worsened disability as an increase in EDSS score of > 0.5 at the end of each year compared with baseline, and improved disability as a reduction in EDSS score of > 0.5 at the end of each year compared with baseline.

The T25FWT (measure of lower limb function) and 9HPT (measure of upper limb function), which are components of multiple sclerosis functional composite (MSFC) will be used additionally to detect disability progression in MS patients. 9HPT and T25FWT are not applicable for patients rolling over from study MA30005.

4.5.7 Brain Magnetic Resonance Imaging

MRI will be used to monitor CNS lesions and potentially other pathophysiology, such as inflammation and neurodegeneration. Brain MRI scans will be obtained at study visits as shown in the Schedule of Assessments (see [Appendix 1](#)). The re-baseline MRI at week 24 is applicable only for patients who have consented to Protocol/Informed Consent Form v5.0 or lower.

MRI scans will be read and assessed by a centralized reading center for effectiveness endpoints. As soon as the scan is received by the central MRI reading center, it will be evaluated for quality, completeness and adherence to the protocol including effectiveness endpoints. Confirmation of acceptable MRI quality or a description of the quality problems, if detected, will be communicated to the site. If the MRI scan is incomplete or incorrectly performed, the study center might be asked to repeat it. After completion of the quality check, all scans will be analyzed according to the MRI protocol.

Investigators must comply with local country regulations for MRI repetition.

The final decision for the repetition of the MRI scans lies with the Investigator.

Further details on MRI acquisition (e.g. sequences, methods, handling, transmission of the data, and certification of site MRI scanners) are described in a separate MRI technical manual.

Assessments will include T1-weighted MRI before and after injection of contrast agent, and may also include, but may not be limited to: 2D/3D FLAIR, proton density-weighted, T2-weighted MRI, and diffusion weighted imaging (DWI). Additional assessments can also be performed on the scans acquired according to the study MRI technical manual. The total brain volume and the different white and grey matter structures will be measured over the full duration of the study and follow-up period.

All efforts should be made to obtain the brain MRI before the next ocrelizumab infusion and the scans should be reviewed locally for the presence of any non-MS pathology, including PML before the next infusion is administered.

If a patient receives corticosteroid treatment for an MS relapse, every effort should be made to obtain the MRI prior to the first steroid dose, if the pre-steroid MRI is within 1 week of the scheduled visit. In patients already receiving corticosteroids for an MS relapse, there should be an interval of at least 3 weeks between the last dose of corticosteroid and the MRI date.

4.5.8 Laboratory, Biomarker, and Other Biological Samples

All laboratory samples can be taken up to 2 weeks prior to the scheduled study visit. If laboratory results are required to confirm retreatment criteria, these need to be available prior to dosing.

Pre-infusion laboratory samples should be drawn so that routine laboratory test results are available for review before the infusion, unless otherwise specified.

- Routine laboratory assessments (performed in local laboratory and according to standard of care) will include the following: Hematology (hemoglobin, hematocrit, platelet count, red blood cell [RBC] count, white blood cell [WBC] count, percent

and/or absolute differential count [neutrophils, eosinophils, lymphocytes, monocytes, basophils]).

- Serum chemistries (AST, ALT, gamma-glutamyl transpeptidase [GGT], total bilirubin, creatinine).
- HBV DNA measured by PCR in patients with positive HBcAb
- Pregnancy test: At the screening visit, urine beta- human chorionic gonadotropin (hCG [sensitivity of at least 25 mIU/mL]) will be performed. On infusion visits, the urine pregnancy test should be performed prior to prophylactic medication in all women of childbearing potential. If positive, the patient will not receive the scheduled dose until a serum pregnancy test is performed for confirmation. If the serum pregnancy test is negative, the patient can receive the scheduled ocrelizumab dose. The follicle-stimulating hormone (FSH) test is only applicable to confirm postmenopausal status in female patients.
- Lymphocytes subtypes
 - Whole-blood samples will be collected to determine B-cell level (CD19⁺) and T-cell counts (CD4⁺, CD8⁺)
- Plasma NfL will be analyzed retrospectively in patients who participated in the CASTING/MA30005 study and whose unused John Cunningham virus (JCV) plasma samples were stored and are valid for plasma NfL analysis. Samples are currently stored in the central lab used in CASTING/ MA30005 study and NfL analysis will be performed in the same lab used in the ocrelizumab program.
- Patient who participated in the CASTING/ MA30005 study will be asked if they consent to give the left over plasma samples to the Research Biosample Repository (RBR).

4.5.9 Optional Samples for Research Biosample Repository

4.5.9.1 Overview of the Research Biosample Repository

The 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, already collected in the CASTING/ MA30005 study will be analyzed for CASTING/ MA30005 study patients participating in this study, 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

4.5.9.2 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 4.5.9) will not be applicable at that site.

4.5.9.3 Sample Collection

There is no new sample collected in this study for the RBR.

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

- Leftover (unused) anti-JCV Abs plasma samples already collected in CASTING/MA30005 study as per schedule of assessments and any derivatives thereof (e.g., DNA, RNA, proteins, peptides) currently stored in the Central Lab.

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).

4.5.9.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number of the CASTING/MA30005 study.

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.

4.5.9.5 Consent to Participate in the Research Biosample Repository

A separate Informed Consent Form will address participation in the RBR which is optional and only applicable to CASTING/MA30005 study patients participating in this study. 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.

4.5.9.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples for this optional research 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.

4.5.9.7 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.

4.5.10 Patient-Reported Outcomes

The MSIS-29 version 2 is the second version of 29-item questionnaire designed to measure the physical and psychological impact of MS from the patient's perspective ([Hobart et al. 2001](#)). Each question is scored on the scale of 1-4. The physical (20 items) and psychological (9 items) scales are scored separately. Scores are transformed into a 0-100 scale with higher scores indicating a greater degree of disability or impact of MS on the daily life of the patient.

The SymptoMScreen is a composite score based upon a battery of seven-point Likert scales for 11 distinct domains commonly affected by MS: mobility, dexterity, vision, fatigue, cognition, bladder function, sensation, spasticity, body pain, depression and anxiety. Total score (0-66) and subscale scores are assessed over the study duration ([Green et al. 2017](#)). Higher scores indicate greater severity of symptoms

The Employment Status WPAI is a questionnaire that assesses working status and the impact of MS on absenteeism, presentism and the ability to perform regular activities.

Please refer to [Appendix 5](#) for a sample copy of the PROs.

The PRO instruments, translated as required in the local language, will be distributed by the investigator staff and completed in their entirety by the patient. To ensure instrument validity and that data standards meet health authority requirements, PRO questionnaires should be self-administered at the investigator site prior to the completion of other study assessments and the administration of study drug. Patients must complete these measures prior to the patient having any tests and prior to any discussion of the patient's progress with their physician or any other healthcare personnel at the site. The recommended order of administration is first the SymptoMScreen followed by MSIS-29 and finally WPAI. PRO assessments will be performed as outlined in the schedule of assessments (see [Appendix 1](#)).

4.5.11 SDMT

The aim of SDMT testing is to detect impairment of key neurocognitive functions that underlie many substitution tasks, including sustained attention, visual scanning, and recent memory. The test consists of a sequence of 110 symbols to be displayed in a maximum 90 seconds and a reference key legend (3 versions are available) with 9 symbols in a given order and their respective matching digits from 1 to 9. This test measures the speed (number of correct paired responses) to pair abstract symbols with specific digits in 90 seconds time ([SDMT manual](#)).

The SDMT should be administered only after the patient has completed all PRO assessments. The SDMT will be scored centrally by a global reader and the results will be provided to the sites.

4.5.12 Patient Diary (optional)

Due to the low frequency of study visits (every 6 months), patient diaries are proposed as an additional optional tool to help further improve the collection and documentation of adverse events and concomitant medications. The decision to use the patient diary is left to the discretion of each investigator. The investigator must ensure that required EC/IRB approval was obtained before implementing the patient diary at his/her site.

Additional instructions around the use of an optional Patient Diary are provided in [Appendix 7](#).

4.5.13 Analysis of immune responses following SARS-CoV-2 vaccination (optional procedure)

This optional procedure is applicable to only selected sites that allow the expedited processing of blood samples to central laboratories that are confirmed processing centers for this sample, as identified by study sponsor feasibility assessment.

The Informed Consent Form will contain a separate section that addresses this optional procedure. A separate, specific signature will be required to document a patient's agreement to undergo the described optional procedure.

Samples for SARS-CoV-2 vaccine immunological assessments

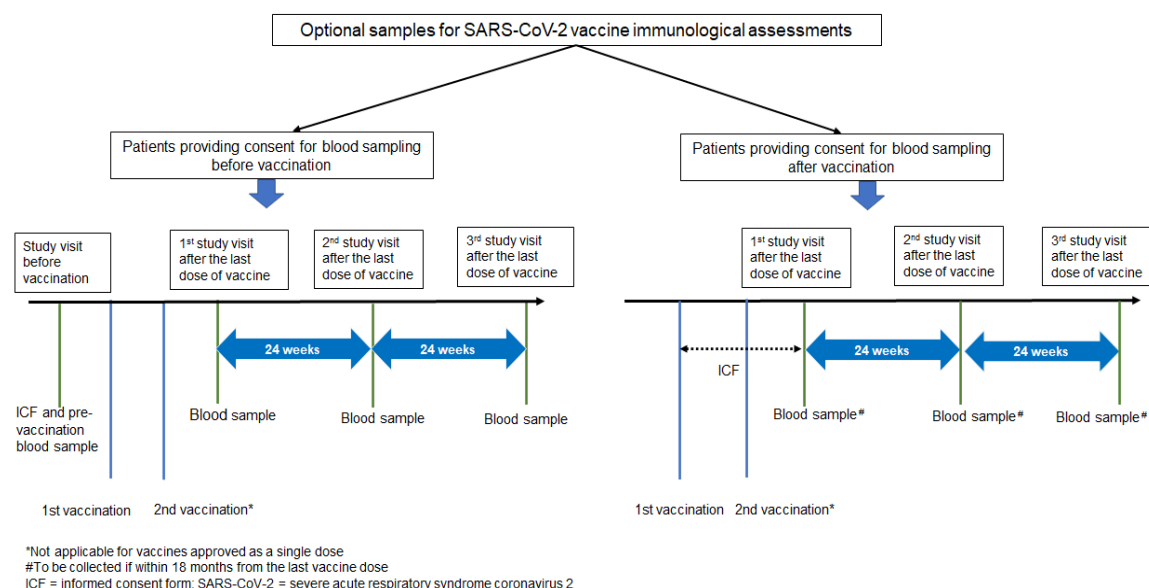
- Patients who receive the SARS-CoV-2 vaccine and who consent to provide the blood samples before the vaccination has occurred: the analyses of anti-SARS-CoV-2 antibody titers and T cell responses will be performed at maximum four time points: (1) at the study visit when the patient signs an optional informed consent form, prior to the administration of the vaccine, (2) at the next consecutive study visit(s) to a maximum of three visits following the last dose of vaccine. Please see [Figure 3](#) for details.
- Patients who receive the SARS-CoV-2 vaccine and who consent to provide the blood samples after the vaccination has occurred: the analyses of anti-SARS-CoV-2 antibody titers and T cell responses will be performed at the next consecutive study visit(s) to a maximum of three visits after patient provided

consent and following the last dose of the vaccine. Please see [Figure 3](#) for details.

- A serum sample will be collected to evaluate the humoral immunity, including antibody titers. A whole blood sample will be collected and then processed centrally to allow for isolation of peripheral blood mononuclear cells (PBMCs) and to measure SARS-CoV-2 antigen-specific T cell responses. Samples collected on the day of the ocrelizumab infusion must be collected prior to the IV methylprednisolone administration.
- The study sponsor will terminate the collection of blood samples for this optional research when it is considered that enough interpretable data has been collected.

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

Figure 3 Overview of Sample Collection for SARS-CoV-2 Vaccine Immunological Assessments for Optional Procedure



ICF = Informed consent form; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Pregnancy: patients becoming pregnant during the study will be withheld from ocrelizumab treatment but will remain in trial and will have the opportunity to re-start the treatment after birth and breastfeeding are over. During pregnancy and breastfeeding, these patients will continue to come for the regular scheduled

visits (whenever possible, adhering to the time of scheduled visits as per protocol) and will perform all assessments except MRI. The total duration of treatment period will be 96 weeks from the enrollment, irrespective of how long the treatment was interrupted due to pregnancy. For patients who had treatment interrupted due to pregnancy at the time of their rollover from the parent study, the total duration on treatment will not extend the total duration in the parent study and this extension study.

- Patients who became pregnant by chance between the last visit of the parent study and screening of this study, as confirmed by pregnancy tests at screening, will enter the safety follow-up immediately and re-start the treatment after birth and breastfeeding are over. The total duration of treatment period will be 96 weeks from the enrollment, irrespective of how long the treatment was interrupted due to pregnancy. For patients who had treatment interrupted due to pregnancy at the time of their rollover from the parent study, the total duration on treatment will not extend the total duration in the parent study and this extension study.
- Patients who plan to become pregnant during the study will be withheld from ocrelizumab treatment and will follow the recommendations for contraception period after the last infusion with ocrelizumab for at least 6 months or longer in accordance with locally applicable ocrelizumab package leaflet. Upon discontinuation of study treatment, these patients will enter the safety follow-up period but will not re-start the study treatment.
- Life-threatening (NCI CTCAE Grade 4) IRR or serious hypersensitivity reaction.
- New onset or reactivation of HBV infection
- PML.
- Any other serious adverse event, including laboratory values abnormalities, that present an unfavorable benefit-risk of treatment with ocrelizumab as deemed by the investigator.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patient discontinuing the study treatment prematurely will be further monitored in a safety follow-up (see Section 3.1.4).

Patients who discontinue study treatment prematurely will not be replaced.

Should this occur, it has to be ensured that the early treatment discontinuation assessments are performed per [Appendix 1](#) for each patient.

Refer to the schedule of activities (see [Appendix 1](#)) for details on follow-up assessments to be performed for patients who permanently discontinue study treatment.

4.6.2 Patient Discontinuation from Study

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 follow dosing instructions or to complete study visits.

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. Patients who withdraw from the study will not be replaced.

Should this occur, every effort should be made to complete the early treatment discontinuation assessments for each patient per [Appendix 1](#).

4.6.3 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
- Ocrelizumab is commercially available and reimbursed in a treating country

Whenever needed, the Investigator should reassess and discuss with the patient the benefits and risks of continuing with ocrelizumab treatment, and should, together with the patient, explore also alternative treatment options.

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

Should this occur, it has to be ensured that the early treatment discontinuation assessments are performed per [Appendix 1](#) for each patient.

4.6.4 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:

- 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)

Should this occur, every effort should be made to complete the early treatment discontinuation assessments for each patient per [Appendix 1](#).

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Ocrelizumab has been recently approved for the treatment of adult patients with relapsing or primary progressive forms of MS in several countries and regions including Australia/New Zealand, Europe, Middle East, South America and the USA and for the treatment of adult patients in relapsing form of MS in Canada. Identified and potential risks associated with ocrelizumab treatment will continue to be closely monitored throughout the clinical program. Patient safety during the ocrelizumab program is ensured by targeting the most appropriate patient population, stringent safety monitoring by the Sponsor, and protocol-specified ocrelizumab treatment interruption criteria. Patients will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, and standard laboratory measurements. Adverse events will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Administration of ocrelizumab will be performed in a hospital, clinic environment or doctor's office/practice under close supervision of the Investigator or a medically qualified staff member with immediate availability of full resuscitation facilities. All adverse events and serious adverse events will be recorded during the study and at 24 and at least 48 weeks (or until B-cell repletion) after the last dose of ocrelizumab as provided through this study. Safety assessments will include the incidence, nature, and severity of (serious) adverse events graded per the NCI CTCAE v5.0. Safety assessments will be conducted per the schedule of assessments in [Appendix 1](#).

The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize these issues, are outlined in the following sections.

5.1.1 Risks Associated with corticosteroids

The adverse reactions of corticosteroids may result from unwanted glucocorticoid actions, or from inhibition of the hypothalamic-pituitary-adrenal axis. Please refer to local Prescribing Information.

5.1.2 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. Please refer to local Prescribing Information.

5.1.3 Risks Associated with Ocrelizumab

5.1.3.1 Identified Risks and Adverse Drug Reactions

Infusion-Related Reactions

All CD20+ cell-depleting agents administered via the intravenous route, including ocrelizumab have been associated with acute IRRs. Following the approved administration regimen (which includes the use of premedication prior to treatment with ocrelizumab in order to reduce frequency and severity of IRRs), symptoms of IRRs may occur during any ocrelizumab infusion but have been more frequently reported during the first infusion. Physicians should alert patients that IRRs can occur within 24 hours of the infusion. 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 should be observed for at least one hour after the completion of the infusion for any symptom of IRR. They 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 ocrelizumab infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each ocrelizumab infusion.

Alternative Shorter Infusion of Subsequent Doses

In a study (MA30143, ENSEMBLE Plus) designed to characterize the safety profile of shorter ocrelizumab infusions in patients with RRMS, no differences were found in the frequency and severity of IRRs associated with shorter (2-hour) infusions compared with longer (3.5-hour) conventional infusions. For further details, refer to the current version of the IB.

Infections

Infection is an identified risk associated with ocrelizumab treatment, predominantly involving mild to moderate respiratory tract infections. Non-disseminated herpes virus-associated infections, mostly mild to moderate, were also reported more frequently with ocrelizumab (approximately 5 to 6%, herpes simplex and zoster) than with comparators (approximately 3%).

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

Serious, opportunistic and fatal infections have occurred in patients with lupus and rheumatoid arthritis (RA) treated with ocrelizumab in Phase III clinical trials. Data from completed studies regarding infection risks with ocrelizumab treatment in these patient populations are provided in the Ocrelizumab IB.

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

In interventional clinical studies, there were no reports of hepatitis B reactivation in MS patients treated with ocrelizumab, but it had been reported in one RA patient treated with ocrelizumab. 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. Please refer to the SmPC.

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

For PML see “Potential risks” below.

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 LLN increased over time and with successive dosing. Based on additional patient exposure, in cases of continuous decrease over time, a higher risk of SI cannot be ruled out.

Serious infections related to decrease in immunoglobulins (particularly in patients previously exposed to immunosuppressive/immunomodulatory drugs or with pre-existing hypogammaglobulinemia)

Based on additional patient exposure an apparent association between decrease in immunoglobulins and SIs with ocrelizumab treatment was observed and was most apparent for IgG. There was no difference in the pattern (type, latency, duration, outcome) of the SIs reported in this subset of patients compared to the overall SIs profile. In addition, risk factors for a subset of patients at higher risk of SIs 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 time-point 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, indicates that the median time to repletion (returned to baseline/LLN whichever occurred first) of B-cells was 72 weeks (range 27–175 weeks).

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 relapsing multiple sclerosis (RMS) raise adequate 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 IB. 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.

5.1.3.2 Potential Risks

Progressive multifocal leukoencephalopathy (PML)

PML is an important potential risk for ocrelizumab and it has been reported in patients receiving ocrelizumab but only in patients where other contributory factors were present, such as prior immunosuppressive treatment (for example, natalizumab or fingolimod). 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, confirmatory CSF testing for JCV DNA and repeat neurological assessments, should be considered. If PML is confirmed, ocrelizumab must be discontinued permanently. Please refer to [Appendix 4](#) for guidance for diagnosis of PML. Please see the IB for more details.

Hypersensitivity Reactions

Hypersensitivity may be difficult to distinguish from IRRs in terms of symptoms. A hypersensitivity reaction may present during any infusion, although typically would not present during the first infusion. For subsequent infusions, 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 infusion must be stopped immediately and permanently. Patients with known IgE-mediated hypersensitivity to ocrelizumab must not be treated.

Malignancies including Breast Cancer

Patients should follow standard breast cancer screening guidelines. Please see the IB for more details.

For US only: An increased risk of malignancy with OCREVUS may exist. In controlled trials in multiple sclerosis, malignancies, including breast cancer, occurred more frequently in OCREVUS-treated patients. Breast cancer occurred in 6 of 781 females treated with OCREVUS and none of 668 females treated with REBIF or placebo.

Neutropenia

In the controlled treatment period, decreased neutrophils were observed in 12 and 15% of MS patients 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, as association between neutropenia and SIs with ocrelizumab treatment was not observed. Additional information can be found in the current IB.

5.1.4 Management of Patients Who Experience Specific Adverse Events

Guidelines for management of specific adverse events are outlined in [Table 2](#). Additional guidelines are provided in the subsections below.

Table 2 Guidelines for Management of Specific Adverse Events

Event	Action to Be Taken
Mild to moderate IRR	• If the event that a patient experience is a mild to moderate IRR (e.g. headache), the infusion rate should be reduced to half the rate at the time of the event • This reduced rate should be maintained for at least 30 minutes. If tolerated, the infusion rate may then be increased according to the patient's initial infusion schedule
Severe IRR (or complex of flushing, fever, and throat pain)	• If a patient experiences a severe IRR or a complex of flushing, fever, and throat pain symptoms, the infusion should be interrupted immediately, and the patient should receive symptomatic treatment • The infusion should be re-started only after all symptoms have resolved • The initial infusion rate at restart should be half of the infusion rate at the time of onset of the reaction

Table 2 Guidelines for Management of Specific Adverse Events (cont.)

Event	Action to Be Taken
Life-threatening or disabling IRR (e.g., anaphylaxis)	• Immediately stop ocrelizumab if there are signs of a life-threatening or disabling IRR during an infusion, such as acute hypersensitivity or acute respiratory distress syndrome • The patient should receive appropriate treatment • Permanently discontinue ocrelizumab in these patients

hr=hour; IRR=infusion-related reaction

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse event 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 Sections [5.3.5.9](#) and [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 include the following:

- 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 5.2.1 for definition) are recorded on the adverse event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4, Section 5.5 and Section 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.

Adverse events that have occurred after the end of the reporting period in the parent study and before initiation of the study drug in this study have to be reported in this long-term extension study.

After initiation of study drug, all adverse events will be reported until up to 48 weeks after the last 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 time points. 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 3 will be used for assessing severity for IRRs and adverse events that are not specifically listed in the NCI CTCAE.

Table 3 Adverse Event Severity Grading Scale for IRRs and Other 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 4):

- 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 4 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	<u>An adverse event will be considered related, unless it fulfills the criteria specified below.</u> 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.

In this study data will be collected on ongoing Adverse Events from the parent study which were ongoing when the subject entered this study. Same applies to serious MS relapse events ongoing from the parent study.

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., “infusion-related 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 eCRF. If a patient experience both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded separately on the adverse event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF. Please consider reporting a local IRR for any symptoms affecting only the skin and localized to only one place.

5.3.5.2 Diagnosis versus Signs and Symptoms

For all adverse events, 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 time points. 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 time points 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 $5 \times$ Upper limit of normal (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 (e.g., 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 ($>3 \times \text{ULN}$) in combination with either an elevated total bilirubin ($>2 \times \text{ULN}$) 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 $>3 \times \text{ULN}$ in combination with total bilirubin $>2 \times \text{ULN}$.
- Treatment-emergent ALT or AST $>3 \times \text{ULN}$ 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 events 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 PMS, “PMS 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 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

Deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature (i.e., deterioration beyond the expected pattern of progression of the underlying disease) 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”). Events that are clearly consistent with the expected pattern of progression of the underlying disease, or other MS-related symptoms, should not be recorded as adverse events. These data will be captured as effectiveness assessment data only. In most cases, the expected pattern of progression will be based on EDSS score. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

Occasional isolated symptoms that according to the investigator are caused by MS, but do not constitute a full MS relapse, should be reported as an adverse event, with the causality “Disease under study” (see Section 5.3.4).

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:

- Hospitalization for respite care
- Elective hospitalizations or surgical procedures that are a result of a patient's pre-existing 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 in the "Surgeries and Procedures" eCRF.

- Hospitalization following an MS relapse as long as the reason for hospitalization is to receive standard treatment with i.v. methylprednisolone (or with another equivalent corticosteroid)
- Planned hospitalization required by the protocol (e.g., for study drug administration).
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
 - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.
 - The patient has not experienced an adverse event.

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.

Adverse events associated with an overdose of ocrelizumab in previous clinical studies include IRRs and infection.

5.3.5.13 Patient-Reported Outcome Data

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

Please note that the methods for collecting and analyzing PRO data are different from those for the ascertainment of observed or volunteered adverse events. Due to these differences, PRO data will not be reported as adverse events and no attempt will be made to resolve any noticeable discrepancies between PRO data and observed or volunteered adverse events.

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 for these events 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

Contact Information for {site location}

Medical Monitor{/Emergency Medical Contact}: [REDACTED]

Mobile Telephone No.: [REDACTED]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week in case the above-listed contacts cannot be reached. 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 toll-free numbers for the Emergency Medical Call Center, will be distributed to 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

Adverse events that have occurred after the end of the reporting period in the parent study and before the initiation of the study drug in this study have to be reported in this long-term extension study. The serious adverse event/ adverse events 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 event and adverse events of special interest will be reported until 48 weeks after the last 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 events 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.

Unrelated serious adverse events must be collected and reported during the study through the end of the safety follow-up period, which is at least 48 weeks after the last infusion. Non-serious adverse event has to be reported until the end of safety follow-up.

Instructions for reporting serious adverse events that occur 48 weeks after the last dose of study drug 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 must withhold study drug for the duration of pregnancy and breastfeeding 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 event 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 about child health up to 1 year should be collected on the infant health questionnaire (see [Appendix 6](#)).

Pregnancy: patients becoming pregnant during the study will be withheld from ocrelizumab treatment but will remain in trial (patients will come at the clinic for the scheduled visits [wherever possible, adhering to the time of scheduled visits as per protocol] and will perform all assessments except MRI) and will have the opportunity to re-start the treatment after birth and breastfeeding are over. The total duration of treatment period will be 96 weeks from enrollment, irrespective of how long the treatment was interrupted due to pregnancy. For patients who had treatment interrupted due to pregnancy at the time of their rollover from the parent study, the total duration on treatment will not extend the total duration in the parent study and this extension study. Patients who became pregnant by chance between the last visit of the parent study and screening of this study, as confirmed by pregnancy tests at screening, will enter the safety follow-up immediately and re-start the treatment after birth and breastfeeding are over. Patients who plan to become pregnant during the study will be withheld from ocrelizumab treatment and will follow the recommendations for contraception period after the last infusion with ocrelizumab for at least 6 months or longer in accordance with locally applicable ocrelizumab package leaflet. Upon discontinuation of study treatment, these patients will enter the safety follow-up period but will not re-start the study treatment.

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 event 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 with a Pregnancy Outcome and Infant Health Information on First Year of life questionnaire provided by the sponsor (see [Appendix 6](#)).

5.5.2 Sponsor Follow-Up

For serious adverse event, 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 up to 48 weeks after the last dose of study drug), if the event is believed to be related to prior exposure to study drug. 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 events 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 event and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, 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 using the reference safety information in the following document:

- Ocrelizumab IB

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.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The analysis of this open label, single arm Extension study will be exploratory and primarily based on descriptive statistical methods. Statistical tests will be used for exploratory purposes and, unless otherwise specified, performed at the 5% significance level. Corresponding 95% CIs will be presented as appropriate. No correction for multiple testing will be applied.

Full details of all statistical aspects and planned statistical analyses will be specified in a separate Statistical Analysis Plan (SAP), which will be finalized prior to the locking of the study database and may include further exploratory analyses not explicitly described in this section, as well as analyses of data from the safety follow-up.

Analysis populations

The primary effectiveness and safety analyses will be performed using the intent-to-treat (ITT) population, which will include all enrolled patients who received any dose of ocrelizumab will be included in the ITT population. Patients who prematurely withdrew from the study for any reason will still be included in the ITT population.

6.1 DETERMINATION OF SAMPLE SIZE

This is an extension study of ocrelizumab where patients will be enrolled from qualifying P-trials. The final sample size will depend on factors such as the number of participating sites and the number of eligible patients from the respective P-trials. Therefore, no formal determination of sample size was performed.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, screening failures, ocrelizumab administration, and discontinuations from the study will be summarized using descriptive statistics (frequency tables for categorical endpoints and mean, median, range, standard, deviation [SD] and 25th-75th quartiles for the continuous endpoints). Patient disposition and the incidence of treatment discontinuation for different reasons will be tabulated. Major protocol violations, including violations of inclusion/exclusion criteria, will also be summarized.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Patients' demographics (age, gender, and self-reported race) will be summarized.

6.4 EFFECTIVENESS ANALYSES

6.4.1 Effectiveness Endpoints

Effectiveness of ocrelizumab will be evaluated by means of a set of endpoints addressing different facets of MS. There is no primary endpoint defined in this study. The effectiveness endpoints include time to onset of confirmed CDP sustained for at least 24 and for at least 48 weeks, proportion of patients who have CDI, CDP for at least 24 and for at least 48 weeks, change from baseline in EDSS score over time of the parent study and this extension study, relapse rates, MRI-based measures of disease activity and progression or degeneration, measures of cognition, and PROs.

For a full list of effectiveness endpoints refer to Section 2.

The last 48-week and 24-week CDP/CDI confirmatory assessments will be performed at the End of Treatment visit (week 96). The primary study analysis will be performed in subpopulations of the P-trials after the last patient from the corresponding P-trial completes the last (End of Treatment) visit in this MN39158/LIBERTO study.

The evaluation of the clinical effectiveness of ocrelizumab will be based upon the events and assessments in-between baseline (start of parent study) and end of Treatment period visit.

A descriptive analysis based on the Kaplan-Meier method will be performed for the time to CDP and other time-to-event endpoints, such as the time to first relapse or the time to first event of disease activity. Cox proportional hazards regression will be used to identify predictors for CDP and other time-to-event endpoints. Variables to be included in the regression model will be P-trial, region, gender, baseline EDSS, and some other variables, as appropriate. Further details will be specified in the SAP.

The change from baseline in EDSS, as well as other continuous variables, will be primarily analyzed using descriptive statistics, the mean, corresponding 95% CI, standard deviation and other statistics will be presented. Furthermore, the change of EDSS from baseline to each visit will be analyzed based on statistical models such as linear mixed models for repeated measures (MMRM) adjusting for covariates such as the respective baseline score, P-trial, geographical region, and baseline EDSS.

For binary endpoints, e.g., NEP, NEDA and NEPAD, the proportion of patients meeting the endpoint at each visit will be calculated and the corresponding two-sided Clopper-Pearson 95% CI will be presented. Logistic regression models will be used to identify prognostic factors.

The annualized relapse rates will be analyzed using a Poisson regression model, adjusting for P-trial, region and baseline EDSS. The total number of T1 Gd-enhanced lesions will be calculated as the sum of the individual number of T1 Gd-enhanced lesions at each visit. The same approach will be applied to FLAIR late enhancing

lesions. A Poisson model will be used to estimate the rate of lesion occurrence. A quasi Poisson or negative binomial regression may be applied as a sensitivity analysis. Exploratory analysis on the correlation between some MRI endpoints may be performed. Details will be specified in the SAP.

An analysis of individual components of the composite endpoint will also be performed.

6.5 SAFETY ANALYSES

6.5.1 Safety Outcome Measures

The safety outcome measures comprise the following: the incidence and nature of all adverse events, including findings on vital sign measurements, neurological examinations, clinical laboratory tests, locally reviewed MRI for safety (non-MS CNS pathology), and concomitant medications.

6.5.2 Safety Analyses

Safety will be assessed through summaries of adverse events (including rates/incidence rates and corresponding 95% CIs) and clinical laboratory abnormalities.

6.6 OTHER ANALYSES

Other information, including exploratory immunology analyses of SARS-CoV-2 antibody titers and SARS-CoV-2 T cell responses will be analyzed as appropriate and details will be specified in a separate biomarker SAP.

6.7 SUBGROUP ANALYSIS

Details of subgroup analyses will be presented in the SAP.

6.8 HANDLING OF MISSING DATA

Details about the handling of missing data will be specified in the SAP.

6.9 INTERIM ANALYSIS

No formal confirmatory effectiveness or safety interim analyses are planned. Exploratory interim analyses of selected endpoints, and in particular periodic analyses of safety data are planned to be performed during the course of the study.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

A contract research organization (CRO) 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 CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will perform oversight of the data management of this study. The CRO will produce eCRF Specifications for the study based on Sponsor's templates including quality checking to be performed on the data. Central imaging review 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 at 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 PRO questionnaires will be entered into the EDC system by site staff. SDMT data will be scored by a central reader and will be sent directly to the Sponsor using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

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 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 7.5.

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.

7.4 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.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, PRO data, Informed Consent Forms, laboratory test results, medication inventory records, and images, 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 US or under a U.S. Investigational New Drug (IND) application will comply with U.S. Food and drug administration (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) 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 a Child's Informed 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) to communicate information that might affect a patient's willingness to continue 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 US, 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 9.7).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse event 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

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.

The aggregate results of any conducted research will be available in accordance with the effective Roche 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 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. Prior to study initiation, 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 prior to study initiation. 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 by Roche and will be managed by Roche and CROs. CROs will provide clinical operations management, data management, biostatistics, and medical monitoring.

An IxRS will be used to assign patient numbers, monitor enrollment and patient status, and to manage study treatment requests and study drug shipments.

Patient data will be recorded via an EDC system using eCRFs.

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, both at scientific congresses 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 other summary 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 Web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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 (e.g., change in Medical Monitor or contact information).

10. REFERENCES

- Anderson DW, Ellenberg JH, Leventhal CM, et al. Revised estimate of the prevalence of multiple sclerosis in the United States. *Ann Neurol* 1992;31:333–6.
- Axelsson M, Malmeström C, Gunnarsson M, et al. Immunosuppressive therapy reduces axonal damage in progressive multiple sclerosis. *Mult Scler* 2014;20:43–50.
- Berger JR et al. PML diagnostic criteria: consensus statement from the AAN Neuroinfectious Disease Section. *Neurology*. 2013;80:1430–8.
- Burman J, Zetterberg H, Fransson M, et al. Assessing tissue damage in multiple sclerosis: a biomarker approach. *Acta Neurol Scand* 2014;130:81–89.
- Calabrese LH, Molloy ES, Huang D, et al. Progressive multifocal leukoencephalopathy in rheumatic diseases. *Arthritis Rheum* 2007;56(7):2116–28.
- Clinical Study Report for WA21493: Phase II, multicenter, randomized, parallel-group, partially blinded, placebo and Avonex® controlled dose finding study to evaluate the efficacy as measured by brain MRI lesions, and safety of 2 dose regimens of ocrelizumab in patients with RRMS. Report No. 1034917, November 2012.
- Clinical Trial Facilitation Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials. 2014. Available at: https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf. Accessed 5 March 2021.
- Confavreux C, Vukusic S, Moreau T, et al. Relapses and progression of disability on Multiple Sclerosis. *N Engl J Med* 2000;343:1430–8.
- Confavreux C and Vukusic S. Age at disability milestones in multiple sclerosis. *Brain* 2006;129:595–605.
- Confavreux C, Vukusic S, and Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. *Brain* 2003;126:770–82.
- DiLillo DJ, Hamaguchi Y, Ueda Y, et al. Maintenance of long-lived plasma cells and serological memory despite mature and memory B-cell depletion during CD20 immunotherapy in mice. *J Immunol* 2008;180:361–71.
- DiSanto G, Barro C, Benkert P, et al. Serum Neurofilament light: A biomarker of neuronal damage in multiple sclerosis. *Ann Neurol* 2017;81(6):857–70.
- Gray O and Butzkueven H. Measurement of disability in multiple sclerosis. *Neurology Asia* 2008;13:153–56.
- Green R, Kalina J, Ford R, et al. Symptomscreen: a tool for rapid assessment of symptom severity in MS across multiple domains. *Appl Neuropsychol Adult*. 2017;24(2):183–89.

- Goodin DS. The epidemiology of multiple sclerosis: insights to disease pathogenesis. *Handb Clin Neurol* 2014;122:231–66.
- Gunnarsson M, Mameström C, Axelsson M, et al. Axonal damage in relapsing multiple sclerosis is markedly reduced by natalizumab. *Ann Neurol* 2011;69:83–89.
- Hauser SL et al. Abstract O190. Presented at: The European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) Congress; Oct. 7–10, 2015; Barcelona.
- Hobart J, Lamping D, Fitzpatrick R, et al. The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. *Brain* 2001;124(5):962–73.
- https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761053lbl.pdf (Accessed on 10 May 2017)
- https://www.neurostatus.net/media/specimen/Definitions_0410-2_s.pdf (Accessed on 15 May 2017)
- Jacobs LD, Cookfair DL, Rudick RA, et al. The Multiple Sclerosis Collaborative Research Group (MSCRG). Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. *Ann Neurol*. 1996;39(3):285–94.
- Kappos L, Bates D, Hartung HP, et al. Natalizumab treatment for multiple sclerosis: recommendations for patient selection and monitoring. *Lancet Neurol* 2007;6(5):431–41
- Kappos L, Li D, Calabresi PA, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicenter trial. *Lancet* 2011;378:1779–87
- Klein C, Lammens A, Schafer W, et al. Epitope interactions of monoclonal antibodies targeting CD20 and their relationship to functional properties. *Mabs* 2013;5:22–33.
- Koch M, Mostert J, Heersema D, et al. Progression in multiple sclerosis: further evidence of an age-dependent process. *J Neurol Sci* 2007;255:35–41.
- Kuhle J, Kropshofer H, Haering DA, et al. Blood neurofilament light chain as a biomarker of MS disease activity and treatment response. *Neurology* 2019;92(10):e1007–15.
- Lavery AM, Verhey LH and Waldman AT. Outcome Measures in Relapsing-Remitting Multiple Sclerosis: Capturing Disability and Disease Progression in Clinical Trials. *Multiple Sclerosis International* 2014; Article ID 262350.
- Leray E, Vukusic C, Debouverie M, et al. Excess mortality in patients with Multiple Sclerosis starts at 20 years from clinical onset: Data from a large-Scale French observational study. *PloS ONE* 2015;10(7): e0132033.
- Loken MR, Shah VO, Dattilio KL, et al. Flow cytometric analysis of human bone marrow. II. Normal B lymphocyte development. *Blood* 1987; 70:1316–24.

- Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis. The 2013 revisions *Neurology* 2014;83(3):278–86.
- Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: Results of an international survey. *Neurology* 1996;46(4):907–11.
- Martin F, Chan AC. B-cell immunobiology in disease: evolving concepts from the clinic. *Annu Rev Immunol* 2006;24:467–96.
- Montalban X, Hemmer B, Rammohan K, et al. Efficacy and safety of ocrelizumab in primary progressive multiple sclerosis – results of the placebo-controlled, double-blind, Phase III ORATORIO study. Abstract O228. Presented at: The European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) Congress; Oct. 7–10, 2015; Barcelona.
- NCT01194570. A study of ocrelizumab in patients with primary progressive multiple sclerosis.
<https://clinicaltrials.gov/ct2/show/NCT01194570?term=NCT01194570&rank=1>. Accessed 15 December 2016.
- NCT01247324. A study of ocrelizumab in comparison with interferon beta-1a (Rebif) in participants with relapsing multiple sclerosis.
<https://clinicaltrials.gov/ct2/show/NCT01247324?term=NCT01247324&rank=1>. Accessed 3 April 2017.
- NCT01412333. A study of ocrelizumab in comparison with interferon beta-1a (Rebif) in participants with relapsing multiple sclerosis.
<https://clinicaltrials.gov/ct2/show/NCT01412333?term=NCT01412333&rank=1>. Accessed 3 April 2017.
- Noonan CW, Kathman SJ, White MC. Prevalence estimates for MS in the United States and evidence of an increasing trend for women. *Neurology* 2002;58:136–38.
- Rio J, Comabella M, Montalban X. Multiple sclerosis: current treatment algorithms. *Curr Opin Neurol* 2011;24:230-7.
- Scafari A, Neuhaus A, Daumer M, et al. Age and disability accumulation in multiple sclerosis. *Neurology* 2011;77:1246–52.
- SDMT manual. <http://www.wpspublish.com/store/p/2955/symbol-digit-modalities-test-sdmt>. Accessed 20 November 2017
- Siger M, Durko A, Nicpan A, et al. Discontinuation of interferon beta therapy in multiple sclerosis patients with high pre-treatment disease activity leads to prompt return to previous disease activity. *J Neurol Sci* 2011;303:50-2.
- Stashenko P, Nadler LM, Hardy R, et al. Characterization of a human B lymphocyte-specific antigen. *J Immunol* 1980;125:1678–85.
- Tanasescu R, Ionete C, Chou I, et al. Advances in the treatment of relapsing-remitting multiple sclerosis. *Biomed J* 2014;37:41–9.

- Tedder TF, Engel P. CD20: a regulator of cell-cycle progression of B lymphocytes. *Immunol Today* 1994;15:450–4.
- Tullman MJ. A review of current and emerging therapeutic strategies in multiple sclerosis. *Am J Manag Care* 2013;19(2 Suppl):S21–7.
- Tutuncu M, Tang J, Zeid NA, et al. Onset of progressive phase is an age-dependent clinical milestone in multiple sclerosis. *Mult Scler* 2013;19:188–98.
- Wiendl H and Meuth SG. Pharmacological Approaches to Delaying Disability Progression in Patients with Multiple Sclerosis. *Drugs* 2015;75:947–77.
- Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. *Brain* 1989;112:133–46.
- Yousry TA, Habi M, Major EO, et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. *N Eng J Med* 2006;354(9):924–33.

Appendix 1 Schedule of Assessments

Visit ^a	Screening	Treatment Period ^a					Early study treatment discontinuation evaluation ^c	Safety Follow-Up 48 weeks after last dose of study drug ^d Refer to Appendix 2
	1	2 (Enrolment) ^b	3	4	5 (last infusion of study drug)	6 (End of Treatment period)		
Week	-2 weeks	0	24 (±14 days)	48 (±14 days)	72 (±14 days)	96 (±14 days)		
Informed consent ^e	X							
Review inclusion & exclusion criteria	X	X						
Review of retreatment criteria ^f	X	X	X	X	X			
Physical examination ^g	X	X	X	X	X	X	X	
Vital signs ^h		X	X	X	X	X	X	
Neurological examination ⁱ		X	X	X	X	X	X	
EDSS score ^j		X	X	X	X	X	X	
T25FWT and 9HPT ^k		X	X	X	X	X	X	
SDMT		X		X		X	X	
Brain MRI ^l			X ^u	X		X	X	
Recording of potential relapses		X	X	X	X	X	X	
WPAI		X	X	X	X	X	X	
SymptoMScreen		X		X		X	X	

Appendix 1 Schedule of Assessments (cont.)

Visit	Screening	Treatment Period					Early study treatment discontinuation evaluation ^c	Follow-Up 48 weeks after last dose of study drug ^d Refer to Appendix 2
	1	2 (Enrolment) ^b	3	4	5 (last infusion of study drug)	6 (End of Treatment period)		
Week	-2 weeks	0	24 (±14 days)	48 (±14 days)	72 (±14 days)	96 (±14 days)		
MSIS-29		X		X		X	X	
Hematology, chemistry, urinalysis ^m	X	X	X	X	X	X	X	
Pregnancy test ⁿ	X	X	X	X	X	X		
Lymphocytes subtypes ^o		X	X	X	X	X	X	
HBV DNA measured by PCR in patients with positive HBcAb ^p		X	X	X	X			
Adverse event assessment ^q	X	X	X	X	X	X	X	
Concomitant treatment review		X	X	X	X	X	X	
Methylprednisolone and antihistaminic drug premedication ^r		X	X	X	X			
Ocrelizumab administration ^s		X	X	X	X			
Optional whole blood and serum samples for SARS-CoV-2 vaccine	Please see Figure 3 for details.							

Visit	Screening	Treatment Period					Early study treatment discontinuation evaluation ^c	Follow-Up 48 weeks after last dose of study drug ^d Refer to Appendix 2
	1	2 (Enrolment) ^b	3	4	5 (last infusion of study drug)	6 (End of Treatment period)		
Week	-2 weeks	0	24 (±14 days)	48 (±14 days)	72 (±14 days)	96 (±14 days)		
immunological assessments ^t								

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CDP = confirmed disability progression; DMT = disease modifying treatment; DNA = deoxyribonucleic acid; eCRF = electronic Case Report Form; EDSS = Expanded Disability Status Scale; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transpeptidase; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; hCG = human chorionic gonadotropin; IRR = infusion-related reaction; IV = intravenous; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSIS = Multiple sclerosis impact scale; 9HPT = nine hole peg test; PCR = polymerase chain reaction; PML = progressive multifocal leukoencephalopathy; RBC = red blood cell; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; SDMT = symbol digit modalities test; T25FWT = Timed 25-foot walk test; WBC = white blood cell; WPAI = Work productivity and activity impairment questionnaire

- ^a The study visits during the treatment period may be spread over more than one day to complete all the assessments before study drug administration. The first infusion of ocrelizumab in this study should be 24 weeks (±14 days) after the last infusion of ocrelizumab in the Parent-trial. Ocrelizumab will be administered every 24 weeks up to Week 72 of this study and the last visit in the treatment period will be conducted 24 weeks after the last dose of ocrelizumab.
- ^b All assessments performed at the last visit of the parent trial do not have to be repeated if they were performed within 14 days (within 22-26 weeks for the MRI).
- ^c In case of discontinuation per Section [4.6](#) every effort should be made that the patient completes the early treatment discontinuation assessments per [Appendix 1](#)

- ^d The safety follow-up period is of 48 weeks after the last infusion of the study drug. When patients begin an alternative treatment for MS, they will be discontinued from the study. Patients who leave the study and switch to ocrelizumab outside of the study, either after completion of the 96-week Treatment Period or after early discontinuation from the 96-week Treatment Period, will not enter the safety follow-up period. For patients who complete the study treatment period, the week 96 visit will include the 24-week safety follow-up assessments.
- ^e Written informed consent will be obtained from all patients during screening in order to be eligible for the study.
- ^f Decisions on re-treatment criteria will be made in accordance with standard of care and the local ocrelizumab label.
- ^g A physical examination should be performed at the screening, baseline visits and at all visits during the treatment period. Any abnormality identified or changes from previously reported abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities not related to MS should be recorded as adverse events on the Adverse Event eCRF.
- ^h Vital signs will include the measurements of heart rate, systolic and diastolic blood pressures, and temperature. Vital signs should be taken within 45 minutes prior to the premedication methylprednisolone (or an equivalent) infusion and administration of antihistaminics. In addition, vital signs should be measured prior to the ocrelizumab infusion then every 15 minutes (± 5 minutes) for the first hour, followed by every 30 minutes (± 10 minutes) until 1 hour after the end of the infusion. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ⁱ Neurological examinations will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Investigators will also screen patients for signs and symptoms of PML by evaluating neurological deficits localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, hemiparesis, cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination). Patients with suspected PML should be withheld from ocrelizumab treatment until PML is ruled out by complete clinical evaluation and appropriate diagnostic testing. A patient with confirmed PML should be withdrawn from the study.
- ^j The last 48-week and 24-week CDP confirmatory assessments will be performed at the End of Treatment visit (week 96). For patients who discontinue the study (e.g., switch to ocrelizumab outside of the study, or start treatment with another DMT), the EDSS CDP confirmatory assessments will not be performed.
- ^k Not expected from patients coming from CASTING/MA30005 study.
- ^l MRI readings should be available before dosing with ocrelizumab for safety reasons.
- ^m Routine laboratory assessments (performed in local laboratory and according to standard of care) will include: Hematology: hemoglobin, hematocrit, RBCs, WBC absolute, percent and/or absolute differential count (neutrophils, eosinophils, lymphocytes, monocytes, basophils), and quantitative platelet count; Chemistry: AST, ALT, GGT, creatinine, total bilirubin. Urine dipstick will be done at site locally.
- ⁿ At the screening visit, urine beta-hCG [sensitivity of at least 25 mIU/mL] will be performed. On infusion visits, the urine pregnancy test should be performed prior to prophylactic medication in all women of childbearing potential. If positive, the patient will not receive the scheduled dose until a serum pregnancy test is performed for confirmation. If the serum pregnancy test is negative, the patient can receive the scheduled ocrelizumab dose. The FSH test is only applicable to confirm postmenopausal status in female patients. Patients who became pregnant by chance between the last visit of the parent study and screening of this study, as confirmed by pregnancy tests at screening, will enter the safety follow-up immediately and re-start the treatment after birth and breastfeeding are over, as per retreatment criteria.
- ^o Lymphocytes subtypes samples should be collected prior to ocrelizumab infusion to screen for CD19+ and T-cell counts (CD4+, CD8+) at a local laboratory.
- ^p If total HBcAb was positive at screening of a subject rolled over from any parent studies, HBV DNA measured by PCR must be negative in order for a patient to be dosed with ocrelizumab in the MN39158 study. For enrolled patients rolling over from any of the parent studies with negative HBsAg and positive total HBcAb, HBV DNA testing

(by PCR) must be repeated every 24 weeks and evaluated prior to ocrelizumab administration. If it becomes positive, treatment with ocrelizumab must be discontinued but the patient should remain in the safety follow up.

- ^q Adverse events will be reported throughout the study and until 48 weeks after the last dose of ocrelizumab as provided during the study period. After this period, the Investigator should report any serious and non-serious adverse events that are believed to be related to prior study drug treatment. At the end-of-treatment evaluation, reasons for study discontinuation will be captured via telephone call unless a site visit is requested by the Investigator.
- ^r All patients must receive prophylactic treatment with 100 mg methylprednisolone (or an equivalent), administered by slow IV infusion, to be completed approximately 30 minutes and not less than 25 minutes prior to each ocrelizumab infusion and an antihistamine, via oral, intramuscular or IV route to be completed approximately 30–60 minutes and not less than 25 minutes prior to each infusion of ocrelizumab (the antihistamine should be the first premedication to be administered). The addition of an antipyretic (e.g., acetaminophen/paracetamol) may also be considered.
- ^s Ocrelizumab will be administered as one 600-mg infusion in 500 mL 0.9% sodium chloride every subsequent dose (i.e., every 24 weeks) for a period of two years. In patients who did not experience a serious IRR with any previous conventional ocrelizumab infusion (~3.5 hours), the next 600 mg infusion can be administered as a shorter (~2 hours) infusion for subsequent doses, after providing written informed consent. If patients develop a serious IRR while on the shorter infusion, they will be switched to the conventional infusion and should not be restarted on the shorter infusion at any following infusion visit. Ocrelizumab will not be administered to pregnant/breastfeeding patient. Treatment with ocrelizumab should also be stopped if the patient decides to become pregnant.
- ^t For the optional procedure related to SARS-CoV-2 vaccination only: Whole blood and serum samples collected on the day of the infusion must be collected prior to the IV methylprednisolone administered as premedication. Samples will be collected up to 18 months after the last vaccine dose.
- ^u Week 24 MRI is only applicable for patients who have consented to Protocol/Informed Consent Form v5.0 or lower.

Note: All lab samples can be taken up to 2 weeks prior to the scheduled study visit. If laboratory results are required to confirm retreatment criteria, these need to be available prior to dosing.

Appendix 2 Safety Follow-Up Schedule of Assessments

(Including Additional B-Cell Monitoring, if required)

The safety follow-up period is of 48 weeks after the last infusion of the study drug. When patients begin an alternative treatment for MS, they will be discontinued from the study. Patients who decide to leave the study and switch to ocrelizumab outside of the study, either after completion of the 96-week Treatment Period or after early discontinuation from the 96-week Treatment Period, will not enter the safety follow-up period.

Assessment	Safety Follow-Up		
	Patients who complete the 96 weeks Treatment Period	Patients who discontinue the study treatment early	
		Week 24 after the last infusion of study drug (± 14 days)	Week 48 after the last infusion of study drug (± 14 days)
Routine safety laboratory tests ^a	X	X	X
Lymphocytes subtypes ^b	X	X	X
Vital signs	X	X	X
EDSS score	X	X	X
Adverse events ^c	X	X	X
Concomitant medication	X	X	X

EDSS = Expanded Disability Status Scale

^a Routine safety lab: hematology, chemistry and urinalysis.

^b Lymphocytes subtypes samples for CD19+ and T-cell counts (CD4+, CD8+)

^c All adverse events should be reported until 48 weeks after the last dose of study drug. After this period, the Investigator should report any serious and non-serious adverse event that are believed to be related to prior study drug treatment.

Appendix 3 Expanded Disability Status Scale (EDSS)

EDSS steps	
0	Normal neurological exam (all FS grade 0)
1.0	No disability, minimal signs in one FS (one FS grade 1)
1.5	No disability, minimal signs in more than one FS (more than one FS grade 1)
2.0	Minimal disability in one FS (one FS grade 2, others 0 or 1)
2.5	Minimal disability in two FS (two FS grade 2, others 0 or 1)
3.0	Fully ambulatory but with moderate disability in one FS (one FS grade 3, others 0 or 1) OR Fully ambulatory but with mild disability in three or four FS (three / four FS grade 2, others 0 or 1)
3.5	Fully ambulatory but with moderate disability in one FS (one FS grade 3) and mild disability in one or two FS (one / two FS grade 2) and others 0 or 1; OR Fully ambulatory with two FS grade 3 (others 0 or 1); OR Fully ambulatory with five FS grade 2 (others 0 or 1)
4.0	Fully ambulatory for ≥500 meters without aid or rest; up and about some 12 hours a day characterised by relatively severe disability consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps
4.5	Ambulatory for 300 - 500 meters without aid or rest; up and about much of the day, characterised by relatively severe disability usually consisting of one FS grade 4 and combination of lesser grades exceeding limits of previous steps
5.0	Ambulatory for 200 - 300 meters without aid or rest (usual FS equivalents include at least one FS grade 5, or combinations of lesser grades usually exceeding specifications for step 4.5)
5.5	Ambulatory for 100 - 200 meters without aid or rest
6.0	Ambulatory for at least 100 meters with intermittent or constant unilateral assistance (cane or crutch) with or without rest OR Ambulatory < 100 meters without help or assistance OR Ambulatory ≥ 50 meters with unilateral assistance OR Ambulatory ≥ 120 meters with bilateral assistance
6.5	Ambulatory for at least 20 meters with constant bilateral assistance (canes or crutches) without rest OR Ambulatory for < 50 meters with unilateral assistance (cane or crutch) OR Ambulatory 5 to 120 meters with constant bilateral assistance (canes or crutches)
7.0	Unable to walk 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need some help in transferring and in wheeling self
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms
8.5	Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions
9.0	Helpless bed patient; can communicate and eat
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10	Death due to MS

Standardised Neurological Examination and Assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale

Slightly modified from J.F. Kurtzke, Neurology 1983;33,1444-52

©2011 Ludwig Kappos, MD, Neurology, University Hospital Basel, 4031 Basel, Switzerland; Version 04/10.2

Functional System Scores

1. Visual FSS

0	normal
1	disc pallor and / or small scotoma and / or visual acuity (corrected) of worse eye less than 20 / 20 (1.0) but better than 20 / 30 (0.67)
2	worse eye with maximal visual acuity (corrected) of 20 / 30 to 20 / 59 (0.67 – 0.34)
3	worse eye with large scotoma and/or moderate decrease in fields and/or maximal visual acuity (corrected) of 20 / 60 to 20 / 99 (0.33 – 0.21)
4	worse eye with marked decrease of fields and/or maximal visual acuity (corrected) of 20 / 100 to 20 / 200 (0.2 – 0.1); grade 3 plus maximal acuity of better eye of 20 / 60 (0.33) or less
5	worse eye with maximal visual acuity (corrected) less than 20 / 200 (0.1); grade 4 plus maximal acuity of better eye of 20 / 60 (0.33) or less
6	grade 5 plus maximal visual acuity of better eye of 20 / 60 (0.33) or less

2. Brainstem FSS

0	normal
1	signs only
2	moderate nystagmus and / or moderate EOM impairment and / or other mild disability
3	severe nystagmus and / or marked EOM impairment and / or moderate disability of other cranial nerves
4	marked dysarthria and / or other marked disability
5	inability to swallow or speak

3. Pyramidal FSS

0	normal
1	abnormal signs without disability
2	minimal disability: patient complains of motor-fatigability or reduced performance in strenuous motor tasks (motor performance grade 1) <u>and/or</u> BMRC grade 4 in one or two muscle groups
3	mild to moderate paraparesis or hemiparesis: BMRC grade 4 in >two muscle groups; <u>and/or</u> BMRC grade 3 in one or two muscle groups (movements against gravity are possible); <u>and/or</u> Severe monoparesis: BMRC grade 2 or less in one muscle group
4	marked paraparesis or hemiparesis: usually BMRC grade 2 in two limbs <u>and/or</u> monoplegia: BMRC grade 0 or 1 in one limb; <u>and/or</u> moderate tetraparesis: BMRC grade 3 in ≥ three limbs
5	paraplegia: BMRC grade 0 or 1 in all muscle groups of the lower limbs; <u>and/or</u> marked tetraparesis: BMRC grade 2 or less in ≥ three limbs; <u>and/or</u> hemiplegia

6	tetraplegia: BMRC grade 0 or 1 in all muscle groups of the upper and lower limbs
----------	---

4. Cerebellar FSS

0	normal
1	abnormal signs without disability
2	mild ataxia <u>and/or</u> moderate station ataxia (Romberg) <u>and/or</u> tandem walking not possible
3	moderate limb ataxia <u>and/or</u> moderate or severe gait/truncal ataxia
4	severe gait/truncal ataxia and severe ataxia in three or four limbs
5	unable to perform coordinated movements due to ataxia
X	pyramidal weakness (BMRC grade ≤ 3) or sensory deficits interfere with cerebellar testing

5. Sensory FSS

0	normal
1	mild vibration <u>or</u> figure-writing <u>or</u> temperature decrease only in 1 or 2 limbs
2	mild decrease in touch / pain / position sense or moderate decrease in vibration in 1 or 2 limbs <u>and/or</u> mild vibration or figure-writing or temperature decrease alone in more than 2 limbs
3	moderate decrease in touch / pain / position sense or marked reduction in vibration in 1 or 2 limbs <u>and/or</u> mild decrease in touch or pain or moderate decrease in all proprioceptive tests in > 2 limbs
4	marked decrease in touch or pain in 1 or 2 limbs <u>and/or</u> moderate decrease in touch or pain and/or marked reduction of proprioception > 2 limbs
5	loss (essentially) of sensation in one or two limbs <u>and/or</u> moderate decrease in touch or pain and/or marked reduction of proprioception for most of the body below the head
6	sensation essentially lost below the head

6. Bowel/Bladder FSS

0	normal
1	mild urinary hesitancy, urgency and/or constipation
2	moderate urinary hesitancy/retention and/or moderate urinary urgency/incontinence and/or moderate bowel dysfunction
3	frequent urinary incontinence or intermittent self-catheterisation; needs enema or manual measures to evacuate bowels
4	in need of almost constant catheterisation
5	loss of bladder or bowel function; external or indwelling catheter
6	loss of bowel and bladder function

7. Cerebral FSS

0	normal
1	signs only in decrease in mentation; mild fatigue
2	mild decrease in mentation; moderate or severe fatigue
3	moderate decrease in mentation
4	marked decrease in mentation
6	dementia

8. Ambulation score

0	unrestricted
1	Fully ambulatory ≥ 500 meters without help or assistance but not unrestricted (pyramidal or cerebellar FS ≥ 2)
2	Ambulatory ≥ 300 meters, but < 500 meters, without help or assistance (EDSS 4.5 or 5.0, defined by FSS)
3	Ambulatory ≥ 200 meters, but < 300 meters, without help or assistance (EDSS 5.0)
4	Ambulatory ≥ 100 meters, but < 200 meters, without help or assistance (EDSS 5.5)
5	Ambulatory < 100 meters without help or assistance (EDSS 6.0)
6	Ambulatory ≥ 50 meters with unilateral assistance (EDSS 6.0)
7	Ambulatory ≥ 120 meters with bilateral assistance (EDSS 6.0)
8	Ambulatory < 50 meters with unilateral assistance (EDSS 6.5)
9	Ambulatory ≥ 5 meters, but < 120 meters with bilateral assistance, (EDSS 6.5)
10	Uses wheelchair without help; unable to walk 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day (EDSS 7.0)
11	Uses wheelchair with help; unable to take more than a few steps; restricted to wheelchair; may need some help in transferring and in wheeling self (EDSS 7.5)
12	essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms (EDSS 8.0)

Standardised Neurological Examination and Assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale

Slightly modified from J.F. Kurtzke, Neurology 1983;33,1444-52

©2011 Ludwig Kappos, MD, Neurology, University Hospital Basel, 4031 Basel, Switzerland; Version 04/10.2

Appendix 4 Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy

Action Steps if PML is Suspected:

- If the clinical presentation is suggestive of PML, further investigations should include brain MRI evaluation as soon as possible. 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 JCV deoxyribonucleic acid (DNA) by polymerase chain reaction (PCR) 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.
- There is no known treatment or cure for PML. Treatment considerations are discussed in the medical literature ([Calabrese et al. 2007](#)).

MRI Assessment

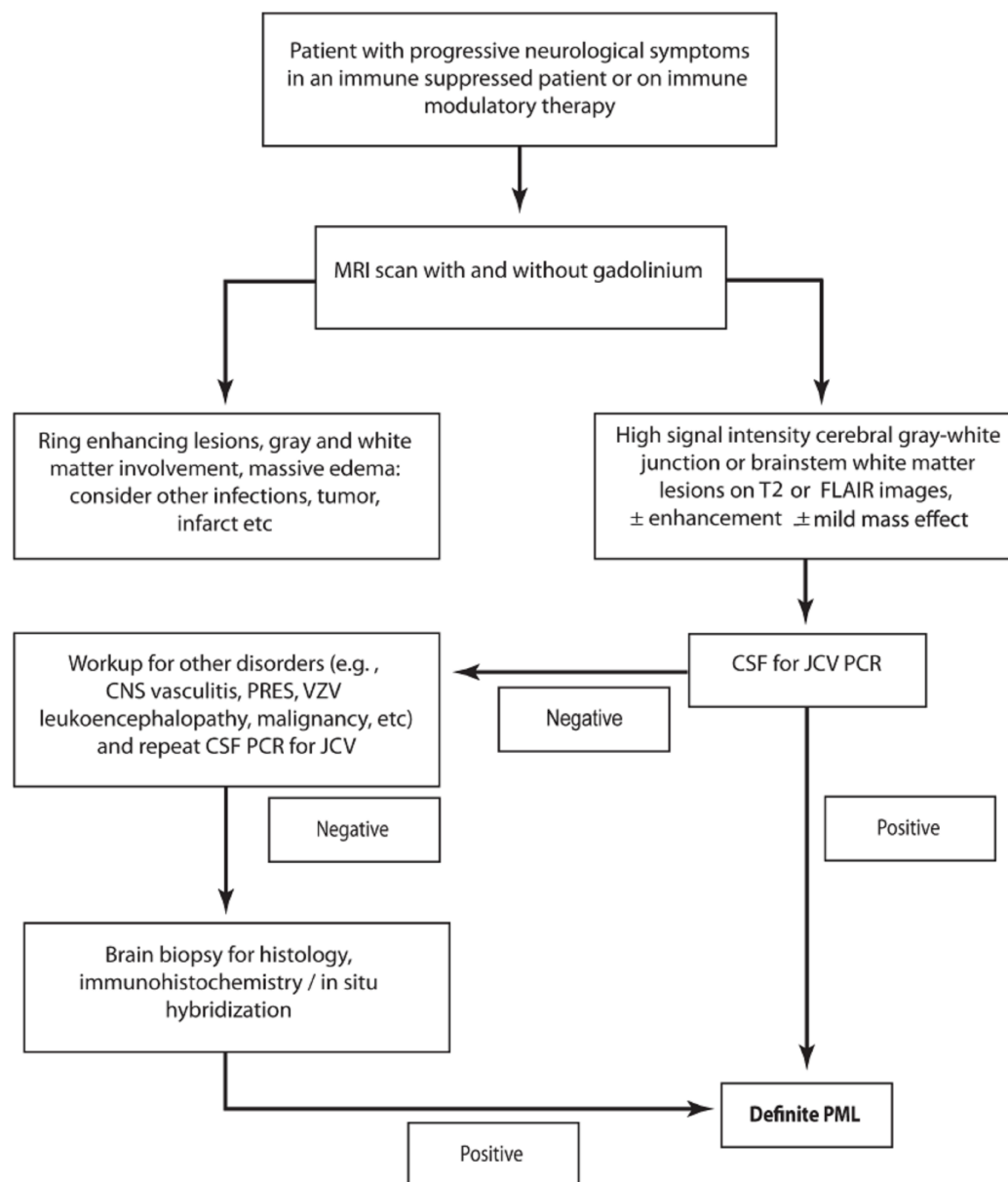
- Although there are no pathognomonic findings that differentiate PML from MS, a brain MRI scan that includes FLAIR and T2-weighted and T1-weighted sequences, with and without gadolinium, should be performed to assess patients with neurological changes suggestive of PML (see [Figure 1](#)).
- Comparison with a baseline scan may assist with interpretation of the findings on the newly acquired MRI (see [Table 2](#) for differences in lesion characteristics that may help differentiate between PML and MS).

CSF 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 4 Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy (Cont.)

Figure 1 Diagnostic Algorithm framework for PML (Berger et al. 2013)



FLAIR = fluid-attenuated inversion recovery; JCV = JC virus; PML = progressive multifocal leukoencephalopathy; PRES = posterior reversible encephalopathy syndrome; VZV = varicella-zoster virus.

Appendix 4 Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy (Cont.)

Table 1 Clinical Signs and Symptoms Typical of MS and PML

Clinical Signs and Symptoms Typical of MS and PML*		
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)

Adapted from [Kappos et al. 2007](#)

Appendix 4 Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy (Cont.)

Table 2 MRI Lesion Characteristics Typical of PML and MS

Feature	MS (relapse)	PML
Location of new lesions	Mostly focal; affect entire brain and spinal cord, in white and possibly gray matter	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; 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 T2-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 T1-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 T2-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
----------------	---	------------------

Adapted from [Yousry et al. 2006](#)

Appendix 5 Patient-Reported Outcomes



Please circle **one number** that best describes how MS has affected each function. For example, if it takes you longer to type or text, you might rate your hand function as 'mildly limited' (circle '2'), but if you gave up typing completely, you might rate your hand function as 'very limited' (circle '4').

	0 – not affected at all	1 – very mild limitation/ I make minor adjustments	2 – mild limitation/ I make frequent adjustments	3 – moderate limitation/ I reduced my daily activities	4 – severe limitation/ I gave up some activities	5 – very severe limitation/ I'm unable to do many daily activities	6 – total limitation/ I'm unable to do most daily activities
Walking	0	1	2	3	4	5	6
Hand function/Dexterity Poor hand coordination, tremors	0	1	2	3	4	5	6
Spasticity & Stiffness Muscle cramping or muscle tightness	0	1	2	3	4	5	6
Bodily Pain Aches, tenderness	0	1	2	3	4	5	6
Sensory symptoms Numbness, tingling, or burning	0	1	2	3	4	5	6
Bladder control Urinary urgency, frequency	0	1	2	3	4	5	6
Fatigue	0	1	2	3	4	5	6
Vision Blurry vision, double vision	0	1	2	3	4	5	6
Dizziness Feeling off balance, 'spinning'/vertigo	0	1	2	3	4	5	6
Cognitive function Memory, concentration problems	0	1	2	3	4	5	6
Depression Depressed thoughts, low mood	0	1	2	3	4	5	6
Anxiety Feelings of stress; panic attacks	0	1	2	3	4	5	6



Appendix 5 Patient-Reported Outcomes (cont.)

Multiple Sclerosis Impact Scale version 2 (MSIS-29v2)

UK original of MSIS-29 v2

- The following questions ask for your views about the impact of MS on your day-to-day life during **the past two weeks**.
- For each statement, please circle the one number that best describes your situation.
- Please answer all questions.

In the <u>past two weeks</u> , how much has your MS limited your ability to ...	Not at all	A little	Moderately	Extremely
1. Do physically demanding tasks?	1	2	3	4
2. Grip things tightly (e.g. turning on taps)?	1	2	3	4
3. Carry things?	1	2	3	4

In the <u>past two weeks</u> , how much have you been bothered by ...	Not at all	A little	Moderately	Extremely
4. Problems with your balance?	1	2	3	4
5. Difficulties moving about indoors?	1	2	3	4
6. Being clumsy?	1	2	3	4
7. Stiffness?	1	2	3	4
8. Heavy arms and/or legs?	1	2	3	4
9. Tremor of your arms or legs?	1	2	3	4
10. Spasms in your limbs?	1	2	3	4
11. Your body not doing what you want it to do?	1	2	3	4
12. Having to depend on others to do things for you?	1	2	3	4

Appendix 5 Patient-Reported Outcomes (cont.)

Multiple Sclerosis Impact Scale version 2 (MSIS-29v2) continued				
In the <u>past two weeks</u> , how much have you been bothered by ...	Not at all	A little	Moderate-ly	Extremely
13. Limitations in your social and leisure activities at home?	1	2	3	4
14. Being stuck at home more than you would like to be?	1	2	3	4
15. Difficulties using your hands in everyday tasks?	1	2	3	4
16. Having to cut down the amount of time you spent on work or other daily activities?	1	2	3	4
17. Problems using transport (e.g. car, bus, train, taxi, etc.)?	1	2	3	4
18. Taking longer to do things?	1	2	3	4
19. Difficulty doing things spontaneously (e.g. going out on the spur of the moment)?	1	2	3	4
20. Needing to go to the toilet urgently?	1	2	3	4
21. Feeling unwell?	1	2	3	4
22. Problems sleeping?	1	2	3	4
23. Feeling mentally fatigued?	1	2	3	4
24. Worries related to your MS?	1	2	3	4
25. Feeling anxious or tense?	1	2	3	4
26. Feeling irritable, impatient, or short-tempered?	1	2	3	4
27. Problems concentrating?	1	2	3	4
28. Lack of confidence?	1	2	3	4
29. Feeling depressed?	1	2	3	4

Appendix 5 Patient-Reported Outcomes (cont.)

Work Productivity and Activity Impairment Questionnaire: Multiple Sclerosis V2.0 (WPAI: MS)

The following questions ask about the effect of your multiple sclerosis on your ability to work and perform normal daily activities. Please fill in the blanks or circle a number, as indicated.

1. Are you currently employed (working for pay)? _____ NO _____ YES
If NO, tick "NO" and skip to question 6.

The next questions refer to the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your multiple sclerosis? Include hours you missed on sick days, times you went in late, left early, etc., because of your multiple sclerosis. Do not include time you missed to participate in this study.

_____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as annual leave, holidays, time off to participate in this study?

_____ HOURS

4. During the past seven days, how many hours did you actually work?

_____ HOURS (If "0", skip to question 6)

Appendix 5 Patient-Reported Outcomes (cont.)

5. During the past seven days, how much did your multiple sclerosis affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If multiple sclerosis affected your work only a little, choose a low number. Choose a high number if multiple sclerosis affected your work a great deal.

Consider only how much multiple sclerosis affected productivity while you were working.

Multiple sclerosis had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Multiple sclerosis completely prevented me from working
---	---	---	---	---	---	---	---	---	---	---	----	---

CIRCLE A NUMBER

6. During the past seven days, how much did your multiple sclerosis affect your ability to perform your normal daily activities, other than work at a job?

By normal activities, we mean the usual activities you perform, such as working around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could perform and times you accomplished less than you would like. If multiple sclerosis affected your activities only a little, choose a low number. Choose a high number if multiple sclerosis affected your activities a great deal.

Consider only how much multiple sclerosis affected your ability to do your normal daily activities, other than work at a job.

Multiple sclerosis had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Multiple sclerosis completely prevented me from doing my daily activities
---	---	---	---	---	---	---	---	---	---	---	----	--

CIRCLE A NUMBER

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993; 4(5): 353-65.

Appendix 6 Pregnancy Outcome and Infant Health Information on First Year of Life

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 authorisation 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 labour - Yes ☐ - No ☐

Table 3: Growth alteration, congenital anomalies and functional deficits

Date of Assessment			
<u>Growth alteration</u> - 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 ☐ Minor structural malformation A defect that occurs infrequently but has neither cosmetic nor functional	Specify: _____ _____ _____ Specify: _____ _____	Contributing factors: _____ _____ Contributing factors: _____

	significance to the child	_____	_____
	☐ 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)?

- ☐ normal
☐ abnormal
☐ unknown

If abnormal, specify test result: _____

If abnormal, date of test: _____

If infection detected at birth then [Tables 5](#) and [6](#) should 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	If abnormal, specify test result: _____	If abnormal, date of test: _____

	☐ unknown		
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 colonisation 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 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			
☐ Haemophilus influenzae 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 7 Patient Diary (OPTIONAL)

Accurate adverse event reporting is essential to ensure patient safety, early detection of safety signals, assess molecule benefit profile, regulatory compliance. In this study protocol, the patient visits will occur every 6 months. Due to the low visit frequency patient diaries have been proposed as an optional tool to mitigate the risk related to adverse events/ concomitant medication low reporting.

The decision to use the patient diary is left to the discretion of each principal investigator (PI). The PI must ensure that required Ethics Committee (EC)/ Institutional Review Board (IRB) approval was obtained before implementing the patient diary at his/her site.

If you are using the patient diary, this is to be considered as patient source documentation. Please ensure the following process is followed at your site:

- The patient diary will be provided to the patient at the Baseline Visit.
- You or your site staff will explain to the patient when/how to complete it and remind him/her to bring it back at each visit at your site.
- Dispensing at Baseline and re-dispensing of patient diary at subsequent on-site visits should be documented in patient notes.
- Completed patient diaries should never be mailed to/ by patients.
- You or your site staff must review the completed patient diary at each visit and discuss the reported data with the patient.
- During each visit you or your site staff should make a copy of the completed patient diary, document your review and assessment, sign and date all pages and file it with the medical records
- In case you or your site staff cannot copy the patient diary, you would need to check the original during each patient study visits at site for any new adverse events / any new concomitant medication which occurred since last patient visit at site and document this in the patient notes (Source Data).
- When the patient early terminated or has completed the study, originals should be filed in the patient notes.
- To increase the patient compliance, please thank the patients for their time and effort and emphasize the importance of their contribution to the study to them.

Appendix 8

Benefit-Risk Assessment of the Conduct of the Study During the COVID-19 Pandemic¹

A benefit risk assessment was conducted to determine whether there is any impact of the COVID-19 pandemic on the conduct of the parent studies including this study. Based on that assessment, no impact is anticipated, and the existing information on identified and potential risks, safety monitoring, and management guidelines and the 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 parent studies protocols' and this study 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 3.1.3, absence of active infection is also required for patients to receive further retreatment with ocrelizumab.

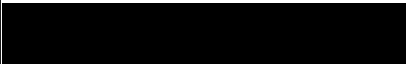
The risk of MS progression may potentially increase over time, if highly effective treatments are delayed.

In summary, protocol-mandated safety monitoring and management guidelines, study eligibility criteria, and the ocrelizumab retreatment criteria are considered adequate 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 Appendix 8 is only applicable to participating sites in Poland.

Signature Page for Protocol - MN39158 - OCREVUS - v7 - Global/Core - Published

System identifier: RIM-CLIN-506490

Approval Task	 11-Oct-2023 22:45:44 GMT+0000
---------------	---