Official Title: An Open-Label, Parallel-Group Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamic Effects of Ocrelizumab in Children and Adolescents with Relapsing-Remitting Multiple Sclerosis

NCT Number: NCT04075266

Document Date: Protocol Version 10: 31-January-2024

PROTOCOL

PROTOCOL TITLE:	**AN OPEN-LABEL, PARALLEL-GROUP STUDY TO EVALUATE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMIC EFFECTS OF OCRELIZUMAB IN CHILDREN AND ADOLESCENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS**
PROTOCOL NUMBER:	WA39085
VERSION NUMBER:	10
TEST PRODUCT:	Ocrelizumab (RO4964913)
STUDY PHASE:	Phase II
EU CT NUMBER:	2023-505269-10-00
REGULATORY AGENCY IDENTIFIERS:	IND Number: 100,593 EudraCT Number: 2016-002667-34 EU CT Number: 2023-505269-10-00 NCT Number: NCT04075266
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APRROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
10	See electronic date stamp on the final page of this document.
9	18 July 2023
8	15 March 2023
7	3 June 2021
6	18 January 2021
5	2 February 2020
4	28 August 2019
3	26 June 2019
2	16 April 2019
1	20 April 2017

PROTOCOL AMENDMENT, VERSION 10
RATIONALE:

Protocol WA39085 has been amended to extend the duration of the safety follow-up period to 104 weeks throughout the protocol to address postmarketing requirements from the United States Food and Drug Administration (FDA). Also as requested by the FDA, the definition of the exposure period has been added and analysis considerations have been specified (Section 6.6).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**AN OPEN-LABEL, PARALLEL-GROUP STUDY TO EVALUATE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMIC EFFECTS OF OCRELIZUMAB IN CHILDREN AND ADOLESCENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS**
PROTOCOL NUMBER:	WA39085
VERSION NUMBER:	10
TEST PRODUCT:	Ocrelizumab (RO4964913)
SPONSOR NAME:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

PROTOCOL TITLE:	**AN OPEN-LABEL, PARALLEL-GROUP STUDY TO EVALUATE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMIC EFFECTS OF OCRELIZUMAB IN CHILDREN AND ADOLESCENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS**
REGULATORY AGENCY IDENTIFIERS	IND Number: 100,593 EudraCT Number: 2016-002667-34 EU CT Number: 2023-505269-10-00 NCT Number: NCT04075266

STUDY RATIONALE

The purpose of this study is to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamic effects of ocrelizumab in children and adolescents ages ≥ 10 to < 18 years with relapsing-remitting multiple sclerosis (RRMS). The data from this study will serve to determine the dosing regimen of ocrelizumab to be further investigated in the subsequent Phase III study in children and adolescents.

OBJECTIVES AND ENDPOINTS

Primary Objectives	
Primary Pharmacokinetic Objectives	**Corresponding Endpoint**
• To characterize the ocrelizumab PK profile in children and adolescents	• Serum concentration of ocrelizumab at specified timepoints
Primary Pharmacodynamic Objective:	**Corresponding Endpoint**
• To evaluate relationship between drug exposure and PD (CD19+ B-cell count) in children and adolescents	• Levels of CD19 + B-cell count in blood
Secondary Objectives	
Secondary Safety Objectives	**Corresponding Endpoints**
• To evaluate safety of ocrelizumab in children and adolescents	• Occurrence and severity of adverse events, with severity determined according to NCI CTCAE v5.0 • Change from baseline in vital signs • Change from baseline in clinical laboratory test results • Level of circulating B cells, T cells, natural killer cells, and other leukocytes • Developmental milestones (e.g., growth, bone age, age at menarche, Tanner staging) • Non-MS CNS pathology as measured by brain MRI scans • Levels of blood immunoglobulins • Antibody titers against standard vaccines

Secondary Immunogenicity Objective	Corresponding Endpoint
• To assess ADA development to ocrelizumab	• Presence of ADAs during the study relative to the presence of ADAs at baseline

ADA = anti-drug antibody; MRI = magnetic resonance imaging; MS = multiple sclerosis; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; PD = pharmacodynamic; PK = pharmacokinetic.

OVERALL STUDY DESIGN AND STUDY POPULATION

This Phase II, open-label, parallel-group, study will evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamic effects of ocrelizumab in children and adolescents with RRMS.

Several key aspects of the study design and study population are summarized below.

Phase:	Phase II	**Population Type:**	Pediatric patients
Control Method:	None	**Population Diagnosis or Condition:**	Relapsing-remitting multiple sclerosis
Interventional Model:	Parallel group	**Population Age:**	≥ 10 years and, < 18 years
Test Compound:	Ocrelizumab	**Site Distribution:**	Multi-site and multi-region
Active Comparator:	Not applicable	**Study Intervention Assignment Method:**	Open-label
Number of Cohorts:	2	**Number of Participants to Be Enrolled:**	Up to a maximum of 36

STUDY TREATMENT

Patients with a body weight from ≥25 kg to <40 kg (Cohort 1) will receive 300 mg ocrelizumab and patients with a body weight ≥40 kg (Cohort 2) will receive 600 mg ocrelizumab as follows:

- The initial dose of ocrelizumab will be administered as two IV infusions given 14 days apart (i.e., Cohort 1: 2×150 mg for a total dose of 300 mg and Cohort 2: 2×300 mg for a total dose of 600 mg) to minimize infusion-related reactions upon the first administration of ocrelizumab.
- Subsequent doses will be administered as single infusions (i.e., Cohort 1: 1×300 mg and Cohort 2: 1×600 mg).

DURATION OF PARTICIPATION

The duration of participation for an individual, from screening to the end of the SFU period (excluding the B-cell monitoring period because it is not known how long it takes for B cells to replete in the pediatric MS population after treatment with ocrelizumab) is expected to be approximately 402 weeks (~8 years).

COMMITTEES

Independent Committees:	Internal Monitoring Committee
Other Committees:	Not applicable

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
ADEM	acute disseminated encephalomyelitis
ARR	annualized relapse rate
AUC	Area under the concentration–time curve
AUC_{ss}	AUC at steady state
AUC_{0-t}	AUC from time 0 to last quantifiable timepoint
β-hCG	beta-human chorionic growth hormone
CD	cluster of differentiation
CDI	confirmed disability improvement
CDP	confirmed disability progression
CNS	central nervous system
C_{max}	maximum plasma concentration
C_{trough}	minimum plasma concentration
AUC_{ss}	AUC at steady state
CSF	cerebrospinal fluid
DMT	disease-modifying therapy
EC	Ethics Committee
eCRF	electronic case report form
EDC	electronic data capture
EDSS	Expanded Disability Status Scale
ETDRS	Early Treatment Diabetic Retinopathy Study
FSS	Functional System Score
GA	glatiramer acetate
Gd	gadolinium
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HepCAb	hepatitis C antibody
HIPAA	Health Insurance Portability and Accountability Act
IFN	interferon
Ig	immunoglobulin
IMC	Internal Monitoring Committee
IMP	Investigational Medicinal Product
ICH	International Council for Harmonisation
IND	Investigational New Drug (application)
IPMSSG	International Pediatric Multiple Sclerosis Study Group

Abbreviation	Definition
IRB	Institutional Review Board
IRR	infusion-related reaction
IWRS	interactive Web-based response system
JCV	JC–virus
KLH	keyhole limpet cyanin
LCVA	low-contrast visual acuity
LLN	lower limit of normal
LPLV	last patient, last visit
mAb	monoclonal antibody
MN	mobile nursing
MOG	myelin oligodendrocyte glycoprotein
MRI	magnetic resonance imaging
MS	multiple sclerosis
NAbs	neutralizing antibodies
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OLE	open-label extension
OOE	optional ocrelizumab extension
PCR	polymerase chain reaction
PD	pharmacodynamic
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PPMS	primary progressive multiple sclerosis
PRMS	progressive-relapsing multiple sclerosis
RBR	Research Biosample Repository
RMS	remitting multiple sclerosis
RRMS	relapsing-remitting multiple sclerosis
SDMT	Symbol Digit Modalities Test
SFU	safety follow-up period
SPMS	secondary progressive multiple sclerosis
TB	tuberculosis
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WES	whole-exome sequencing
WGS	whole-genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic, inflammatory, and demyelinating disease of the CNS that affects approximately 2.3 million people worldwide (MSIF 2013). Although MS is a global disease, its prevalence increases with distance from the equator. The prevalence of MS is highest in North America and Europe (140 and 108 per 100,000 people, respectively) and lowest in sub-Saharan Africa and East Asia at 2.1 and 2.2 per 100,000 people, respectively (MSIF 2013). MS typically begins between the ages of 20 to 40 years (Tullman 2013). Overall, women are affected approximately twice as often as men, except in individuals with the primary-progressive form of the disease, where there is no gender prevalence difference (MSIF 2013; Tullman 2013).

MS is a serious, disabling disease and the leading cause of non-traumatic disability in young adults (Tullman 2013). The disease course culminates in deterioration of physical and cognitive functions of patients, which significantly impacts quality of life and independence. Patients suffer from a range of MS-associated symptoms including motor weakness, spasticity, gait and coordination imbalance, sensory dysfunction, vision loss, sexual dysfunction, fatigue, depression, chronic pain, sleep disorders, and cognitive impairment (Damal et al. 2013). Diagnosis of MS is based on the application of structured diagnostic criteria that rely on clinical observation, neurologic examination, brain and spinal cord magnetic resonance imaging (MRI) scans, and at times evoked potential tests, and cerebrospinal fluid (CSF) examination (Polman et al. 2011; Thompson et al. 2018).

Prognosis is highly variable, and if left untreated, half of patients with MS would require assistance to walk within 15 years of disease onset (Expanded Disability Status Scale [EDSS] score >6.0). MS also imposes a substantial economic burden on patients, their families, and society as a whole (Trisolini et al. 2010; Adelman et al. 2013). The cost of MS, including the impact on employment (such as reduced working hours or early retirement) and major investment in equipment (such as wheelchairs or housing modifications), has been shown to increase more than 3– or 4–fold for patients with severe disease (EDSS >7.0) compared with patients with less severe disease (EDSS <4.0) (Kobelt et al. 2006a; 2006b). The potential risk of irreversible disease progression is therefore an important factor in the therapeutic decision–making of patients and their physicians (Gold et al. 2010).

For the past two decades, MS has been clinically subcategorized into four phenotypic disease patterns distinguished by the occurrence and timing of episodes of transient neurologic compromise (relapses) relative to disease onset and disability progression (Lublin and Reingold 1996): relapsing–remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and progressive-relapsing MS (PRMS). A recently proposed revision to this classification recommends that the term PRMS be dropped, as it is considered vague and overlapping with other disease course subtypes,

and that PRMS and PPMS should therefore no longer be considered distinct entities but rather characterized both as PPMS, with or without activity (Lublin 2014). More recently, it has been proposed that PPMS is not a separate entity but rather a part of the spectrum of progressive disease (Ontaneda and Fox 2015), and as such RRMS and PPMS can be considered closely related diseases.

1.1.1 Features of Pediatric Multiple Sclerosis

Pediatric onset MS is rare, with between 3% and 5% of patients with MS having their first symptom before reaching the age of 18 years (Chitnis et al. 2012). During childhood and adolescence, the CNS goes through several developmental steps, including ongoing myelination. Therefore, MS–related inflammatory demyelination may result in atypical or incomplete formation of white matter pathways. Probably because of the brain maturation process and myelin immaturity, children have a distinctive clinical course, neuroimaging features, and laboratory results compared with adult-onset MS. Pediatric–onset MS appears to have more inflammatory activity.

Optic neuritis is a common presenting symptom in adolescents. Encephalopathy, seizures, and polyfocal (polyregional) onset occur as the initial manifestation more frequently in children than in adults. Children tend to experience their second (MS–defining) clinical exacerbation more rapidly than adults; approximately 40% of children will be diagnosed within 1 year of initial symptoms, 60% by 2 years, and 66% by 3 years. In comparison, approximately 45% of adults will be diagnosed with MS within 2 years after onset of symptoms, and approximately 50% will be diagnosed within 3 years. Residual physical disability after the initial demyelinating event is present in less than 10% of children, while residual deficits from initial relapse may occur in up to 25% of adults (Banwell 2013).

As compared with adult MS where approximately 85% of patients have RRMS, more than 95% of pediatric patients have a relapsing-remitting course (Boiko et al. 2002; Banwell et al. 2007). Several studies have demonstrated that individuals with pediatric onset MS have slower progression of physical disability than those with adult onset, particularly during the early stages of the disease (Boiko et al. 2002; Simone et al. 2002; Trojano et al. 2004; Renoux et al. 2007; Harding et al. 2012). This discrepancy may suggest greater plasticity, less neurodegeneration, and potentially more capability for repair and remyelination in the younger CNS (Gorman et al. 2009). Although the time to secondary progressive disease and neurologic disability may take longer to achieve relative to adult-onset MS, it is important to keep in mind that the age at which pediatric onset patients experience progressive disease and disability is ultimately younger (Boiko et al. 2002). Finally, PPMS, is exceedingly rare in children (Ghezzi et al. 1997; Boiko et al. 2002; Simone et al. 2002; Waubant and Chabas 2009).

Fatigue is one of the most common problems that affect children and adolescents with MS, and it has been reported in over 60% of patients (MacAllister et al. 2009). Depression is also often associated with fatigue (Goretti et al. 2012).

Cognitive impairment is increasingly recognized in children and adolescents with MS. Up to 35% of pediatric patients with MS have some identifiable cognitive dysfunction at the time of diagnosis, and about 50% of children continue to accrue cognitive deficits within the 5 years after disease onset (MacAllister et al. 2005; Ghezzi et al. 2010; Julian et al. 2013; Charvet et al. 2014). Cognitive deficits may include problems with general mentation, attention and information processing, language, visual motor integration skills, and verbal and visual memory (Kalb et al. 1999; Banwell and Anderson 2005; Suppiej and Cainelli 2014).

Fatigue and cognitive impairment are associated with limitations in social, academic, and recreational activities. Some patients have to repeat a year of school because of missed school days or academic difficulties (Ghezzi et al. 2010). The ability to engage in hobbies and sport activities can also be negatively affected.

The definitions proposed by the International Pediatric MS Study Group (IPMSSG) for the diagnosis of pediatric MS and other pediatric demyelinating disorders were revised in 2012 to incorporate advances in research and to include components of the 2010 revision of the McDonald criteria, given that pediatric-onset MS is formally included in the revised McDonald criteria (Polman et al. 2011; Krupp et al. 2013; Pena and Lotze 2013). The 2012 IPMSSG criteria (but not the McDonald 2010 criteria) required an age of 12 years or older for applying dissemination in time and dissemination in space criteria to diagnose MS at the time of the initial clinically isolated syndrome. Recently, it has been proposed to incorporate in IPMSSG criteria the 2010 McDonald criteria for MS for children of all ages, when MRI-defined dissemination in time and dissemination in space requirements for MS are present at the first attack, provided that the sentinel event is consistent with acute demyelination and that the attack does not conform with the criteria of acute disseminated encephalomyelitis (ADEM) (Tardieu et al. 2016).

1.1.2 Therapies and Prevention Strategy in Pediatrics

Current treatment strategies in pediatric MS are similar to those employed in adults. They focus on the treatment of acute relapses, disease modification, and treatment of MS symptoms.

Therapy of acute relapses is reserved for children in whom the symptoms of demyelination impair function or cause discomfort. Mild symptoms that do not impair function are not always treated. On the basis of experience in adults, glucocorticoids are standard first-line treatments (usually IV methylprednisolone), with IV immunoglobulin (Ig) as a second-line therapy for children who either fail to respond to glucocorticoids or have contraindications to their administration (Pena and Lotze 2013; Banwell 2013).

Despite the lack of formal clinical trials, injectables interferon (IFN) beta and glatiramer acetate (GA) are frequently used as first line treatment for pediatric patients with MS (Ghezzi et al. 2016). The three IFN beta agents (two IFN beta-1a and one IFN beta-1b)

are approved in the European Union for the use in adolescent patients with relapsing MS aged 12 years and above on the basis of studies suggesting that the safety profile in adolescents is similar to that seen in adults. Recently in 2018, the U.S. Food and Drug Administration and European Commission have approved Gilenya® (fingolimod) to treat relapsing–remitting MS in children and adolescents 10 to 17 years old following the completion of the first clinical trial of fingolimod in pediatric patients with MS.

Studies have demonstrated that tolerability and efficacy of disease-modifying therapies (DMTs) in pediatric patients with MS have been reported to parallel those seen in adults (Chitnis 2013; Tenembaum et al. 2013; Narula et al. 2015). About 40% of pediatric patients with MS discontinue treatment because of intolerance, toxicity, persisting relapses, or non-adherence, supporting a need for developing new therapies in this population (Pena and Lotze 2013).

In cases of inadequate treatment response to the IFN or GA, alternative treatment options include changing between these therapies or switching to more potent immunomodulators. Oral medications with novel mechanisms of action, which have been approved for MS in adults (e.g., teriflunomide and dimethyl fumarate), are not routinely used in pediatric patients at this time given the limited data regarding the safety and efficacy of these treatments in children (Chitnis et al. 2012; Pena and Lotze 2013; Narula et al. 2015).

Given the potential severe long-term consequences of pediatric-onset MS, the current recommendation from IPMSSG is that children and adolescents with MS should have access to treatments currently approved for adults, and therapy should be started as early as possible in the disease course (Chitnis et al. 2012).

With the availability of more potent DMTs, the ultimate therapeutic goal would be to achieve a complete remission of clinical and MRI activity in the absence of tolerability or safety issues, through optimization of drug treatment early in order to prevent the consequent eventual accrual of disability and accumulation of cognitive deficits (Thomas and Banwell 2008; Narula et al. 2015).

1.2 BACKGROUND ON OCRELIZUMAB

Ocrelizumab is a recombinant humanized mAb that selectively depletes cluster of differentiation (CD)20–expressing B cells (Kappos et al. 2011; Klein et al. 2013). CD20 is a cell surface antigen found on pre–B cells and mature and memory B cells but not expressed on lymphoid stem cells and plasma cells (Stashenko et al. 1980; Loken et al. 1987, Tedder and Engel 1994). Although ocrelizumab selectively depletes CD20–expressing B cells, the capacity for B–cell reconstitution and preexisting humoral immunity are preserved (Martin and Chan 2006; DeLillo et al. 2008). In addition, innate immunity and total T–cell numbers are not affected.

The precise mechanisms through which ocrelizumab is thought to exert its therapeutic clinical effects in MS are not fully elucidated but involve immunomodulation through reduction in the number and function of B cells. These changes are thought to be responsible for the consequent improvement in the disease course of MS (Avivi et al. 2013).

1.2.1 Nonclinical Information

Repeat-dose toxicology studies of ocrelizumab at doses of up to 100 mg/kg, administered as 2 doses every 2 weeks (Days 1 and 15), 4 doses weekly (Days 1, 8, 15, and 22), or 8 doses every 3 weeks (Days 1, 22, 43, 64, 85, 106, 127, and 148), have been conducted. An embryo–fetal development study, a pre– and post–natal development study, male and female fertility studies, and a juvenile toxicity study in cynomolgus monkeys have also been completed.

In general toxicology studies, no adverse ocrelizumab–associated findings were identified, and pharmacological findings were consistent with the anticipated depletion of B cells in peripheral blood and lymphoid tissues. However, the following two studies did identify adverse findings that may be secondary to ocrelizumab-associated immunosuppression.

In a pre– and post–natal development study in cynomolgus monkeys, administration of ocrelizumab (15/20 and 75/100 mg/kg loading/study doses, which correspond to human equivalent doses of approximately 3000 mg [approximately 5 × clinical dose] and 15000 mg [approximately 25 × clinical dose], respectively) was associated with glomerulopathy (7 of 24 animals), lymphoid follicle formation in bone marrow (9 of 24 animals), and lymphoplasmacytic inflammation in the kidney (2 of 24 animals). Testicular weights of the neonates were significantly reduced in the 75/100 mg/kg group compared with controls. There were two cases of moribundity on study (2 of 24), one attributed to weakness due to premature birth accompanied by opportunistic infection and the other to an infective meningoencephalitis involving the cerebellum of the offspring from a maternal dam with an active infection (mastitis). The course of both neonatal infections could have potentially been affected by B–cell depletion. Newborn offspring of maternal animals exposed to ocrelizumab were noted to have depleted B–cell populations during the postnatal phase.

In an 8–week juvenile immunotoxicology study in cynomolgus monkeys, administration of ocrelizumab was associated with one mortality and one moribundity resulting in early euthanasia, both occurring in high-dose male cage–mates (100 mg/kg/week) and both occurring relatively early in the recovery period prior to recovery of peripheral blood B cells. Immunosuppression, secondary to the pharmacologic mechanism of action of ocrelizumab, B–cell depletion, is considered likely to have been an important contributing factor in both cases. No other deaths were observed in the study; all remaining animals survived to completion of the study. Ante–mortem immunophenotyping and postmortem microscopic findings confirmed ongoing

B−cell depletion leading to immunosuppression in both animals; however, the degree of B−cell depletion in peripheral blood and lymph nodes were not remarkable relative to other monkeys in this dose cohort. There was also evidence of generalized stress and debilitation in both animals. In the animal euthanized moribund, clinical pathology parameters and anatomic pathology findings consistent with a systemic inflammatory process were suggestive of breakdown of intestinal mucosal barrier function and the potential for systemic extension of intestinal endotoxemia and/or enteric infection, which could have developed secondary to immunosuppression. Of note, during the dosing period, all animals on study were 9−13 months of age, which in cynomolgus monkeys is roughly equivalent to a 4−year-old human in terms of overall development. Although the immune system is reasonably developed and humoral immunity is functional at this age, this is still a presumed period of heightened susceptibility as immune memory takes time to develop as host exposure to multiple foreign challenges occurs slowly over time, particularly for young study animals housed in controlled laboratory conditions. Therefore, the unique susceptibilities in this animal population due to lack of cumulative adaptive immune memory are not representative of the risk to the proposed pediatric population, in which a robust exposure to common pathogens during the first decade of life have occurred.

In the juvenile immunotoxicology study, although ocrelizumab did suppress T−dependent antibody responses to keyhole limpet cyanin (KLH), there was no evidence of lasting effects on humoral immunity as there was no ocrelizumab-associated effect on a neo-antigen challenge (tetanus toxoid) when antigen was administered following a recovery period (drug clearance and full B−cell recovery). In this study, 20 mg/kg was considered to be the no observable adverse effect level, which provides the following safety factors over the estimated exposures in the proposed pediatric trial:

- Maximum plasma concentration (C_{max}) at 20 mg/kg was 5-fold above projected C_{max} in pediatric trial
- Area under the concentration−time curve (AUC) from time 0 to last quantifiable timepoint (AUC_{0-t}) at 20 mg/kg was 13-fold above projected AUC at steady state (AUC_{ss}) in pediatric trial.

For details of the completed nonclinical ocrelizumab program, see the current Ocrelizumab Investigator's Brochure.

1.2.2 Clinical Pharmacology

The pharmacokinetics of ocrelizumab in adults was approximately linear and dose proportional between 400 and 2000 mg; higher clearance due to target−mediated drug disposition was observed at lower dose levels.

The pharmacokinetics of ocrelizumab in the adult MS studies was accurately described by a two-compartment model with time−dependent clearance and with pharmacokinetic (PK) parameters typical for an IgG1 mAb. Constant clearance and

central volume were estimated at 0.17 L/day and 2.78 L, respectively; peripheral volume and intercompartmental clearance at 2.68 L and 0.294 L/day, respectively; and initial time–dependent clearance at 0.0489 L/day. Terminal half-life was 26 days. Body weight was identified as the main covariate.

In Studies WA21493, WA21092, and WA21093 in adult patients with relapsing multiple sclerosis (RMS), treatment with 600 mg ocrelizumab (and 1000 mg × 2 [total 2000 mg] in Study WA21493) led to rapid and complete depletion of B cells in blood by 14 days post-treatment. B–cell depletion was sustained throughout the treatment period and through subsequent doses of open-label treatment. After the last dose of 600 mg ocrelizumab in Study WA21493, median time to repletion was 72 weeks (range 27–175 weeks).

1.2.3 Immunogenicity

Patients in MS Phase III trials (Studies WA21092, WA21093, and WA25046) were tested for anti–drug antibodies (ADA) at multiple timepoints (baseline and every 6 months post-treatment [i.e., just prior to the next ocrelizumab infusion]) for the duration of the trial. Of 1311 patients treated with ocrelizumab, 12 (~1%) patients tested positive for treatment–emergent ADAs during the controlled treatment period, and 2 of these patients tested positive for neutralizing antibodies (NAbs). There was no obvious signal of an impact of ADA on safety or efficacy. However, because ocrelizumab demonstrated very low incidence of immunogenicity in the Phase III trials, no final conclusion can be made on the impact of treatment–emergent ADAs on pharmacokinetics, pharmacodynamics, safety, and efficacy.

1.2.4 Current Clinical Development

Study WA21493 (which started in January 2008) is a Phase II, randomized, multicenter, placebo–controlled, double–blind, dose-finding study to evaluate the efficacy and safety of ocrelizumab in patients with RRMS. The controlled treatment period of Study WA21493 was completed at Week 24, and the open-label period of the study is ongoing. Data from the 96–week treatment period and the 48–week treatment–free period (Week 144 data) are presented in the Ocrelizumab Investigator's Brochure.

The Phase III clinical program in adult patients with MS has been completed and consisted of two identical studies in patients with RMS (WA21092, OPERA I and WA21093, OPERA II) and one Phase III study in patients with PPMS (WA25046, ORATORIO). The double-blinded control periods for these three pivotal studies were completed in 2015, and eligible patients were able to enter the open–label extension (OLE) period of each study.

Recently, participants who completed the OLE of Studies WA21092, WA21093 and WA25046 were allowed to roll over to Study MN43964 (OLERO) to continue treatment with ocrelizumab and the collection of long-term safety and efficacy data.

The controlled period of the Phase IIIb study (BN29739) to evaluate the effects of ocrelizumab on the immune response of patients with RMS to vaccines has been completed. Additional open−label Phase IIIb studies are ongoing.

Data from these studies are presented in the current Ocrelizumab Investigator's Brochure.

1.2.4.1 Efficacy in Relapsing Multiple Sclerosis

Data presented below are from the completed double−blind, double-dummy treatment period of the two pivotal Phase III studies in RMS (Studies WA21092 and WA21093) up to the clinical cutoff dates of 2 April 2015 and 12 May 2015, respectively. The efficacy results as well as the pooled analysis from these pivotal studies show that ocrelizumab suppresses relapses and disease progression (clinical and subclinical disease activity) compared with IFN beta−1a 44 μg SC in patients with RMS over the course of 2 years (96 weeks).

Efficacy outcomes were consistent between trials and across the primary and key clinical and imaging secondary endpoints.

In comparison with IFN beta−1a 44 μg SC, ocrelizumab 600 mg demonstrated:

- Relative reductions of 46% and 47% for the primary endpoint of protocol-defined annualized relapse rate (ARR) in Studies WA21092 and in WA21093, respectively (both $p < 0.0001$)
- A 40% risk reduction for 12−week confirmed disability progression (CDP) in the pooled Study WA21092/WA21093 analysis ($p = 0.0006$). Each individual trial also demonstrated a significant reduction of 12−week CDP (43% reduction [$p = 0.0139$] in Study WA21092 and 37% [$p = 0.0169$] in Study WA21093).
- Relative reductions of 94% and 95% in the number of T1 gadolinium (Gd)−enhancing lesions in Studies WA21092 and WA21093, respectively (both $p < 0.0001$)
- Relative reductions of 77% and 83% in the total number of new and/or enlarging T2 lesions in Studies WA21092 and WA21093, respectively (both $p < 0.0001$).
- A 33% relative increase in proportion of patients with 12-week confirmed disability improvement (CDI) in the pooled Study WA21092/WA21093 analysis ($p = 0.0194$). Study WA20192 demonstrated a 61% relative increase in the proportion of patients with 12−week CDI ($p = 0.0106$), whereas in Study WA21093, there was no statistically significant difference between treatment groups (14% relative increase, $p = 0.4019$).
- A 40% risk reduction for 24−week CDP in the pooled Study WA21092/WA21093 analysis ($p = 0.0025$). Each individual trial also demonstrated a significant reduction of 24−week CDP (43% reduction [$p = 0.0278$] in Study WA21092 and 37% [$p = 0.0370$] in Study WA21093).

- Relative reductions of 57% and 64% (both $p < 0.0001$) in the total number of new T1 hypointense lesions (chronic black holes) in Studies WA21092 and WA21093, respectively.

Ocrelizumab also showed numerically superior outcomes in additional secondary efficacy endpoints in the following hierarchical order (for results where the formal testing procedure had previously concluded, p–values are indicated as "non–confirmatory"):

- Greater mean improvement in the Multiple Sclerosis Functional Composite Scale from baseline to Week 96 in Study WA21092 ($p = 0.3261$) and Study WA21093 ($p = 0.0040$)
- Relative reduction in the rate of brain volume loss from Week 24 to Week 96 of 22.8% in Study WA21092 (non–confirmatory, $p = 0.0042$) and 14.9% in Study WA21093 ($p = 0.0900$)
- Higher mean change in SF-36 Physical Component Summary score from baseline to Week 96 in Study WA21092 (non–confirmatory, $p = 0.2193$) and Study WA21093 (non–confirmatory, $p = 0.0404$)
- 74% and 81% relative increases in the proportion of patients with no evidence of disease activity in Studies WA21092 and WA21093, respectively (non–confirmatory, $p < 0.0001$ for both studies in patients with EDSS ≥ 2)

Robust data from the two pivotal Phase III studies WA21092 and WA21093 presented above provide compelling evidence of the efficacy of ocrelizumab in patients with RMS.

The efficacy data from the RMS studies are further supported by the results from the pivotal Phase III PPMS study WA25046, which showed superiority of ocrelizumab 600 mg compared with placebo on the following primary and secondary endpoints:

- A 24% risk reduction for the primary endpoint 12–week CDP ($p = 0.0321$)
- A 25% risk reduction for 24–week CDP ($p = 0.0365$)
- A 29% relative reduction in the progression rate in T25–FW ($p = 0.0404$)
- A 3.4% decrease in T2 hyperintense lesion volume on ocrelizumab, compared with an increase of 7.4% on placebo ($p < 0.0001$)
- A 17.5% relative reduction in the rate of brain volume loss (from Week 24 to 120, $p = 0.0206$).

1.2.4.2 Safety in Multiple Sclerosis

Safety data presented below are from the completed controlled treatment periods of the two pivotal Phase III studies in RMS (WA21092 and WA21093) and the Phase III study in PPMS (WA25046). For more information on data from controlled treatment periods and OLE periods from ongoing studies, refer to the current Ocrelizumab Investigator's Brochure.

In the 96−week controlled treatment period of the Phase III RMS studies (WA21092 and WA21093), a total of 1651 patients received study drug and were included in the safety analyses of the pooled data (IFN beta−1a: 826 patients; ocrelizumab: 825 patients).

The safety profile in the IFN beta-1a treatment group was consistent with the labeled safety information available for IFN beta−1a. Compared with results from the Phase II study in RRMS (WA21493), there were no new or unexpected safety findings associated with ocrelizumab during the 96-week controlled treatment period.

The number of patients who experienced any adverse event (83.3% in both groups) and the total number of adverse events (IFN beta−1a: 4141 adverse events; ocrelizumab: 4194 adverse events) were well balanced between the two treatment groups; the majority of adverse events were Grade 1 or Grade 2. The proportion of patients who experienced a serious adverse event (IFN beta−1a: 8.7% vs. ocrelizumab: 6.9%) was similar between treatment groups. Overall, the rates of adverse events, including serious, remained stable with additional exposure to ocrelizumab.

A total of 725 patients in the Phase III PPMS controlled treatment period received study drug and were included in the safety analysis (placebo: 239 patients; ocrelizumab: 486 patients). The proportion of patients who experienced at least one adverse event was 90% in the placebo treatment group compared with 95.1% in the ocrelizumab treatment group; the majority of adverse events were Grade 1 or 2. The proportion of patients who experienced a serious adverse event (placebo: 22.2% vs. ocrelizumab: 20.4%) was similar in both groups. The intensity of most serious adverse events was reported as Grade 3.

Infusion-Related Reactions

Infusion-related reactions (IRRs) are known to occur with the administration of mAbs and were the most common adverse events in ocrelizumab-treated patients. In the RMS and PPMS trials, symptoms associated with IRRs included, but were not limited to, pruritus, rash, urticaria, erythema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, nausea, and tachycardia. There were no fatal IRRs in the controlled clinical trials.

In active−controlled (RMS) clinical trials, IRRs were the most common adverse event in patients treated with ocrelizumab, with an overall incidence of 34.3% compared with an incidence of 9.9% in the IFN beta−1a treatment group (placebo infusion).

The incidence of IRRs was highest during Dose 1, Infusion 1 (27.5%) and decreased over time to $<10\%$ at Dose 4. The majority of IRRs in both treatment groups were mild to moderate.

In the placebo−controlled (PPMS) clinical trial, the incidence of IRRs was highest during Dose 1, Infusion 1 (27.4%) and decreased with subsequent doses to $<10\%$ at Dose 4.

A greater proportion of patients in each group experienced IRRs with the first infusion of each dose compared with the second infusion of that dose. The majority of IRRs were mild to moderate.

IRRs were managed with premedication prior to each infusion (mandatory steroid pretreatment and additional recommendation for analgesic/antipyretic and/or antihistamine treatments); by treating symptoms; and by slowing, interrupting, or discontinuing the infusion of ocrelizumab.

Infections

In both the RMS and PPMS populations during the controlled treatment period, the rates of urinary tract infections, gastrointestinal infections, skin infections (no particular type), lower respiratory tract infections, infectious biliary disorders, sepsis/systemic inflammatory response syndrome, and CNS infections were comparable between the ocrelizumab and comparator groups (IFN beta−1a or placebo).

In the active-controlled (RMS) and the placebo-controlled (PPMS) clinical trials, respiratory tract infections and herpes infections were more frequently reported in the ocrelizumab treatment arm.

The proportion of respiratory tract infections was higher in the ocrelizumab-treated patients compared with IFN beta−1a and placebo−treated patients. The infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections (including nasopharyngitis) and bronchitis.

In active-controlled (RMS) clinical trials, herpes infections were reported more frequently in ocrelizumab−treated patients than IFN beta−1a treated patients including herpes zoster (2.1% vs. 1.0%), herpes simplex (0.7% vs. 0.1%), and oral herpes (3.0% vs. 2.2%), genital herpes (0.1% vs. 0%), and herpes virus infection (0.1% vs. 0%). Infections were predominantly mild to moderate in severity and patients recovered with treatment by standard therapies. There were no reports of disseminated herpes.

In the placebo−controlled (PPMS) clinical trial, a higher proportion of patients with oral herpes (2.7% vs. 0.8%) were observed in the ocrelizumab treatment arm. There was no increase in serious infections associated with ocrelizumab treatment (in patients with RMS the rate of serious infections was lower than for IFN beta−1a treated patients, and in patients with PPMS, the rate was similar to placebo−treated patients).

No opportunistic infections, including progressive multifocal leukoencephalopathy (PML), were reported during the controlled treatment periods.

Event rates for most types of infections were generally stable with no consistent increase or decrease between doses of ocrelizumab, with the exception of upper

respiratory tract infection, which was reported at a higher rate following Dose 1 and then declined over time.

Malignancy

In the controlled treatment period of the MS program (Studies WA21493, WA21092, WA21093, and WA25046), there were 20 malignancies in 18 patients receiving ocrelizumab.

During the 96–week controlled treatment period of RMS studies (WA21092 and WA21093), a total of 6 malignancies were reported: 2 events (1 mantle cell lymphoma and 1 squamous cell carcinoma) occurred in 2 patients (0.2%) in the IFN beta–1a treatment group, and 4 events (2 invasive ductal breast carcinoma, 1 renal cancer, and 1 malignant melanoma) occurred in 4 patients (0.5%) in the ocrelizumab treatment group.

In the controlled treatment period of PPMS study (WA25046), a total of 15 malignancies in 13 patients were reported: 2 events (basal cell carcinoma and adenocarcinoma of the cervix) occurred in 2 patients (0.8%) in the placebo treatment group and 13 events (5 basal cell carcinoma, 2 invasive ductal breast carcinoma, 1 anaplastic large–cell lymphoma, 1 breast cancer, 1 endometrial cancer, 1 invasive breast carcinoma, 1 malignant fibrous histiocytoma, and 1 pancreatic carcinoma metastatic) occurred in 11 patients (2.3%) in the ocrelizumab treatment group.

In the Phase II study (WA21493) 1 malignancy (breast cancer) was reported in the ocrelizumab treatment group.

For detailed information and most recent analyses of malignant events reported during controlled and OLE treatment periods of the MS program, refer to the current Investigator's Brochure.

Laboratory Data

Immunoglobulins

Treatment with ocrelizumab resulted in a decrease in total Igs over the controlled period of the studies, mainly driven by reduction in IgM, with no apparent association with serious infections.

In the active-controlled (RMS) studies (Studies WA21492 and WA21493), the proportion of patients at baseline reporting IgG, IgA and IgM less than the lower limit of normal (LLN) in the ocrelizumab treatment arm was 0.5%, 1.5%, and 0.1%, respectively. Following treatment, the proportion of ocrelizumab–treated patients reporting IgG, IgA, and IgM less than the LLN at 96 weeks was 1.5%, 2.4%, and 16.5%, respectively. The proportion of patients with a decrease in Ig below LLN increased over time and successive dosing. There was no association between sustained decreases in

Ig (defined as IgA, IgG, or IgM levels below LLN for at least two consecutive visits) and infection rates.

In the placebo–controlled (PPMS) study (Study WA25046), the proportion of patients at baseline reporting IgG, IgA and IgM less than the LLN in the ocrelizumab treatment arm was 0.0%, 0.2% and 0.2%, respectively. Following treatment, the proportion of ocrelizumab–treated patients reporting IgG, IgA, and IgM less than the LLN at 120 weeks was 1.1%, 0.5%, and 15.5%, respectively.

CD19+ B Cells

In RMS, treatment with ocrelizumab led to rapid depletion of CD19+ B cells in blood with near complete depletion by Day 14 post–treatment as the expected pharmacologic effect (B–cell counts decreased from a baseline mean of 257.64 cells/μL to 0.98 cells/μL by Week 2). This peripheral blood B–cell depletion was sustained over the course of treatment, and only 4.1%, 3.3%, and 2.2% of patients after Doses 2, 3, and 4, respectively, had repleted their CD19+ B cells (defined as CD19+ B cells ≥ LLN [80 cells/μL] or back to baseline levels, whichever was lower) before the next infusion. In PPMS, CD19+ B-cell depletion in blood was similar to that observed in patients with RMS. CD19+ B cells decreased from a baseline mean of 231 cells/μL to a mean of 2.7 cells/μL by Day 14 post–treatment, and B cells remained low throughout treatment.

The longest follow-up time after the last ocrelizumab infusion from the 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).

Neutrophils

In the active-controlled (RMS) treatment period, decreased neutrophils were observed in 14.7% of patients treated with ocrelizumab as compared with 40.9% of patients treated with IFN beta–1a. In the placebo–controlled (PPMS) clinical trial, the proportion of patients treated with ocrelizumab presenting decreased neutrophils was slightly higher (12.9%) than patients treated with placebo (10.0%).

The majority of the decreased neutrophils were transient (only observed once for a given patient treated with ocrelizumab) and were Grades 1 and 2 in severity. Overall, approximately 1% of the patients in the ocrelizumab treatment group had Grade 3 or 4 neutropenia and was not temporally associated with an infection.

Antibody Titers

In the controlled treatment period of RMS studies, ocrelizumab did not appear to have an effect on specific humoral immunity to common bacterial and viral antigens over the 96-week study period (*Streptococcus pneumoniae*, mumps, rubella, varicella zoster). The proportions of patients with positive antibody titers against rubella, mumps, and varicella at Week 96 were similar to the proportions at baseline. Similarly for PPMS, no effect on specific humoral immunity to common bacterial and viral antigens was

observed with ocrelizumab during the controlled treatment period at Week 120 (*S. pneumoniae*, mumps, rubella, varicella zoster). The proportions of patients with positive antibody titers against rubella, mumps, and varicella at Week 120 were similar in both groups.

ADAs

Of 807 adult patients with RMS who received ocrelizumab and had an ADA assay result from a post–baseline sample during the controlled treatment period, 0.4% (3 patients) showed positive (treatment–induced and –enhanced) ocrelizumab ADAs. Of these, 1 patient tested positive for NAbs to ocrelizumab. No IRRs or other relevant adverse events such as hypersensitivity reactions were observed in the patient who developed NAbs.

Of the 481 adult patients with PPMS who received ocrelizumab and had an ADA assay result from a post-baseline sample during the controlled treatment period, 9 patients (1.9%) showed positive (treatment–induced and –enhanced) ocrelizumab ADAs. Of these, 1 patient tested positive for NAbs to ocrelizumab. The patient who developed NAbs did not experience any IRR or hypersensitivity reactions.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Preventing the accrual of irreversible neurological impairment is a key goal of MS therapy and is particularly important in pediatric patients where the onset of the disease is much earlier and patients reach higher EDSS milestones at a younger age than in adult onset MS. Subclinical inflammatory activity and neurodegenerative changes occur early and persist throughout the course of RMS. Emerging evidence suggests that brain volume loss along with cognitive and behavioral changes may be evident by the time the first clinical evidence of MS has appeared (Rocca et al. 2003; Azevedo et al. 2015; Labiano-Fontcuberta et al. 2015; Rojas et al. 2015; Sinay et al. 2015; Labiano-Fontcuberta et al. 2016). Left untreated or undertreated, over time both clinically apparent and subclinical disease activity result in CNS tissue damage, disability accrual, and diminishing quality of life.

Suppression of disease activity as early as possible remains an important goal of therapy in MS. With the emergence of more efficacious therapies and a better understanding of the consequences of subclinical disease activity in recent years, physicians have a lower tolerance for allowing disease activity to persist in recognition of the fact that what is lost in MS cannot typically be regained. The potential risk of irreversible disease progression is therefore an important factor in the therapeutic decision-making of patients and their physicians (Gold et al. 2010). The prompt initiation of therapies in children and adolescents is supported by the IPMSSG (Chitnis et al. 2012). Its consensus statement advocates offering therapy to all patients diagnosed with MS regardless of clinical presentation, as there are no reliable means to identify patients destined to have a benign course.

Thus, there is a need for highly effective therapies with a benefit–risk profile that supports expeditious use at any time during the course of disease to preserve CNS tissue and neurologic function, stem accrual of irreversible disability, and improve the quality of life for people living with RMS, including patients with pediatric–onset disease.

The Phase III program of ocrelizumab comprised three pivotal Phase III studies (WA21092 and WA21093 in RMS, and WA25046 in PPMS) that evaluated ocrelizumab 600 mg administered as an IV infusion at a fixed–interval schedule every 24 weeks. These studies contribute to the evaluation of the safety and efficacy of ocrelizumab in RMS and PPMS and provide data from a total of 2381 patients.

The two pivotal RMS studies show that compared with IFN beta-1a, ocrelizumab significantly reduced protocol–defined ARR, both 12– and 24–week CDP in the pooled analysis of the two studies as well as in each individual study. The magnitude of the treatment effect on CDP was highly consistent between the 12– and 24–week endpoints and between studies, representing a substantial improvement over available therapies. The CDP results are complemented by increases in the number of patients with 12–week CDI. MRI findings provide additional evidence of suppression of subclinical disease activity by ocrelizumab in patients with RMS, with profound and continued near–complete suppression of T1 Gd–enhancing lesions and marked, consistent reductions in new and/or enlarging T2 hyperintense lesions, T1 hypointense brain lesions, and reduced rate of brain volume loss compared with IFN beta–1a.

These robust treatment effects on clinical and subclinical measures of inflammation and disease progression demonstrate superiority of ocrelizumab compared with IFN beta–1a, a well–characterized and established MS therapy that is one of the current mainstays of pediatric MS therapy.

Overall results across the three pivotal Phase III studies show that depletion of CD20+ B cells leads to a significant impact on a broad range of clinical measures of disease, including disability progression, in addition to an impact on MRI outcomes. These findings further support the hypothesis that B cells are central to the pathogenesis of MS.

In adults, ocrelizumab demonstrates a favorable overall safety profile over multiple doses. The main risks associated with treatment were IRRs, which were manageable by appropriate measures, and infections, both mostly Grade 1 or 2 in intensity, which are consistent with the mAb nature and mechanism of action of ocrelizumab. The favorable benefit–risk profile of ocrelizumab observed in adult patients with RMS when compared with IFN beta–1a is expected to be similar in children and adolescents ages from $\geq$10 to $<$18 years with RRMS.

This study is the first clinical trial investigating the use of ocrelizumab in pediatric patients. Therefore, only a small number of patients with RRMS will be enrolled, and an open–label design has been adopted to assess all safety, PK, and pharmacodynamic (PD) data closely in an ongoing manner.

1.3.1 Rationale for Ocrelizumab Dose

On the basis of its therapeutic class (IgG1 antibody), mechanisms of clearance (by the specific CD20 receptor–mediated pathway and the non–specific IgG clearance pathway, rather than via CYP450 or renal elimination as for small molecules), and PK properties, the pharmacokinetics of ocrelizumab in children and adolescents is expected to be similar to that in adults. Pediatric studies with rituximab (a chimeric anti–CD20 mAb with a mechanism of action similar to ocrelizumab) support this view (Bennett 2006) and also suggest the pattern of peripheral blood B–cell depletion and repletion in children and adolescents to be similar to that in adults, although available data are limited.

As the PK/PD relationship for the mechanism of action of ocrelizumab (i.e., B–cell depletion) is expected to be comparable in adults and children/adolescents with MS, a bridging approach is proposed (i.e., select a dose for children and adolescents age 10–17 years that achieves the same systemic PK exposure to ocrelizumab as observed in adult patients with MS at the identified therapeutic dose [600 mg every 24 weeks]). Pharmacokinetics and pharmacodynamics (B–cell count in blood) will be measured in this first PK/PD study in children and adolescents to confirm this expectation.

Body weight was identified as the most relevant covariate in the population PK analysis conducted with the data from the three pivotal Phase III studies in adult patients with RMS and PPMS (body weight: 38–170 kg). The population PK model was used to predict the pharmacokinetics (i.e., the median average concentration over the 24–week dosing interval) in children and adolescents with a body weight range of 25–100 kg (representing children and adolescents from 10–17 years). Therefore, a body weight limit of 25 kg (which is at the very low end of the range for a 10–year-old child) is added to the eligibility criteria to avoid overexposing very lean patients.

mAbs are not metabolized via CYP450s or renally excreted (factors that are known to be different between children and adults), and therefore, body weight—which was identified as the main covariate in adult patients—is also expected to be the most relevant covariate for individual exposure in children and adolescents. On the basis of this population PK model, it is therefore predicted that in children and adolescent patients with a body weight $\geq$40 kg, a dose of 600 mg ocrelizumab will result in an exposure similar to the adult exposure range observed at 600 mg in the Phase III studies in adults. For pediatric patients from $\geq$25 kg to $<$40 kg, a dose of 300 mg is predicted to result in an exposure below or similar to the adult exposure range at 600 mg, even in young children at the very low end of the age (10 years) and body weight (25 kg) range.

Therefore, in this pediatric PK/PD study, a cohort of 6 patients with a body weight from ≥25 kg to <40 kg (at least 2 patients with body weight from ≥25 kg to ≤35 kg) will receive 300 mg ocrelizumab (half of the adult dose). In parallel, a cohort of at least 6 pediatric patients with a body weight ≥40 kg (at least 2 patients with body weight ≥40 kg but ≤50 kg) will receive 600 mg (equivalent to the adult dose) of ocrelizumab. The study is designed to identify the appropriate dose in pediatric patients who are below the body weight of patients included in the adult Phase III studies (approximately 40 kg) and to confirm that the adult dose of 600 mg is also appropriate for pediatric patients ≥40 kg. This range of body weight should also ensure that the study enrolls pediatric patients at both the lower and higher end of the age range (10–17 years).

If the dose of 600 mg in pediatric patients ≥40 kg results in a similar exposure and similar PD effects as observed in adult patients with MS, then this dose will be selected for the subsequent Phase III study in patients with a body weight ≥40 kg. If the exposure and/or PD effects are different from those observed for adults, another dose level will be explored in a new cohort of 6 pediatric patients ≥40 kg. The dose in this additional cohort will be selected on the basis of all PK and PD results obtained in this PK/PD study at that point.

If the dose of 300 mg in pediatric patients from ≥25 kg to <40 kg results in a similar exposure and similar PD effects as observed in adult patients with MS at the identified therapeutic dose (i.e., 600 mg every 24 weeks), the dose of 300 mg will be selected as the Phase III study dose in pediatric patients from ≥25 kg to <40 kg. If the exposure and/or PD effects are different from those observed for adults at 600 mg, another dose level will be explored in a new cohort of 6 pediatric patients from ≥25 kg to <40 kg. The dose in this additional cohort will be on the basis of all PK and PD results obtained in this PK/PD study at that point.

As stated above, B–cell depletion upon administration of ocrelizumab is anticipated to be similar in children/adolescents and adult patients with MS. There is, however, literature indicating higher B–cell counts in children (healthy subjects) compared with adults (Morbach et al. 2010; Duchamp et al. 2014). Because of the target–mediated drug disposition, a dose higher than 600 mg may be required and may be administered on the basis of the review of the PK and PD (B cells) data obtained with the 300– and 600–mg dose in pediatric patients from ≥25 kg to <40 kg and ≥40 kg, respectively. The protocol allows administration of a dose up to a maximum of 1200 mg in the additional cohort(s) of patients. A dose of 2000 mg had a similar safety profile compared with 600 mg in adult patients (Phase II RRMS Study WA21493).

In summary, the aim of this study is to identify a dose in children and adolescents which results in the same exposure (PK) and blood B-cell depletion (PD) as observed in adult patients with MS at the approved dose of 600 mg and with significant safety margin. The PK model predicts this to be achieved with a dose of 300 mg in patients

with 25–40 kg body weight, and with a dose of 600 mg in patients above 40 kg body weight. The PK and PD data will be closely assessed in the cohort of 6 patients (weight 25–40 kg) at 300 mg and at least 6 patients (weight ≥40 kg) at 600 mg. Only if the PK and PD data derived from these initial 6 patients per dose level indicate that a lower or higher dose of ocrelizumab is required to achieve the same PK and PD effects as observed for adult patients with MS with 600–mg dose will a lower or higher dose be assessed in a maximum total of approximately 36 patients.

2. OBJECTIVES AND ENDPOINTS

This 8–year study will evaluate the safety, tolerability, pharmacokinetics, and PD effects of ocrelizumab in children and adolescents ages ≥10 to <18 years with RRMS.
The data from this study will serve to determine the dosing regimen of ocrelizumab to be further investigated in the subsequent Phase III study in children and adolescents.
In addition, new emergent data (e.g., Real World Evidence data) may be used to support the dose selection. Specific objectives and corresponding endpoints for the study are outlined below.

Table 1 Objectives and Corresponding Endpoints

Primary Pharmacokinetic Objective	Corresponding Endpoint
To characterize the ocrelizumab PK profile in children and adolescents	• Serum concentration of ocrelizumab at specified timepoints
Primary Pharmacodynamic Objective	**Corresponding Endpoint**
To evaluate relationship between drug exposure and PD (CD19+ B–cell count) in children and adolescents	• Levels of CD19+ B-cell count in blood
Secondary Safety Objective	**Corresponding Endpoints**
To evaluate safety of ocrelizumab in children and adolescents	• Occurrence and severity of adverse events, with severity determined according to NCI CTCAE v5.0 • Change from baseline in vital signs • Change from baseline in clinical laboratory test results • Level of circulating B cells, T cells, natural killer cells, and other leukocytes • Developmental milestones (e.g., growth, bone age, age at menarche, Tanner staging) • Non–MS CNS pathology as measured by brain MRI scans • Levels of blood immunoglobulins • Antibody titers against standard vaccines
Secondary Immunogenicity Objective	**Corresponding Endpoint**
To assess ADA development to ocrelizumab	• Presence of ADAs during the study relative to the presence of ADAs at baseline
Exploratory Objective	**Corresponding Endpoints**
To evaluate exploratory parameters	• Nature, frequency, and severity of clinical and protocol–defined relapses • Change in EDSS • Change in total number of new and/or enlarging T2 hyperintense lesions • Total number of T1 gadolinium–enhancing lesions at Week 12 • Change in Symbol Digit Modalities Test • Change in low-contrast visual acuity

ADA = anti–drug antibody; EDSS = Expanded Disability Status Score; MRI = magnetic resonance imaging; MS = multiple sclerosis; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; PD = pharmacodynamic; PK = pharmacokinetic.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design and Dosing Regimen

The study will enroll at least 12 patients and up to a maximum of approximately 36 patients.

Patients who are prematurely discontinued from the study (for reasons other than safety findings) before completion of the 24–week period will be replaced to ensure adequate numbers of evaluable patients in order to select the appropriate dosing regimen in children/adolescents for the subsequent efficacy study. In this case more patients may have to be enrolled.

Two dose levels will initially be assessed as follows:

- Cohort 1 (300 mg, for patients with a body weight from ≥25 kg to <40 kg): 300–mg ocrelizumab will be evaluated in a cohort of 6 patients with a body weight from ≥25 kg to <40 kg, with at least 2 patients with a body weight from ≥25 kg to ≤35 kg.
- Cohort 2 (600 mg, for patients with a body weight ≥40 kg): 600–mg ocrelizumab will be evaluated in a cohort of at least 6 patients with a body weight ≥40 kg (with at least 2 patients with a body weight ≥40 kg but ≤50 kg).

  Note: enrollment of patients with a body weight ≥40 kg is closed.

Safety, tolerability, pharmacokinetics, and PD effects will be frequently assessed (see schedule of activities, Appendix 1) and monitored in an ongoing manner.

Consistent with the Phase III studies in adult patients, the first dose of ocrelizumab must be divided and administered as two IV infusions given 14 days apart (i.e., 2×150 mg for a total dose of 300 mg, and 2×300 mg for a total dose of 600 mg) to minimize IRRs upon the first administration of ocrelizumab.

Thereafter, subsequent doses will be administered as single infusions (i.e., 1×300– or 1×600–mg infusions). A visit will be required within 2 weeks prior to the planned dosing visit to collect blood samples and patient information to confirm re–treatment criteria are met (see Section 4.3.6).

Safety, tolerability, pharmacokinetics, and PD data (i.e., B–cell depletion and repletion as observed within the given treatment period) obtained in each cohort will be assessed by an Internal Monitoring Committee (IMC).

Different decisions may be taken by the IMC to enable the identification of the most appropriate dosing regimen. These include but are not limited to:

- Assess a dose level other than the one investigated in Cohort 1 or Cohort 2, without exceeding the dose of 1200 mg over 6 months. In this case, at least 6 new patients

will be enrolled at any new investigated dose level, up to a total of approximately 36 patients in this study.

- Allow the enrollment of more patients to expand the knowledge of the effects of ocrelizumab at the already tested dose levels, without exceeding a total of approximately 36 patients enrolled in this study.
- Assess different dosing intervals/regimens, without exceeding a total dose of 1200 mg over 6 months for a total of approximately 36 patients enrolled in this study.

Recruitment of new patients in a new cohort may be stopped if additional data from this cohort is not judged to be required.

The potential additional dosing level(s)/regimens of ocrelizumab to be assessed in additional cohort(s) will be determined on the basis of PK, PD, safety, and tolerability data analyses of all data available at the time of such analysis. The additional dose level(s) may be lower than 300 mg, between 300 mg and 600 mg, or higher than 600 mg, but will under no circumstances be higher than 1200 mg.

As soon as relevant data are available, the IMC will review all accumulated safety, tolerability, PK, and PD data and decide on the appropriate dosing regimen to be investigated in the subsequent Phase III study in children and adolescents. At that point, all patients enrolled in this study will change to this final selected pediatric dosing regimen.

In addition to reviewing data for each cohort, the IMC may review available safety/PK/PD data on an ad-hoc basis, as deemed necessary by the Study Management Team or by the IMC on the basis of emerging data. The IMC will be informed immediately of any serious adverse events (see IMC Charter for more details).

Once a dose is determined for one or both of the body weight ranges (i.e., patients from $\geq$25 kg to $<$40 kg and/or patients $\geq$40 kg), the subsequent Phase III study in children and adolescents with RRMS will start using the dose levels/regimens determined for the specified body weight range.

The 600 mg dose for patients $\geq$40 kg has now been determined and will be used accordingly in the ongoing Phase III study in children and adolescents with RRMS.

This study may remain open for a specific body weight range should additional patient data be needed to determine the dose within this specific weight range.

264-Week Optional Ocrelizumab Extension

At Week 24, patients who have completed the 24–week period will be offered to continue ocrelizumab treatment in an optional treatment extension period with the dose initially assigned to them until the appropriate dosing regimen for the subsequent

Phase III study in children and adolescents is selected by the IMC. At that time, patients will be assigned to this selected dosing regimen.

Should a subsequent dose be higher than the dose in the initial treatment regimen, that dose must be administered as two infusions of half the dose 14 days apart to mitigate the risk and severity of IRRs.

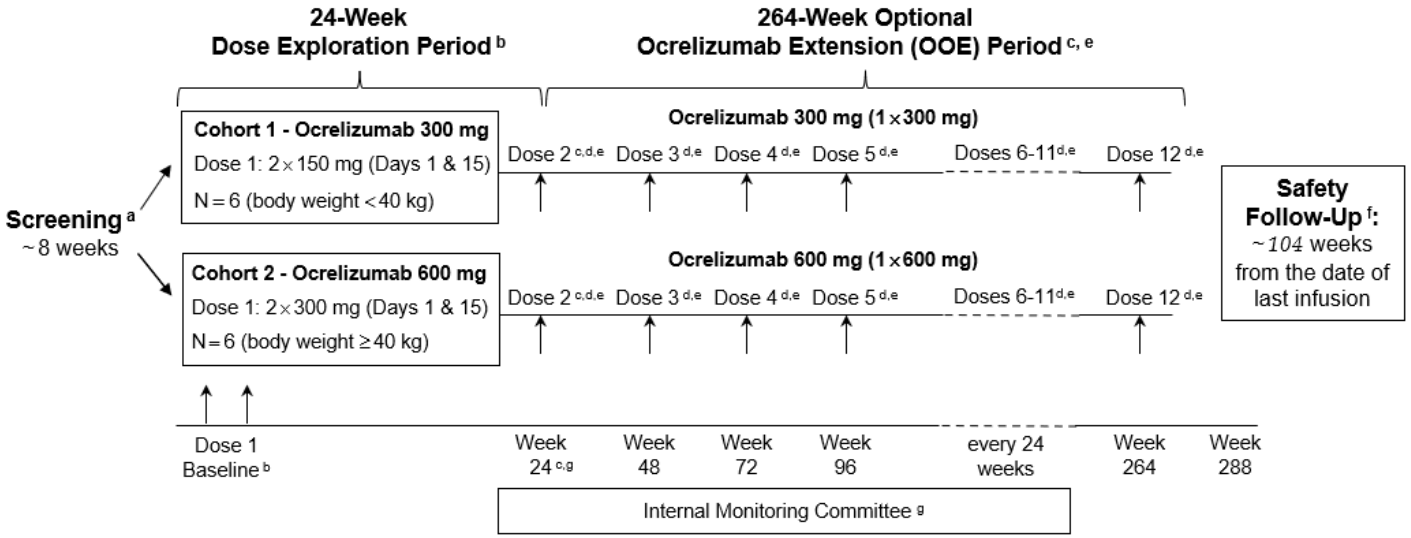
A re–evaluation of the benefit-risk of continuing study treatment by the treating investigator must be performed for each patient at the end of the first 24 weeks and prior to any further dosing, and therapy extension will only be granted to those patients where the benefit-risk is considered to be favorable.

The investigator should discuss the benefits and risks of continuing study treatment with the parents/legal guardian and patient in advance and prior to any further dosing.

For patients continuing the study, the second dose of ocrelizumab will be administered if all re-treatment criteria are met (Section 4.3.6).

See Figure 1 for the study schema. A schedule of activities is provided in Appendix 1.

Figure 1 Overview of Study Design



IMC = Internal Monitoring Committee; OOE = Optional Ocrelizumab Extension.

[a] Screening for the study may be extended but cannot exceed 10 weeks for relevant clinical, administrative, or operational reasons.

[b] Eligible patients will be allocated into one of two treatment groups depending on their body weight at screening. The first dose of ocrelizumab for the 24-week period must be administered as two infusions of half the dose 14 days apart. Patients who receive a partial or complete dose of ocrelizumab and discontinue from the 24–week period will enter the safety follow-up period (at least *104* weeks).

[c] At Week 24, patients will have the opportunity to continue with ocrelizumab treatment by entering a 264–week optional ocrelizumab extension period. For patients continuing the extension, subsequent doses of ocrelizumab will be administered if all re-treatment criteria are met.

[d] Treating investigator must ensure patients meet criteria for re-treatment with ocrelizumab before each subsequent infusion (Section 4.3.6).

[e] It is planned that patients will continue in the optional ocrelizumab extension period with the dose corresponding to their initial treatment regimen until the appropriate dosing regimen is selected by the IMC. At that time, patients will be assigned to this selected dose level. In a situation where a subsequent dose is higher than the initial treatment regimen, that dose must be administered as two infusions of half the dose 14 days apart.

Figure 1 Overview of Study Design (cont.)

[f] Patients completing the 288–week treatment period, or patients who discontinue treatment prematurely for any reason at any time during the study, will enter the safety follow–up period (for more details see Section 3.1.1.4).

[g] The IMC will review all data obtained in each cohort (for more details see Section 3.1.1).

3.1.1.1 Screening and Re-screening

Consenting patients will enter the 8-week screening period to be evaluated for eligibility. The screening period may be extended but cannot exceed 10 weeks for relevant clinical, administrative, or operational reasons.

Procedures at screening will include thorough medical history, physical examination, medical examination including thorough neurologic examination, EDSS score, ECG, and blood and urine samples. See the schedule of activities provided in Appendix 1 for further details.

Local Ethics Committees (ECs) or National Competent Authorities may require additional diagnostic testing for selected patients or selected centers to exclude tuberculosis, Lyme disease, HTLV-1 associated myelopathy, AIDS, hereditary disorders, connective tissue disorders, or sarcoidosis.

Patients may be re-screened if the underlying reason for previous screen failure no longer applies in the investigator's clinical judgment. Additionally, a patient may be re-screened if the inclusion/exclusion criteria leading to previous non-eligibility have been amended in the protocol, rendering the patient potentially eligible for the study. If a patient is re-screened, all screening assessments must be repeated for the same protocol, using a new screening number.

3.1.1.2 24-Week Dose Exploration Period

Initially, eligible patients will be assigned to one of two treatment groups depending on their body weight at screening: ocrelizumab 300-mg regimen (Cohort 1, from $\geq$25 kg to $<$40 kg body weight) or ocrelizumab 600-mg regimen (Cohort 2, $\geq$40 kg body weight).

Each cohort will enroll 6 patients as follows:

- Cohort 1: 6 patients with a body weight from $\geq$25 kg to $<$40 kg, with at least 2 patients with a body weight from $\geq$25 kg to $\leq$35 kg
- Cohort 2: at least 6 patients with a body weight $\geq$40 kg (with at least 2 patients with a body weight $\geq$40 kg, but $\leq$50 kg)

The first dose of ocrelizumab for the 24–week period must be administered as two infusions of 150 mg 14 days apart (300–mg dose) or two infusions of 300 mg 14 days apart (600–mg dose).

During the treatment period, patients will be assessed for safety, tolerability, pharmacokinetics, and PD effects and for exploratory outcomes as per the schedule of activities (see Appendix 1).

Prior to the second infusion of study drug on Day 15, patients will be evaluated for pre-specified conditions and laboratory abnormalities to allow for re-treatment with ocrelizumab (see Section 4.3.6 for more details).

Any patients who receive a partial or complete dose of ocrelizumab and discontinue from the 24-week period will enter the 104-week safety follow-up (SFU) period (see Section 3.1.1.4).

3.1.1.3 264-Week Optional Ocrelizumab Extension

At Week 24, patients continuing with ocrelizumab treatment by entering a 264–week optional ocrelizumab extension (OOE) period will receive subsequent doses if re–treatment criteria are met (see Section 4.3.6).

A re–evaluation of the benefit-risk of continuing study treatment by the treating investigator must be performed for each patient at the end of the first 24 weeks and prior to any further dosing, and therapy extension will only be granted to those patients where the benefit-risk is considered to be favorable.

The treating investigator should discuss the benefits and risks of continuing study treatment with the parents/legal guardian and patient in advance and prior to any further dosing.

During the OOE period, patients will be evaluated for prespecified conditions and laboratory abnormalities as per the schedule of activities (see Appendix 1). The treating investigator must ensure patients meet criteria for re-treatment with ocrelizumab, as defined under Section 4.3.6, before each subsequent infusion.

Patients will continue in the OOE period with the dosing regimen initially assigned until the preferred and final pediatric dosing regimen is selected by the IMC. In a situation where a subsequent dose is higher than the initial treatment regimen, that dose must be administered as two infusions of half the dose 14 days apart to mitigate the risk and severity of IRRs.

The OOE period will last 264 weeks, and may be extended until the patient turns 18 years old (or as required per local regulation) or until commercial ocrelizumab is approved for children and available in the country for these patients, whichever occurs first. Initiation of an alternative treatment for MS may be considered by the investigator in which case the patient will enter the SFU period.

Patients completing the 264–week OOE period or patients who discontinue treatment prematurely will enter the 104–week SFU period.

3.1.1.4 *104*-Week Safety Follow-Up Period (Including B-Cell Monitoring Period, if Required)

Patients completing the 288–week treatment period or patients who discontinue treatment prematurely for any reason at any time during the study will enter the SFU period.

The SFU period will last for at least *104* weeks starting from the date of the last infusion of ocrelizumab. However, patients whose peripheral blood B cells remain depleted will continue to be monitored until their B–cell counts have returned to baseline level or to the LLN range (whichever is lower) (see Figure 2).

The decision to initiate an alternative treatment for MS during this SFU period will be at the discretion of the treating investigator.

A dedicated SFU visit (scheduled or unscheduled) directly prior to the start of an alternative MS treatment is required in order to assess the patient's clinical status and safety. Information about the alternative treatment, such as dose, route, and frequency, will be recorded on the electronic case report form (eCRF).

Patients who receive MS therapies that may change B-cell levels during the SFU period will not be entered into the prolonged B–cell monitoring period thereafter.

Because sufficient data are not available to inform risks associated with switching to other products, caution is advised while patients remain B cell depleted.

Because of the unknown safety risk of administering DMTs for MS after discontinuation of ocrelizumab, certain treatments for MS such as lymphocyte–depleting agents or lymphocyte–trafficking blockers (e.g., alemtuzumab, natalizumab, fingolimod, dimethyl fumarate, cyclophosphamide, azathioprine) are strongly discouraged for as long as the patient remains B cell depleted on account of unknown effects on the immune system (e.g., increased risk, incidence, or severity of infection).

SFU visits will be performed at 12–week intervals starting from the date of the patient's last visit (e.g., withdrawal from treatment visit or Week 288 visit). For sites where mobile nursing (MN) is used, SFU visits can alternate between site visits and MN visits for the patient's convenience.

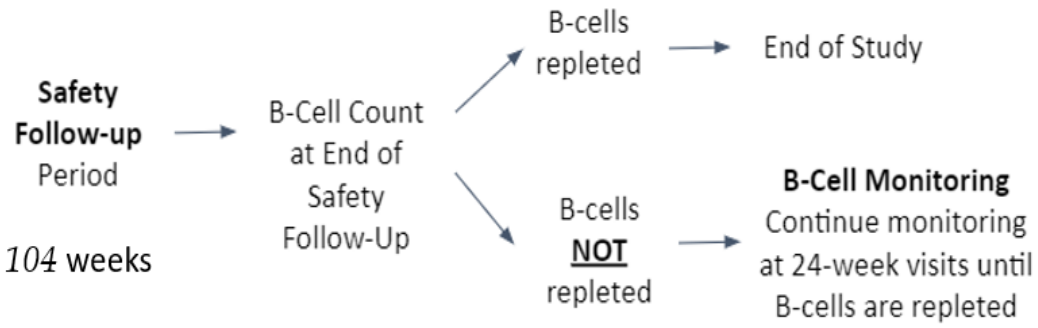
Structured telephone interviews will be performed every 4 weeks. The purpose of the telephone interview is to identify and collect information on any changes in the patient's health status (including any signs of infection, any new or worsening neurologic symptoms) that warrant an unscheduled visit. Patients/legal guardian will also be instructed to report immediately to study personnel any changes in the patient's health status.

If prolonged B-cell monitoring is required for patients whose B cells are not repleted, patients will be assessed at clinical visits every 24 weeks and structured telephone interviews will be performed every 12 weeks. For patients who undergo an alternative treatment for MS while in the B–cell monitoring period, telephone interviews will continue to be performed every 4 weeks.

See the schedule of activities in Appendix 1 for further details about SFU visits.

Every effort should be made to have patients who withdraw from treatment or who complete the 288–week treatment period complete the SFU period and all related assessments, regardless of whether or not they receive alternative treatment for MS.

Figure 2 Safety Follow-Up



Note: Patients who receive multiple sclerosis therapies that may change B–cell levels during the Safety Follow–Up period will not be entered into the prolonged B–cell monitoring period thereafter.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of study is defined as either the last patient, last visit (LPLV) of the study or the LPLV in the SFU period or B–cell monitoring period of the SFU period, whichever is later, or when the Sponsor decides to discontinue the study or development program in pediatric MS.

The total length of the study, from screening of the first patient up to LPLV is expected to be approximately *11* years.

3.3 DURATION OF PARTICIPATION

The total duration of study participation for an individual from screening to the end of the SFU period (excluding the B-cell monitoring period because it is not known how long it takes for B cells to replete in the pediatric MS population after treatment with ocrelizumab) is expected to be approximately *402*weeks (~*8* years).

3.4 RATIONALE FOR STUDY DESIGN

3.4.1 Rationale for Dosing Strategy

On the basis of the population PK model developed using adult data from Studies WA21493, WA21092, and WA21093, which included patients with a body weight between 38 kg and 170 kg, and the modeling and simulation results, it is predicted that a 600-mg ocrelizumab dose in children and adolescent patients with a body weight $\geq$40 kg will result in an exposure similar to the exposure range observed in the pivotal adult studies. The dose of 300 mg in patients with a body weight from $\geq$25 kg to $<$40 kg is predicted to result in an exposure below or similar to the adult exposure, even in young children at the very low end of the body weight range (i.e., 25 kg).

Therefore, the 300-mg dose will be explored in a cohort of 6 pediatric patients with a body weight from $\geq$25 kg to $<$40 kg, and the 600−mg dose will be evaluated in a cohort of 6 pediatric patients with a body weight $\geq$40 kg, to confirm the predicted pharmacokinetics as well as the PD (peripheral blood B cells) responses.

If the dose of 600 mg in pediatric patients $\geq$40 kg results in a similar exposure and similar PD effects as observed in adult patients with MS, then this dose will be selected for the subsequent Phase III study in patients with a body weight $\geq$40 kg. If the exposure and/or PD effects are different from those observed for adults, another dose level will be explored in a new cohort of at least 6 pediatric patients $\geq$40 kg.

If the dose of 300 mg in pediatric patients from $\geq$25 kg to $<$40 kg results in a similar exposure and similar PD effects as observed in adult patients with MS at the identified therapeutic dose (i.e., 600 mg every 24 weeks), the dose of 300 mg will be selected as the Phase III study dose in pediatric patients from $\geq$25 kg to $<$40 kg. If the exposure and/or PD effects are different compared with those observed for adults, another dose will be tested in a new cohort of at least 6 pediatric patients from $\geq$25 kg to $<$40 kg.

The dose level(s) in this/these additional cohort(s) will be chosen on the basis of all available safety, PK, and PD results obtained in this PK/PD study at that point.

3.4.2 Rationale for Patient Population

MS is extremely rare in preterm, term newborn infants, infants, and toddlers. MS onset before 10 years of age is also rare, accounting for less than 1% of all MS cases in nearly all population-based series.

Inclusion of patients below 10 years of age is not considered appropriate on the grounds of safety with respect to the immaturity of the immune system of young children and the potential risks this could present following treatment with ocrelizumab. Furthermore, the safety and effectiveness of immunization with vaccines in children treated with ocrelizumab have not been studied, and neither has the use of live vaccines in the adult or pediatric populations. This would specifically prohibit vaccination against measles, mumps, rubella, and poliomyelitis. Since the vaccination schedule in childhood may be

an important factor that precludes safe use of ocrelizumab in some age groups, the Sponsor proposes to enroll in this clinical trial only children and adolescents of 10 years and more who have received all required vaccinations as per the local calendar of vaccinations.

Nearly all of the childhood onset cases begin as a relapsing–remitting form. Relapse as the first manifestation of the disease has been found in 85.7%–100% of cases. Patients with childhood-onset MS tend to convert to the SPMS phase only when they become adults, and PPMS is exceptionally rare in children and adolescents (Banwell 2013).

Therefore, this study plans to enroll children and adolescents ages ≥ 10 to < 18 years with RRMS.

3.4.3 Rationale for 24-Week Dose Exploration Period

The safety, tolerability, pharmacokinetics, and PD effects of ocrelizumab will be assessed after administration of a single dose of ocrelizumab given as two IV infusions of half the dose 14 days apart (on Day 1 and Day 15).

Ocrelizumab is administered in adult patients with MS as a 600–mg dose at a fixed–interval schedule every 24 weeks. Therefore, the observation period in this study after administration of a single dose of ocrelizumab will be at minimum 24 weeks.

3.4.4 Rationale for 24-Week Re-Treatment Interval

A fixed–treatment schedule every 24 weeks should adequately maintain peripheral blood B-cell depletion as observed in the Phase III studies WA21092 and WA21093 in adults with RMS and should have the potential to confer a treatment benefit to children and adolescents with RRMS. A greater time interval between doses could result in a reduction or loss of efficacy. No clinical indices or biomarkers exist to reliably predict return of clinical activity in patients. Thus, a 24–week re-treatment interval is selected on the basis of the expected maintenance of peripheral blood B–cell depletion and the Sponsor's clinical experience with ocrelizumab in RMS as well as in PPMS. However, on the basis of emerging data from this study, the final treatment interval in pediatric patients will be confirmed for the subsequent Phase III study in children and adolescents.

3.4.5 Rationale for 264-Week Treatment Extension Period

MS is a disease that requires chronic DMT in order to reduce the frequency of relapses and accumulation of disability over time. In MS trials, at least 2 years of treatment is considered adequate to show a treatment effect on clinical outcomes including disease progression. In pediatric MS, where progression of disability is usually slower than in adults, longer treatment periods might be required. The present study will assess longer-term safety and tolerability and explore the preliminary efficacy of ocrelizumab in this young population with RRMS during an optional additional 264–week treatment period.

3.4.6 Rationale for SFU Period (Including Prolonged B-Cell Monitoring)

The safety and PD profile after stopping ocrelizumab has not yet been established in the pediatric MS population. Therefore, all patients treated with at least one dose of ocrelizumab during the study will be monitored in the Safety Follow-Up (SFU) period for *104* weeks after stopping ocrelizumab. Patient who do not replete their B-cells after the SFU period to LLN or baseline concentrations (whichever is lower) will then be followed in a B-cell monitoring period until repletion of B-cells to LLN or baseline concentrations.

Data collected during the SFU and B-cell monitoring period will allow evaluation of B–cell repletion after stopping ocrelizumab treatment and collection of safety and efficacy data to document maintenance of the effect and/or the potential for a withdrawal effect.

3.4.7 Safety Considerations

3.4.7.1 Premedication for Infusion-Related Reactions with Methylprednisolone, Antihistamines, and Anti-Pyretics

Methylprednisolone has been shown to decrease the incidence and the severity of infusion reactions. To reduce the frequency and severity of potential infusion reactions, all patients will receive mandatory prophylactic treatment with methylprednisolone, administered by slow IV infusion. In the event that the use of methylprednisolone is contraindicated, an equivalent dose of alternative steroid should be used as a premedication prior to the infusion.

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

The addition of an analgesic/antipyretic (e.g., acetaminophen/paracetamol [1 g]) may also be considered (see Section 4.3.3).

3.4.7.2 Vaccinations

The safety of immunization with live or live-attenuated vaccines, following ocrelizumab therapy has not been studied and vaccination with live-attenuated or live vaccines (i.e., measles, mumps, rubella, oral polio vaccine, Bacille Calmette–Guerin, typhoid, yellow fever, vaccinia, cold-adapted live influenza strain vaccine, or any other vaccines not yet licensed but belonging to this category) is not recommended during treatment and until B–cell repletion (in clinical trials, the median time for B–cell repletion was 72 weeks).

In a randomized open-label study (Study BN29739), RMS patients treated with ocrelizumab were able to mount humoral responses, albeit decreased, to tetanus toxoid, 23-valent pneumococcal polysaccharide, keyhole limpet hemocyanin neoantigen, and seasonal influenza vaccines. For more information regarding vaccinations and

associated recommendations for adults, neonates, and infants, see Sections 5.1.2 and 5.1.5.

Physicians must review the immunization status of children and adolescents being considered for this Phase II study and follow local/national recommendations for childhood vaccination against infectious diseases before starting treatment with ocrelizumab. Recommendations for special medical conditions and high–risk groups may be considered (CDC 1993; Rubin et al. 2014; MSCCPG 2001).

Children and adolescents must have received all required childhood vaccinations as per local/national calendar of immunization to be eligible for the study. Known dates of immunizations will be recorded on specific eCRF pages.

Before a patient starts ocrelizumab therapy, depending on the patient benefit–risk profile, the investigator should consider the administration of any vaccines (e.g., live or live–attenuated, inactivated) independently of local/national recommendations for immunization. For instance, immunization of children with vaccines that are recommended to older children/adolescents may be considered to obtain full effectiveness of the vaccine.

Patients who require vaccination or booster injections must have completed his or her immunization course at least 6 weeks prior to the first dose of ocrelizumab. Patient may be re-screened as needed.

During the study, it is recommended that all vaccinations other than live or live-attenuated should follow the local/national immunization schedule, and it is recommended to vaccinate patients treated with ocrelizumab with inactivated seasonal influenza vaccines, as a humoral response to the vaccine, even if attenuated, can be expected. During the study, it is recommended to vaccinate patients at least 12 weeks after the last infusion and at least 6 weeks prior to the subsequent dose of ocrelizumab.

4. MATERIALS AND METHODS

4.1 PATIENTS

At least 12 children and adolescents ages ≥ 10 to < 18 years, with RRMS, will be enrolled in this study. Additional pediatric patients may be enrolled (i.e., up to a total of approximately 36 patients in this study), if required for dose selection for the subsequent Phase III study in children and adolescents, on the basis of emerging data from this PK/PD study.

4.1.1 Inclusion Criteria

Patients must meet the criteria in the following sections for study entry.

4.1.1.1 General Inclusion Criteria

Patients must meet the following general criteria for study entry:

- Informed consent for study participation signed by the parents or a legal guardian, with patient assent obtained verbally and when possible, in writing, from all pediatric patients old enough to fully comprehend the assent document prior to any study-specific screening procedures, as per local requirements
- Able to comply with the study protocol, in the investigator's judgment

  Patients who are unable to complete exploratory assessments due to physical/disease limitations will not be excluded from the study.
- Age at screening between ≥10 and <18 years
- Body weight ≥25 kg

  Note: enrollment of patients with a body weight ≥40 kg is closed.
- Children and adolescents must have received all childhood vaccinations as per local/national recommendations for childhood vaccination against infectious diseases (see Section 3.4.7.2)
- For female patients of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Female patients must remain abstinent or use two methods of contraception, including at least one method with a failure rate of <1% per year, during the treatment period and for at least 24 weeks after the final dose of ocrelizumab. Adherence to local requirements, if more stringent, is required.

  A female is considered to be of childbearing potential if she is postmenarchal (i.e., in Tanner Stages ≥2 or post-onset of menarche) and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of <1% per year include the following:

  – Established hormonal contraception: combined (estrogen– and progestogen–containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal) or progestogen–only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
  – Intrauterine devices: intrauterine device, intrauterine hormone–releasing system, and copper intrauterine device

  A barrier method may be used as the second contraceptive method, such as the following:

  – A male or female condom with or without spermicide
  – A cap, diaphragm, or sponge with spermicide

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

4.1.1.2 Inclusion Criteria Related to Pediatric MS

Patients must meet the following criteria related to pediatric MS for study entry:

- Diagnosis of RRMS in accordance with the IPMSSG criteria for pediatric MS, Version 2012, and McDonald criteria 2017 (Thompson et al. 2018)

  Note: For consistency, the same diagnosis criteria will be used for the recruitment of patients in this study.

- EDSS at screening: 0–5.5, inclusive

- Patients naive to prior DMT or patients who have had less than a total of 6 months of DMT (e.g., any IFN or GA) within the past 1 year must have one of the following:

  At least two relapses in the last 2 years, with at least one relapse experienced in the previous year

  At least two relapses in the last 2 years and ≥ 1 Gd-enhancing lesion(s) (silent or not) on T1–weighted brain MRI at any time within the previous year

  At least one relapse in the previous year and ≥ 1 Gd-enhancing lesion(s) on T1–weighted brain MRI at any time within the last year

  Note: A relapse is a monophasic clinical episode with patient-reported symptoms and objective findings typical of MS, reflecting a focal or multifocal demyelinating event in the CNS, developing acutely or subacutely, with a duration of at least 24 hours, with or without recovery, and in the absence of fever or infection. "Attack," "relapse," and "exacerbation" are synonyms (McDonald 2017 criteria; Thompson et al. 2018).

- Patients who have had at least 6 contiguous months of DMT (e.g., any IFN or GA) within the past 1 year must have evidence of disease activity occurring after the full 6–month course of treatment, that is, at least one relapse or ≥ 1 Gd–enhancing lesion(s) on a T1–weighted brain MRI

  Note: Evidence of disease activity (i.e., at least one relapse or ≥ 1 Gd–enhancing lesion(s) on a T1–weighted brain MRI) <u>after</u> a full 6-month course of treatment may occur either on DMT or off DMT.

4.1.2 <u>Exclusion Criteria</u>

While participating in this Roche study patients are not allowed to take part in other investigational research projects involving administration of any drug or substance or involving any procedure that would place patients at risk or could jeopardize this study results.

4.1.2.1 Exclusions Related to General Health

Patients who meet any of the following criteria related to general health will be excluded from study entry:

- Pregnancy or lactation
- Known presence or suspicion (based on clinical or laboratory parameters) of other neurologic disorders that may mimic MS, including, but not limited to, ADEM, neuromyelitis optica or neuromyelitis optica spectrum disorders; and any neurologic (other than MS), somatic, or metabolic condition that could interfere with brain function or normal cognitive or neurological development

  Patients that are aquaporin 4 positive and myelin oligodendrocyte glycoprotein (MOG) antibody positive are not eligible to participate in the study.

  In case of an ADEM–like appearance of the first MS attack, a second attack with clear MS-like features is required.
- Clinical or laboratory findings at first presentation not typical for MS, such as signs of infection or signs of encephalopathy, such as confusion, convulsion, or reduced state of consciousness
- Abnormal findings in the cerebrospinal fluid at first presentation; protein >100 mg/dL; pleocytosis >50 cells per mm^3; or presence of neutrophils, eosinophils, or atypical cells
- Atypical MRI findings: ADEM–like presentation of lesions; lesions in atypical location for MS; bilateral optic neuritis; extensive spinal cord lesions (≥ 3 spinal segments)
- Significant or uncontrolled somatic diseases or any other significant condition that may preclude patients from participating in the study
- Known active bacterial, viral, fungal, mycobacterial infection, or other infection, excluding fungal infection of nail beds
- Infection requiring hospitalization or treatment with IV anti-infective agents within 4 weeks prior to baseline visit or oral anti-infective agents within 2 weeks prior to baseline visit
- History or known presence of recurrent or chronic infection (e.g., HIV, syphilis, tuberculosis)
- Receipt of a live or live–attenuated vaccine within 6 weeks prior to treatment allocation. The patient's vaccination record and a need for immunization should be carefully reviewed (scheduled vaccinations should be completed at least 6 weeks prior to receiving ocrelizumab, according to local guidelines).
- History or laboratory evidence of coagulation disorders
- Peripheral venous access that precludes IV administration and venous blood sampling as required per study protocol
- Inability to complete an MRI scan (e.g., due to weight, cochlear implants, presence of foreign substances in the eye, intracranial vascular clips)

- Teeth braces interfering with MRI acquisition: see Section 4.5.16 for more information.
- History of cancer, including solid tumors, hematologic malignancies, and carcinoma in situ (except basal cell and squamous cell carcinoma of the skin that have been excised and cured)
- Currently active alcohol or drug abuse or history of alcohol or drug abuse

4.1.2.2 Exclusions Related to Medications

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

- History of a severe allergic or anaphylactic reaction to humanized or murine mAbs or known hypersensitivity to any component of ocrelizumab solution
- Contraindications to or intolerance of oral or IV corticosteroids, antihistamines, or antipyretics according to the country label, including the following:
  - Psychosis not yet controlled by a treatment
  - Hypersensitivity to any of the constituents
- Treatment with any investigational agent within 24 weeks of screening or 5 half-lives, whichever is longer (or longer if indicated by the PD action of the drug)
- Previous treatment with B-cell–targeted therapies (i.e., rituximab, ocrelizumab, obinutuzumab, atacicept, belimumab, or ofatumumab)
- Any previous treatment with alemtuzumab, anti–CD4, cladribine, mitoxantrone, daclizumab, laquinimod, total body irradiation, or bone marrow transplantation
- Treatment with cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine, or methotrexate within 24 months prior to treatment allocation
- Treatment with natalizumab within 12 months prior to treatment allocation
- Treatment with teriflunomide within 24 weeks prior to treatment allocation
- Treatment with fingolimod within 6 weeks prior to treatment allocation and lymphocyte count $<$ LLN for age– and sex–specific reference range; treatment with any other S1P receptor modulator (e.g., BAF312/siponimod) within 24 weeks prior to treatment allocation
- Treatment with dimethyl fumarate within 4 weeks prior to treatment allocation and lymphocyte count $<$ LLN for age- and sex–specific reference range
- Treatment with IVIg within 12 weeks prior to treatment allocation
- Treatment with plasmapheresis within 4 weeks prior to treatment allocation
- Systemic corticosteroid therapy within 7 days prior to treatment allocation

  The screening period may be extended (but cannot exceed 10 weeks) for patients who have used systemic corticosteroids for MS before treatment allocation.

Patients screened for this study should not be withdrawn from therapies for the sole purpose of meeting eligibility for the trial. Patients who discontinue their current therapy

for non–medical reasons should specifically be informed of their treatment options before deciding to enter the study.

4.1.2.3 Exclusions Related to Laboratory Findings

Patients who meet any of the following criteria related to laboratory findings will be excluded from study entry:

- Positive serum beta-human chorionic growth hormone (β–hCG) measured at screening, or positive pregnancy test prior to the first infusion of ocrelizumab
- Positive screening tests for hepatitis B (hepatitis B surface antigen [HBsAg] positive, or positive hepatitis B core antibody [total HBcAb] confirmed by a positive viral DNA polymerase chain reaction [PCR]) or hepatitis C antibody (HepCAb)
- Positive rapid plasma reagin if confirmed by microhemagglutination assay or fluorescent treponemal antibody absorption test
- Percentage of CD4 $<30\%$ (central laboratory age-specific reference range %CD4: 35%–57%)
- AST or ALT levels ≥ 2.0 times the upper limit of normal (ULN) (value as per central laboratory) for age- and sex-specific reference range
- Levels of serum IgG 18% below the LLN (value as per central laboratory) for age- and sex-specific reference range
- Levels of serum IgM 8% below the LLN (value as per central laboratory) for age– and sex–specific reference range
- Absolute Neutrophil Count $< 1.5 \times 10^3/\mu L$
- Lymphocyte count below the LLN (value as per central laboratory) for age– and sex–specific reference range

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This study is an open-label study. All eligible patients will be assigned to receive ocrelizumab treatment.

Patients will be allocated to receive either a dose of 300 or 600 mg (6 patients at each dose level) depending on their body weight at screening as follows:

- Cohort 1 (ocrelizumab 300 mg): 6 patients with a body weight from ≥ 25 kg to <40 kg at screening, with at least 2 patients with a body weight from ≥ 25 kg to ≤ 35 kg.
- Cohort 2 (ocrelizumab 600 mg): at least 6 patients with a body weight ≥ 40 kg at screening with at least 2 patients with a body weight ≥ 40 kg but ≤ 50 kg

  Note: The recruitment in Cohort 2 is now closed.

As indicated by the data obtained in each cohort, the decision may be taken that another dose level should be investigated to enable the identification of the most appropriate dose in children and adolescents. In this case, additional patients may be enrolled to

another dose in patients from ≥25 kg to <40 kg and/or ≥40 kg. This dose for each cohort will be determined based on all available safety, PK, and PD data at that timepoint and will under no circumstances be higher than 1200 mg. If required and indicated by the data, knowledge on the effects of ocrelizumab 300 mg and/or 600 mg may be expanded in this/these additional cohort(s) by administration of 300 mg and/or 600 mg ocrelizumab to the additionally enrolled patients.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is ocrelizumab. Appendix 7 identifies all IMPs and auxiliary medicinal products for this study.

4.3.1 Ocrelizumab Formulation, Packaging, and Handling

Ocrelizumab will be supplied by the Sponsor as a sterile, clear to slightly opalescent and colorless to pale brown solution for IV infusion and contains no preservatives.
The ocrelizumab drug is provided as a liquid in a single–use 15–mL type 1, glass vial fitted with a 20-mm fluoro–resin–laminated stopper and an aluminum seal with a flip–off plastic cap. Each single-use, 15–mL vial supplied by the Sponsor contains 300 mg (nominal) of ocrelizumab formulated with 30 mg/mL ocrelizumab in 20 mM sodium acetate at pH 5.3, with 106 mM trehalose dihydrate and 0.02% polysorbate 20. Each vial contains 300 mg ocrelizumab at a nominal fill volume of 10 mL.

Ocrelizumab drug product 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 hospital units/pharmacy will receive study medication kits for each patient.
One study medication kit contains one single-use liquid vial with 300 mg ocrelizumab.

Ocrelizumab vials are stable at 2°C–8°C (refrigerated storage) and must be stored refrigerated until use. Ocrelizumab should not be used beyond the expiration date stamped on the carton. Expiration dating may be extended during the trial; the Sponsor will provide documentation.

Ocrelizumab is a protein. It is therefore important to handle the drug gently and to avoid foaming during product handling, dosage preparation, and drug administration, as foaming may lead to denaturing of the protein. Ocrelizumab vials should not be frozen or shaken and should be protected from light during storage.

The study medication labels will be produced in accordance with the local requirements.

4.3.2 Study Treatment Dosage, Administration, and Compliance

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF. Section 5.3.5.13 summarizes available safety data related to overdosing of ocrelizumab.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 4.6.2.

4.3.2.1 Ocrelizumab

The study drug infusions should always be administered in a hospital or clinic environment under close supervision of the investigator or a medically qualified staff member with immediate availability of full resuscitation facilities. Patients may be hospitalized for observation at the discretion of the investigator (in some countries, this is the standard procedure).

Preparation of Infusion Bags

Ocrelizumab dose solutions for IV administration must be prepared/diluted under appropriate aseptic conditions, as the drug does not contain antimicrobial preservatives.

Ocrelizumab drug must be diluted into normal saline (0.9% sodium chloride) infusion bags prior to administration by IV infusion.

It is important not to use evacuated glass containers (to prepare the infusion solution), which require vented administration sets because this causes foaming as air bubbles pass through the solution.

The ocrelizumab infusion solution should be prepared on the day of infusion and used immediately to limit microbial growth in case of potential accidental contamination. If not used immediately, the prepared infusion solution can be stored for up to 24 hours at 2°C–8°C. Because ocrelizumab solutions for infusion do not contain a preservative, the prepared infusion solution of ocrelizumab is physically and chemically stable for up to 24 hours at 2°C–8°C and subsequently 8 hours at room temperature. The ocrelizumab infusion solution must be completely administered to the patient within 32 hours of preparation (not exceeding 24 hours at 2°C–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.

To avoid an infusion reaction associated with the administration of a low-temperature solution, the bag must be brought to room temperature before infusion. To do this, place the bag at room temperature for approximately 1 hour.

Transportation of the dose solution must be at 2°C–8°C to ensure stability of diluted ocrelizumab solution.

Specific instructions are provided separately in the Dose Preparation Guidelines and must be followed exactly.

4.3.2.2 Monitoring prior to and during Infusions

All patients should receive premedications before any infusion (for detailed information see Section 4.3.3).

12-Lead ECG

ECGs should be performed prior to any procedures, such as vital sign measurements and blood draws. Whenever possible, the same machine should be used for each patient. Lead placement should be as consistent as possible. To minimize variability, it is important that patients be in a resting position for at least 10 minutes prior to each ECG evaluation.

Prior to study drug infusion, recording of 12–lead ECG will be done within 45 minutes prior to the methylprednisolone infusion.

After study drug infusion, recording of 12–lead ECG will be done within 60 minutes after completion of the infusion.

Further details are provided in Section 4.5.11.

Vital Signs

Prior to study drug infusion, vital signs (i.e., pulse rate, systolic and diastolic blood pressure, respiratory rate, and temperature) will be taken within 45 minutes prior to the methylprednisolone infusion in all patients. In addition, vital signs should be obtained prior to the study drug infusion.

During the infusions, vital signs will be assessed every 15 (±5) minutes for the first hour, then every 30 (±10) minutes until1 hour after the completion of the infusion.

Additional vital sign readings and/or 12–lead ECG recordings may be taken at the discretion of the investigator in the event of an IRR or if clinically indicated and should be recorded on the corresponding unscheduled eCRF.

4.3.2.3 Infusion Procedures

Ocrelizumab drug product is a clear to slightly opalescent and colorless to pale brown liquid. 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.

Prior to the start of the infusion, please be sure that the content of the bag is at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures. To do this, place the bag at room temperature for approximately 1 hour.

The infusion solution must be administered using a polyvinyl chloride, polyethylene, polybutadiene, or polyetherurethane infusion set equipped with a 0.2 or 0.22 μm (or less) polyethersulfone or polysulfone filter.

Ocrelizumab should be given as a slow IV infusion. It must not be administered as an IV push or bolus. Well-adjusted infusion pumps should be used to control the infusion rate, and the study drug should be infused through a dedicated line.

A physician should be available on site with immediate availability of full resuscitation facilities.

After completion of the infusion, the IV cannula should remain in situ for at least 1 hour in order to be able to administer drugs IV, if necessary, in the event of a delayed reaction. If no adverse events occur during this period, the IV cannula may be removed.

Physicians should alert caregivers (and patients) that IRRs can occur within 24 hours of infusion.

In the event an infusion cannot be completed the same day, the remaining liquid in the infusion bag must be discarded.

Initial Dose (Dose 1) as Two Infusions of Half the Dose 14 Days Apart

The initial ocrelizumab dose must be administered as two separate IV infusions of 150 mg (Cohort 1, 300–mg regimen) or 300 mg (Cohort 2, 600–mg regimen), which are given 14 days apart (i.e., Day 1 and Day 15).

It is recommended that the first infusion of ocrelizumab (Day 1 of Dose 1) be scheduled in the morning to allow the patient to stay at the hospital (or infusion center) with medical supervision and monitoring as required, as long as possible (e.g., until 6 p.m. or 8 p.m. according to the hospital rules), with a minimum of 1 hour after completion of the infusion. Patients may be hospitalized for a 24–hour observation after completion of the infusion at the discretion of the treating investigator.

Note: Any adverse event that results in hospitalization or prolonged hospitalization has to be reported as a serious adverse event (see Section 5.3.5.12). If the reason for hospitalization is not associated with an adverse event (e.g., for patient supervision purposes), no serious adverse event will be reported (Section 5.3.5.12).

It is also recommended to administer the second infusion (Day 15 of Dose 1) in the morning, as patients should remain under observation for at least 1 hour after the completion of the infusion and up to 24 hours at the treating investigator's discretion.

For each infusion (Day 1 and Day 15), it is necessary to prepare a single infusion bag (250 mL, 0.9% saline solution) containing either 150– or 300–mg ocrelizumab.

The infusion of ocrelizumab 150 or 300 mg should be initiated at a rate of 30 mL/hr. Thereafter, the rate can be increased in 30–mL/hr increments every 30 minutes to a maximum of 180 mL/hr.

Infusion of 150 and 300 mg of ocrelizumab should be given over approximately 2.5 hours.

Because of a possible need to vary infusion rates depending on tolerance of the infusion, patients and parents should be informed that the total infusion time may exceed the time stated.

Unless an infusion reaction occurs that necessitates discontinuation, the entire content of infusion bag must be administered to the patient.

Specific instructions will be provided separately in the Dose Preparation Guidelines and must be followed exactly.

Subsequent Doses in the Optional Ocrelizumab Extension

Subsequent doses will be administered only to patients continuing in the OOE period as a single infusion (e.g., 300 or 600 mg) of ocrelizumab every 24 weeks, if safety and tolerability in children and adolescents allow it, until the appropriate dose of ocrelizumab for the subsequent Phase III study in children and adolescents is selected by the IMC. At that time, patients will switch to this selected dosing regimen of ocrelizumab at their next infusion visit.

Patients in Cohort 1 who reach a stable body weight of ≥40 kg during the study will be automatically switched to the appropriate dose for patients with body weight ≥40 kg (see Section 3.1.1).

In a situation where the subsequent dose is higher than the dose in the initial treatment regimen, that subsequent dose will be administered as two infusions of half the dose 14 days apart to mitigate the risk and severity of IRRs.

It is recommended that subsequent infusions be administered in the morning, as patients should remain under observation for at least 1 hour after the completion of the infusion and up to 24 hours at the treating investigator's discretion.

Infusion of ocrelizumab 300 mg (250–mL infusion bag, 0.9% saline solution) should be initiated at a rate of 30 mL/hr. Thereafter, the rate can be increased in 30-mL/hr increments every 30 minutes to a maximum of 180 mL/hr. Infusion of 300 mg of ocrelizumab should be given over approximately 2.5 hours.

Infusion of ocrelizumab 600 mg (500–mL infusion bag, 0.9% saline solution) should begin at a rate of 40 mL/hr. Thereafter, the rate can be increased in 40-mL/hr increments every 30 minutes to a maximum of 200 mL/hr. Infusion of 600 mg of ocrelizumab should be given over approximately 3.5 hours.

Because of a possible need to vary infusion rates depending on tolerance of the infusion, patients, and parents should be informed that the total infusion time may exceed the time stated.

Unless an infusion reaction occurs that necessitates discontinuation, the entire content of infusion bag must be administered to the patient.

Specific instructions will be provided separately in the Dose Preparation Guidelines and must be followed exactly.

4.3.2.4 Assessment of Compliance

Accountability will be assessed by maintaining adequate drug preparation and dispensing records. A call for drug administration to the interactive web–based response system (IWRS) will also be used to assess compliance.

4.3.3 Premedication for Infusion-Related Reactions with Antihistamines, Anti-Pyretics, and Methylprednisolone

4.3.3.1 Antihistamines and Anti-Pyretics

During the controlled treatment periods of Studies WA21092 and WA21093, the addition of oral antihistamine to methylprednisolone pretreatment for each dose was associated with at least a 2-fold lower incidence in infusion reactions compared with pretreatment with methylprednisolone alone. Therefore, all patients will receive mandatory prophylactic treatment with an antihistamine drug (e.g., diphenhydramine) approximately 30–60 minutes before each infusion of ocrelizumab to further reduce the frequency and severity of IRRs.

The addition of an analgesic/antipyretic (e.g., acetaminophen/paracetamol) may also be considered.

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

Since transient hypotension may occur during ocrelizumab infusion, patients with low blood pressure should be monitored carefully.

4.3.3.2 Methylprednisolone

All patients will also receive mandatory prophylactic treatment with methylprednisolone, administered by slow IV infusion to be completed approximately 30 minutes before the start of each ocrelizumab infusion. In the event that the use of methylprednisolone is

contraindicated, an equivalent dose of alternative steroid should be used as premedication prior to the infusion.

The dose recommendation for slow IV infusion of methylprednisolone is as follows: dose adjusted to weight for patients $<$40 kg (2 mg/kg) and for patients $\geq$40 kg (100 mg).

4.3.4 Managing Infusion-Related Reactions

4.3.4.1 Treatment of IRRs

IRRs should be treated symptomatically with oral acetaminophen/paracetamol, and intramuscular or slow IV antihistamine administration, such as diphenhydramine, both according to labeled age-related doses. Acetaminophen/paracetamol and antihistamine administration should be repeated as clinically indicated. Non–allergic events should be treated symptomatically as judged clinically relevant by the investigator.

In patients with associated respiratory symptoms (stridor, wheeze, or bronchospasm), additional treatment with bronchodilators may be indicated.

Physicians should monitor patients with a history of asthma carefully and institute an appropriate treatment if signs and symptoms of asthma are noticed.

Note: As an IRR can occur within 24 hours of an infusion, a structured telephone interview will be conducted by site personnel 24 ($\pm$4) hours after each infusion to identify and collect information on any changes in the patient's health status (i.e., any unusual signs or symptoms since they left the clinic after the infusion) (see Appendix 4).

4.3.4.2 Infusion-Rate Modifications and Interruptions for Infusion–Related Reactions

Slowing of the infusion rate or interruption of the infusion may be necessary in the event of an IRR. In rare cases, ocrelizumab treatment may need to be discontinued. Guidance is provided below.

Handling of IRRs will depend on the intensity of symptoms (see Section 5.3.3 for severity grading scale of IRRs).

Mild-to-Moderate Infusion-Related Reactions

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

Severe Infusion-Related Reactions

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

Life-Threatening Infusion-Related Reactions

Immediately stop ocrelizumab if there are signs of a life-threatening or disabling infusion-related event (Grade 4) during an infusion, such as acute hypersensitivity or acute respiratory distress syndrome. The patient should receive appropriate treatment (including use of resuscitation medications and equipment that must be available and used as clinically indicated). Permanently discontinue ocrelizumab in these patients who should be withdrawn from treatment and should enter the SFU period.

4.3.5 Delayed Dosing

If a scheduled dosing visit cannot occur within the time window or if an infusion cannot be administered as planned, a delayed dosing visit should be scheduled as soon as possible. To ensure that patients meet re-treatment criteria (Section 4.3.6), an unscheduled site visit (or unscheduled MN visit) should be scheduled within 2 weeks in advance of that delayed dosing visit.

The treating investigator must verify that all re-treatment criteria (Section 4.3.6), including safety laboratory parameters, are met before proceeding with the infusion of ocrelizumab. Any repeat laboratory tests must be performed, analyzed, and reviewed before administration of ocrelizumab.

Ocrelizumab should not be administered to patients with an active infection. Patients who develop infection following ocrelizumab administration should be promptly evaluated and treated appropriately. The subsequent infusion should be delayed until the infection has completely resolved and treatment with any anti–infective medications has been completed. Receipt of further ocrelizumab infusions is at the discretion of the investigator.

If the delayed dosing visit occurs more than 4 weeks from a scheduled dosing, the dose should be administered as two infusions of half the dose 14 days apart to mitigate the risk and severity of IRRs (see Section 4.3.2.3).

It is recommended that delayed infusions be administered in the morning, as patients should remain under observation for at least 1 hour after the completion of the infusion and up to 24 hours at the treating investigator's discretion.

4.3.6 Criteria for Re-Treatment with Ocrelizumab

A re-evaluation of the benefit-risk of continuing study treatment by the treating investigator must be performed for each patient at the end of the first 24 weeks and prior to any further dosing, and therapy continuation will only be granted to those patients where the benefit-risk is considered to be favorable.

A visit within 2 weeks prior to any dosing visit (i.e., scheduled dosing visit or delayed dosing visit) will be required to collect blood samples and patient information to enable the treating investigator to assess whether a patient meets re-treatment criteria at the time of an infusion with study drug.

Treating investigator must ensure he or she has reviewed the laboratory results of the patient prior to re-treatment with ocrelizumab. Any repeat laboratory tests must be performed, analyzed, and reviewed before administration of ocrelizumab.

Prior to re-treatment, the following conditions must be met:

- Absence of life-threatening (Grade 4) infusion-related event that occurred during a previous ocrelizumab infusion
- Absence of severe allergic or anaphylactic reaction to an ocrelizumab infusion
- Absence of active infection regardless of the grade (including active tuberculosis [TB] infection, either new onset or reactivation) and treatment with any anti-infective medications has been completed (see Section 5.1.1.2)

  A patient with active TB infection or a Grade 3 infection must suspend ocrelizumab treatment for as long as needed to ensure full resolution of the infection.

  The patient should receive medical care in adherence with local/national requirements until complete resolution of the infection and should be monitored subsequently as per local medical plans. Upon resolution of the infection and based on individual benefit-risk assessments, the patient will have the opportunity to re-start ocrelizumab treatment if it is considered beneficial for him or her. Otherwise, the treating investigator can decide to permanently stop ocrelizumab.
- Absence of any significant or uncontrolled medical condition or treatment-emergent, clinically significant, laboratory abnormality
- ANC $\geq 1.5 \times 10^3/\mu L$
- CD4 levels:
  - For children and adolescents: percent CD4 $\geq 25\%$
  - For patients ≥ 18 years of age, the adult reference applies: CD4 cell count $\geq 250/\mu L$
- IgG Level:
  - For children and adolescents: IgG ≥ 4.6 g/L
  - For patients ≥ 18 years of age, the adult reference applies: IgG ≥ 3.3 g/L

- No initiation of protocol–prohibited medications
- Body weight ≥25 kg
- Absence of ongoing pregnancy or positive pregnancy test or breastfeeding (for female patients)

  In the event of pregnancy, the investigator must counsel the patient as to the risks of continuing with the pregnancy and the possible effects on the fetus. Given that there are insufficient, well–controlled data from studies testing the use of ocrelizumab in pregnant or breastfeeding women, all infusions of ocrelizumab must be suspended until the completion of pregnancy and breastfeeding. Pregnant and breastfeeding patients should continue to follow the schedule of assessments for the study; however, no infusions of ocrelizumab will occur. If there is a concern with the ability of a pregnant or breastfeeding patient to perform all scheduled assessments, the investigator must contact the Medical Monitor for further discussion. Re–start of ocrelizumab treatment following pregnancy and breastfeeding will be decided as a result of a thorough benefit-risk discussion between the patient and investigator.

If any of these conditions are not met prior to re-dosing, further administration of ocrelizumab will be suspended (paused) until resolved or held indefinitely (see Section 4.6.1).

A patient experiencing a life-threatening (Grade 4) infection will be permanently discontinued from ocrelizumab treatment and will enter the safety follow-up period (see Section 4.6.1).

Any critical laboratory values will be provided to the treating investigator and the Medical Monitor. Investigators notified of their patient's critical laboratory test result will be instructed to suspend further treatment with study drug until the patient can be further evaluated. A repeat laboratory test may be necessary to confirm the results. Patients with critical values should not be re-treated until the re-treatment criteria are met and these laboratory values have normalized.

See also Section 5.3.5.6 for reporting of abnormal laboratory values.

4.3.7 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (ocrelizumab) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs using the IWRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

Temperature conditions for all IMPs will be monitored during transit, and any discrepancies will be 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.

IMPs either will 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 IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any 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 Inventory Log.

4.3.8 Continued Access to Ocrelizumab

Currently, the Sponsor does not have any plans to provide Sponsor study drug (ocrelizumab) or any other study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing ocrelizumab in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

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

However, until the benefits/risks of ocrelizumab in children and adolescents have been fully assessed in a Phase III study, continued access to ocrelizumab will be evaluated cautiously by the Sponsor on an individual basis.

4.4 CONCOMITANT THERAPY

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

Concomitant medications will be reported at each visit in the relevant eCRFs starting from the baseline visit (including medication taken between screening and baseline). Any medications taken for the treatment of MS and any medications taken for the symptoms of MS prior to the baseline visit will be recorded at the baseline visit. Additionally, medications administered for any non–MS condition within 12 months prior to the baseline visit will also be recorded at the baseline visit.

4.4.1 Permitted Therapy

4.4.1.1 Treatment for Symptoms of Multiple Sclerosis

The treating investigator should attempt to maintain therapies or treatments for symptoms related to MS (e.g., walking ability, spasticity, incontinence, pain, fatigue) reasonably constant throughout the study.

Treatment of Relapses

Patients who experience a relapse during the study may receive treatment with IV or oral corticosteroids, if judged to be clinically appropriate by the investigator. The following standardized treatment regimen may be used as warranted: methylprednisolone IV 30 mg/kg/day (maximum daily dose of 1000 mg) for 3–5 days. In addition, at the discretion of the investigator, corticosteroids may be stopped abruptly or tapered over a maximum of 10 days. Such patients should not discontinue the treatment period solely based on the occurrence of a relapse, unless the patient or investigator considers him or her to have met the criteria for withdrawal.

4.4.2 Prohibited Therapy

Therapies for MS noted in the exclusion criteria under Section 4.1.2.2 are not permitted during the treatment periods (i.e., 24–week dose exploratory period and during the OOE period), with the exception of systemic corticosteroids for the treatment of a relapse.

For patients who complete or withdraw from treatment with ocrelizumab, an alternative treatment for MS may be initiated as judged clinically appropriate by the treating investigator.

However, because sufficient data are not available to inform risks associated with switching to other products, the following recommendations are given:

- Caution is advised while patients remain B–cell depleted.
- Because of the unknown safety risk of administering DMTs for MS after discontinuation of ocrelizumab, certain treatments for MS such as lymphocyte–depleting agents or lymphocyte–trafficking blockers (e.g., alemtuzumab, natalizumab, fingolimod, dimethyl fumarate, cyclophosphamide, azathioprine, etc.) are strongly discouraged for as long as the patient remains B–cell depleted because of unknown effects on the immune system (e.g., increased risk, incidence, or severity of infection).

4.4.3 Vaccinations

See Sections 3.4.7.2, 5.1.1.3, and 5.1.5.

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.

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

4.5.1 Informed Consent and Informed Assent Forms and Screening Log

The most current, approved Institutional Review Board (IRB)/EC written Informed Consent Form for study participation signed by parent(s) or legal guardian(s), with patient informed assent obtained verbally and when possible, in writing, from all pediatric patients old enough to fully comprehend the assent document must be obtained prior to any study–specific screening procedures or assessments are performed.

Informed Consent and Assent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site. Each patient screened must be registered in the IWRS by the investigator or the investigator's research staff at screening. Reasons for screen failure must be captured in the IWRS.

A screening examination (medical history and physical examination including vital signs and weight and neurologic examination with EDSS assessment) should be performed within 8 weeks prior to the start of the study. An ECG and laboratory tests (e.g., routine safety, pregnancy test in women of childbearing potential, thyroid function tests, hepatitis screening tests, Igs, rapid plasma reagin, and CD4 count) will also be performed. The screening period can be extended to a total of 10 weeks should a laboratory blood test or baseline brain MRI scan need to be repeated for confirmation during the screening interval or for other relevant clinical, administrative, or operational reasons. Patients must fulfill all the entry criteria for participation in the study (see Section 4.1.1).

An Eligibility Screening Form documenting the investigator's assessment of each screened patient with regard to the protocol's inclusion and exclusion criteria is to be completed by the investigator. It should be stated in the medical record that the patient is participating in this clinical study.

4.5.2 Procedures for Enrollment of Eligible Subjects

Patient lists will be created using an IWRS. The screening ID will be allocated by IWRS. Sites should log in to the IWRS to enter the subject into screening and to register a screen failure. This log in to the IWRS should occur on Day 1 (baseline visit) after the patient's eligibility (i.e., review of inclusion/exclusion criteria) has been confirmed.

The investigator will be provided with an email notification of each patient's registration.

No patient may begin treatment prior to assignment of a medication number. Under no circumstances are patients who enroll in this study and who have completed treatment as specified permitted to be re-enrolled to this study.

The investigators will be notified by the Sponsor when the study is completed or closed to further patient enrollment.

4.5.3 Overview of Clinical Visits during the Study

At each visit and each telephone interview, the site should remind parents/legal guardians/patients to call the treating investigator immediately to report any changes in patient's health status (i.e., new or worsening neurologic symptoms, signs of infection, any unusual signs or symptoms since the patient left the clinic after the infusion) that may warrant an unscheduled visit.

Visits will take place as described in the schedule of activities (see Appendix 1). Visits should be scheduled with reference to the date of the baseline visit (Day 1, Visit 2).

Treatment with the first study drug infusion should occur within 24 hours of treatment allocation. In exceptional cases where all baseline assessments cannot be completed within 24 hours, the first study drug infusion can be administered within 48 hours of allocation provided that the investigator ensures that all inclusion and exclusion criteria are met on the day of dosing. In particular, there should be no evidence of an ongoing infection at the time of dosing (see criteria for re–treatment in Section 4.3.6).

For the first dose (i.e., Dose 1) ocrelizumab needs to be administered as two infusions of half the dose. A minimum interval of 20 weeks should be maintained between the second infusion (e.g., Day 15 of Dose 1) and the next infusion (e.g., Dose 2 of Week 24).

For doses administered as single infusions, a minimum of 22 weeks should be maintained between each infusion.

However, the frequency of the dose administration may be changed if emerging data from this study indicate that a different dosing frequency/regimen is more appropriate in this pediatric population. The decision to test a different dosing frequency/regimen will be endorsed by the IMC. The total maximum allowed dose is 1200 mg over 6 months.

If for logistical reasons a subsequent ocrelizumab infusion cannot be administered on the same study visit day, the infusion should be given within the next 24 hours provided that the patient still meets re–treatment criteria (see Section 4.3.6).

Patients who cannot receive their infusion at the scheduled visit or within 24 hours of the visit should be re-scheduled for a delayed dosing visit (Section 4.5.3.2).

Additional unscheduled visits for the assessment of potential relapses, new neurologic symptoms, or any other safety events may occur at any time.

4.5.3.1 Infusion Visits

It is recommended that the first infusion of ocrelizumab (Day 1 of Dose 1) should be scheduled in the morning to allow the patient to stay at the hospital (or infusion center)

with medical supervision and monitoring as required, as long as possible (e.g., until 6 p.m. or 8 p.m. according to the hospital rules), with a minimum of 1 hour after completion of the infusion. Patients may be hospitalized for a 24-hour observation after completion of the infusion at the discretion of the treating investigator.

Note: Any adverse event that results in hospitalization or prolonged hospitalization has to be reported as a serious adverse event (see Section 5.3.5.12). If the reason for hospitalization is not associated with an adverse event (e.g., for patient supervision purposes), no serious adverse event will be reported (Section 5.3.5.12).

Subsequent infusions should also be administered in the morning, as patients should remain under observation for at least 1 hour after the completion of the infusion and up to 24 hours at the treating investigator's discretion.

Physicians should alert patients that IRRs can occur within 24 hours of infusion. For this reason, a structured telephone interview will be conducted by site personnel 24 (±4) hours after each infusion to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit (i.e., any unusual signs or symptoms since the patient left the clinic after the infusion).

4.5.3.2 Delayed Dosing Visits

Delayed dosing visits may be scheduled only if the infusion cannot be administered at the timepoints defined in the schedule of activities (see Appendix 1). Thus, a patient who had all assessments of a dosing visit performed, but could not receive his/her infusion, should be rescheduled for the infusion.

If the delayed dosing visit occurs more than 4 weeks from a scheduled dosing, the dose will be administered as two infusions of half the dose 14 days apart to mitigate the risk and severity of IRRs (see Section 4.3.2.3).

To ensure that patients meet re-treatment criteria (see Section 4.3.6), an unscheduled site visit (or unscheduled MN visit) should be scheduled within 2 weeks in advance of any delayed dosing visit. The treating investigator must verify that all re-treatment criteria, including safety laboratory parameters, are met before proceeding with the infusion of ocrelizumab and that the benefit-risk of continuing ocrelizumab treatment is still favorable.

A delayed dosing visit should not be scheduled for the first infusion of the first dose (Dose 1, Day 1), as treatment with the first study drug infusion should occur within 24 hours of treatment allocation (in exceptional cases within 48 hours of treatment allocation provided that the investigator assures that all eligibility criteria are still met on the day of dosing).

In unforeseen situations, if the infusion of the first dose (Day 1) is delayed, then the visit for the second infusion should be scheduled 14 (±2) days after the delayed first infusion.

At the delayed dosing visit, additional tests or assessments, such as routine safety laboratory tests, may be performed when the investigator judges that these are warranted.

Patients with active infection during the study should be promptly evaluated and treated appropriately; infusion should be delayed until the infection has completely resolved.

4.5.3.3 Unscheduled Visits

Unscheduled visits for the assessment of potential relapses, new neurologic symptoms, and safety events, such as infection, may occur at any time.

Patients developing new or worsening neurologic symptoms or with signs of infection during the study should be seen at the investigational site as soon as possible regardless of the dates of their preplanned, scheduled study visits and regardless of the study period. Assessments performed at unscheduled (non–dosing) visits will depend on the clinical needs of the patient.

Patients with new neurologic symptoms suggestive of relapse should have an EDSS assessment within 7 days of the symptom onset.

Also, see Section 5.1.1.3 for guidance on the diagnosis of PML.

4.5.3.4 Telephone Interviews

Patients (or caregivers of patients, as appropriate) will be called by the investigator or designee to monitor patient status between visits. Assessments will include new or worsening neurological symptoms, adverse events, concomitant medication review, and any other clinically significant events.

The purpose of this structured interview is to identify and collect information on any changes in the patient's health status (i.e., new or worsening neurologic symptoms, signs of infection, any unusual signs or symptoms since the patient left the clinic after the infusion) that warrant an unscheduled visit. The telephone interview will be conducted by site personnel familiar with the patient(s) at the following points of time:

- Within 24 (±4) hours after completion of each infusion.
- Every 4 weeks between study visits *during OOE and during* SFU period (see schedule of activities, Appendix 1).
- Thereafter, for those patients who require additional SFU for B–cell repletion, telephone interviews will continue every 12 weeks between study visits (see schedule of activities, Appendix 1).

For patients who undergo an alternative treatment for MS while in the B−cell monitoring period, telephone interviews will continue to be performed every 4 weeks.

The site will record in the eCRF the date of interview or if the site was unable to contact the patient. The documentation of the interview will be maintained in the patient's study file and all relevant safety information recorded in the eCRF (e.g., completion of MS Relapse and Adverse Event eCRFs).

4.5.3.5 Mobile Nursing Visits

At applicable sites, certain study assessments, procedures, and blood draws may be performed by an MN professional at the patient's home or another suitable location to improve access and convenience for patients participating in the study. The Sponsor will select a healthcare company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a patient and the caregiver (and patient as appropriate) gives written informed consent, the MN network will communicate with the caregiver (and/or patient as appropriate) and the patient's site.

MN visits will be scheduled on specified visit days to allow for relevant assessments, procedures, and blood draw to be performed by the MN professional. If during a visit the MN professional identifies any change in patient's health status (e.g., new or worsening neurologic symptoms or any other situation that may warrant an unscheduled visit), the MN professional will contact the site immediately to report and discuss the findings. If required, an unscheduled visit will be scheduled as soon as possible with the site (i.e., within 7 days of symptom onset if possible). The schedule of activities (see Appendix 1) will specify which visits/assessments, procedures, and blood draw may be performed by an MN professional.

4.5.3.6 Withdrawal Visit

At the moment a patient meets one or more of the withdrawal criteria, or if a patient does not want to continue in the OOE period, this patient is regarded as withdrawn from treatment. Patients who withdraw from ocrelizumab treatment must complete all assessments (i.e., withdrawal visit) as shown in the schedule of activities (see Appendix 1) and will enter the SFU period.

It is important to distinguish between "withdrawal from treatment" and "withdrawal from study." Patients who withdraw from treatment should be encouraged to remain in the study for the full duration of the SFU period (*104* weeks following the last infusion).

Despite all efforts, patients who withdraw from the study before entering the SFU period or during the SFU period should undergo the assessments shown in the schedule of activities.

At the withdrawal visit, an MRI scan will be required only if one was not performed in the previous 4 weeks. Thereafter, it is at the discretion of the treating investigator to decide on further treatment of the underlying disease. However, since sufficient data are not available to inform risks associated with switching to other products, the following recommendations are given:

- Caution is advised while patients remain B–cell depleted.
- Because of the unknown safety risk of administering DMTs for MS after discontinuation of ocrelizumab, certain treatments for MS such as lymphocyte-depleting agents or lymphocyte-trafficking blockers (e.g., alemtuzumab, natalizumab, fingolimod, dimethyl fumarate, cyclophosphamide, azathioprine) are strongly discouraged for as long as the patient remains B cell depleted because of unknown effects on the immune system (e.g., increased risk, incidence, or severity of infection).

4.5.4 Medical History and Demographic Data

Medical history includes thorough recording of MS history, including prior MS therapies, and clinically significant non-MS diseases, including therapies and procedures, reproductive status, vaccination status, and any other clinically relevant information.

Demographic data will include age, sex, and self–reported race/ethnicity.

4.5.5 Physical Examinations

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

At subsequent visits as indicated in the schedule of activities, a limited, symptom-directed physical examination should be performed.

Diagnosis of new abnormalities or clinically significant worsening of preexisting abnormalities should be recorded as adverse events if appropriate.

For consistency, it is recommended that at each visit the same examiner perform the same assessment using the same instrument with the same patient.

4.5.6 Growth Velocity: Height

Child height should be measured in a standing position using the same wall-mounted stadiometer (or an equivalent validated machine) with the same individual every 6 months, as outlined in the schedule of activities.

Three standing height measurements should be made. The average of the three measurements will be considered to be the true height of the child, provided the measurements are within 0.3 cm. The average value will be recorded on the eCRF.

Note: Height should be collected from consenting biological mothers and fathers to determine the expected height of the child. This information should be entered directly on the eCRF, and the eCRF may be considered as the source document. If both parents are not able to attend the same visit, the missing height evaluation should be made at the next clinic visit. If the biological parents are unknown this part will not be applicable.

4.5.7 Body Weight

Body weight is to be determined to the nearest 0.1 kg. For body weight measurements, the patient should wear clothes, without any shoes, outerwear, or accessories.

Weight should be measured every 6 months, as outlined in the schedule of activities (see Appendix 1).

Patient with a body weight <25 kg should not be treated with ocrelizumab (see Section 4.1.1.1 and 4.3.6).

4.5.8 Tanner Staging

Tanner stages (1–5) (Tanner 1986) should be determined yearly as outlined in Appendix 2 and according to schedule of activities (see Appendix 1).

At baseline, all patients will have their Tanner stage documented or assessed. Patients who have not yet reached Stage 5 at study entry should have their Tanner stages documented or assessed until they reach Stage 5.

At sites where Tanner staging is not performed routinely, data can be obtained from the child's primary pediatrician, if available. If these data are not available, this section will not be applicable.

Tanner staging assessment will be contingent on IRB/EC approval, written informed consent from the patient's parent/legal guardian, and patient assent (as applicable). If anyone does not approve the Tanner staging assessment, this section will not be applicable.

4.5.9 Female Reproductive Status

The date of menarche should be recorded on the eCRF.

4.5.10 Bone Age Assessment: Wrist/Hand Radiographs

Bone age should be assessed by obtaining one combined standard posterior–anterior radiograph of the left wrist and hand. The radiographs should be obtained within 4 weeks of baseline and repeated yearly (±4 weeks).

If evidence of growth-plate fusion is not demonstrated at baseline but during subsequent X–rays, no further hand/wrist X–rays will be necessary provided that final growth/bone maturation has unequivocally been reached.

It is recommended that bone age be reported according to the Greulich and Pyle Atlas (Greulich and Pyle 1959); however, the practice may vary between institutions. In any case, the grading system used should be referenced on the eCRF.

This radiographic assessment will be contingent on IRB/EC approval, written informed consent from the patient's parents/guardian, and patient assent (where possible). If a site's IRB/EC does not approve the radiographic assessment, this section will not be applicable.

4.5.11 ECGs (Predose and Postdose)

Twelve-lead ECGs should be performed as outlined in the schedule of activities (see Appendix 1), at screening, before any ocrelizumab infusion, and after completion of the infusion (see Section 4.3.2.2).

The investigator or his or her designee must review, sign, and date all ECG tracings.

Whenever possible, the same machine should be used for each patient. Lead placement should be as consistent as possible. To minimize variability, it is important that patients be in a resting position for at least 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, or conversation) should be avoided during the pre–ECG resting period and during ECG recording.

Paper copies should be kept as part of the patient's permanent study file at the site. Digital recordings will be stored at study sites. ECG outcomes should be reported on the eCRF. Abnormalities should be specified. New or worsened abnormalities should be recorded as adverse events on the Adverse Event eCRF if clinically appropriate.

An ECG is also required if the patient prematurely withdraws from the study. Additional ECGs may be taken at the discretion of the treating investigator if clinically indicated. ECG outcomes should be reported on the unscheduled eCRF.

4.5.12 Vital Signs

Vital signs (pulse rate, systolic and diastolic blood pressure, respiratory rate, and temperature) should be taken at the visits indicated in the schedule of activities (see Appendix 1). Blood pressure measurements should be obtained using a child–appropriate cuff size.

For vital signs monitoring on the infusion days, see Section 4.3.2.2. On non–infusion days, vital signs may be taken at any time during the visit.

Additional vital signs readings may be taken at the discretion of the treating investigator if clinically indicated and should be recorded on the unscheduled vital signs eCRF.

All readings will be recorded on the eCRF.

4.5.13 Assessment of Relapses

All patients complaining of new or worsening neurologic symptoms defined at a site visit, MN visit (if applicable), or over the phone should be referred to the treating investigator for Functional System Score (FSS)/EDSS assessment, within 7 days of the onset of the relapse (see Section 4.5.14).

All new or worsening neurologic events consistent with MS and representing a clinical relapse (i.e., regardless of whether events meet criteria for a protocol–defined relapse) should be recorded on the prespecified MS Relapse eCRF.

Protocol–defined relapse is the occurrence of new or worsening neurologic symptoms attributable to MS. Symptoms must persist for $>$24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, and adverse reactions to medications) and immediately preceded by a stable or improving neurologic state for at least 30 days. The new or worsening neurologic symptoms must be accompanied by objective neurologic worsening consistent with an increase of at least half a step on the EDSS scale, or 2 points on one of the appropriate FSS scales, or 1 point on two or more of the appropriate FSS scales. The change must affect the selected FSS (i.e., 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 protocol-defined relapse.

4.5.14 Kurtzke Expanded Disability Status Scale

The EDSS is based on a standard neurologic examination, incorporating seven functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral [or mental]) and ambulation rated and scored as an FSS. 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.

The EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10 (death). The EDSS will be assessed by the treating investigator.

All patients with new or worsening neurologic symptoms consistent with MS should have an EDSS assessment performed during an unscheduled visit, within 7 days of the onset of the symptoms.

For consistency, it is recommended the same rater assess the same patient at each visit.

4.5.15 Neurologic Examination

A neurologic examination should be performed at every planned visit and unscheduled visit if applicable.

In the presence of newly identified or worsening neurologic symptoms at any given time in the study, a neurologic evaluation should be scheduled promptly. In case of events suggestive of relapse, the EDSS assessment (see Section 4.5.14) is to be performed within 7 days of the onset of the relapse. If the relapse is confirmed, it will be reported on the prespecified MS Relapse eCRF. In case the relapse is not confirmed, an adverse event will be reported as applicable.

Study investigators will screen patients for signs and symptoms of PML by evaluating neurologic deficits localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, hemiparesis, and cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination; see Section 5.1.1.3 for more information). A brain MRI scan and CSF analysis may be warranted to assist in the diagnosis of PML. See Appendix 5 for guidance on the diagnosis of PML.

Patients with suspected PML, which necessitates MRI and/or lumbar puncture and CSF analyses to rule out PML, should be withheld from study treatment until PML is ruled out by complete clinical evaluation and appropriate diagnostic testing (see Appendix 5). The Sponsor's Medical Monitor should be immediately contacted (see Section 5.4.1).

A patient with confirmed PML should be withdrawn from treatment. PML should be reported as a serious adverse event (with all available information) with immediate notification of the Sponsor's Medical Monitor (see Section 5.4.1).

4.5.16 Brain Magnetic Resonance Imaging

MRI is a useful tool for monitoring CNS lesions in MS. Different MRI-derived parameters have been related to clinical activity, and T1–weighted Gd-enhancing lesions or new and/or enlarging hyperintense T2 lesions have been related to relapses.
Brain MRI scans should be obtained in all patients as detailed in the schedule of activities (see Appendix 1). In addition, brain MRI scans should be obtained in patients

withdrawn from the study (at the withdrawal visit) if not performed during the previous 4 weeks.

Scans will be performed by trained and certified MRI technicians. The MRI should include the acquisition of scans without and with IV–administered Gd–contrast enhancement. The following time windows apply:

- A "baseline" MRI should be performed with and without a Gd–contrast agent; it should be performed after the screening visit but at least 10 days prior to the baseline visit.
- A brain MRI with and without a Gd–contrast agent should also be performed at Week 12 (±2 weeks).
- Subsequent brain MRIs will be performed without a Gd–contrast agent at Week 24 (a window of minus 4 weeks can apply), Weeks 48, 72, 96, 144, 192, 240, and 288 or at the withdrawal visit (if applicable) (window of ±4 weeks of these scheduled visits). During SFU and B–cell monitoring as applicable, brain MRI scans will also be performed without a Gd–contrast agent (window of ±4 weeks of the scheduled visits).

Note: Metal braces can cause significant artifacts on the MRI sequences. Therefore, they would need to be removed, if possible, prior to scanning the patient and replaced afterwards. If the patient/caregiver refuses, then the patient will not be eligible for this study (Section 4.1.2). Ceramic braces usually do not interfere with the analyses; however, this must be confirmed with the orthodontist or manufacturer of the braces. Permanent retainers (typically a single wire used behind the lower teeth and bonded to them) will not interfere with the images acquired for this MRI protocol, while removable retainers should be removed prior to scanning.

If patients receive corticosteroids for an MS relapse, every effort should be made to obtain the scan prior to the first steroid dose if the pre-steroid scan is within 1 week of the scheduled visit. In patients receiving corticosteroids for an MS relapse, there should be an interval of 3 weeks between the last dose of corticosteroids and the scan.

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

All MRI scans should also be reviewed locally by a radiologist for safety. During the study, the MRI scan report containing MS and non–MS pathology will be provided to the treating investigator. The treating investigator can have access to MRI scans as deemed necessary.

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

4.5.17 Low-Contrast Visual Acuity Testing

Low–contrast visual acuity (LCVA) charts (Sloan charts) have gained validity in the assessment of visual dysfunction in patients with MS not readily apparent on commonly used high-contrast acuity tests. Reductions in low-contrast letter acuity are associated with MS and correlate with increasing disability, MRI abnormalities, and reduced retinal nerve fiber layer thickness as measured by optical coherence tomography.

Determination of the LCVA will include a measure of high-contrast acuity using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart as described in Appendix 3.

LCVA and ETDRS assessments should be performed by the treating investigator or a qualified designee accordingly to the procedure described in Appendix 3, at the timepoints indicated in the schedule of activities (see Appendix 1).

For consistency, it is recommended at each visit the same examiner perform these measurements with the same patient.

4.5.18 Symbol Digit Modalities Test

The Symbol Digit Modalities Test (SDMT) has demonstrated sensitivity in detecting not only the presence of cognitive impairment but also changes in cognitive functioning over time and in response to treatment. The SDMT is brief, easy to administer, and involves a simple substitution task that normal children and adults can easily perform.
The SDMT will be administered orally, and administration time is just 5 minutes.
SDMT should be assessed at the timepoints indicated in the schedule of activities (see Appendix 1).

For consistency, it is recommended at each visit the same examiner administer the SDMT with the same patient.

4.5.19 Laboratory, Biomarker and Other Biologic Samples

Samples for laboratory tests should be taken at the timepoints indicated in the schedule of activities (see Appendix 1). Whenever possible, laboratory samples should be drawn in the morning. Unscheduled laboratory assessments for safety issues are permitted at any time. The total volume of blood taken for laboratory assessments (including all safety, PK/PD, and immunologic assessments) will not exceed the per–visit and per-cumulative visit recommendations made by the National Institutes of Health for the expected average weights of the patients enrolled in this study.

The procedures for the collection, handling, and shipping of laboratory samples are specified in the Sample Handling and Logistics Manual.

Full details of the central laboratory sample collection, handling, shipment, and reporting of results will be described in the Laboratory Manual supplied to sites.

The samples for this study should be classified, packed, and shipped as UN3373 Biological Substance, Category B.

4.5.19.1 Local Laboratory Assessments

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Urinalysis: A urine dipstick for blood, protein, nitrite, and glucose (using the dipsticks provided) will be performed according to the schedule of activities (see Appendix 1). If abnormal and applicable, a microscopic examination will be performed on site (local laboratory).
- Pregnancy test: Urine pregnancy test (sensitivity of at least 25 mIU/mL β–hCG) for all females of childbearing potential (Tanner Stage 2 or above or onset of menarche during the study)

On infusion visits, the urine samples for the urinalysis and pregnancy test should be performed prior to the methylprednisolone infusion and the ocrelizumab dose withheld for a positive pregnancy test result.

A positive urine pregnancy test should be confirmed with a serum test through the central laboratory prior to any further dosing with ocrelizumab.

4.5.19.2 Central Laboratory Assessments

In order to ensure patient safety in the study and to allow for assessments of the retreatment criteria, a central laboratory will provide study investigators and Medical Monitors with reflex messages triggered by critical laboratory results.

The reflex messages from a central laboratory, together with laboratory results, should be carefully reviewed at every visit before continuing with ocrelizumab treatment.

Investigators notified of a patient's critical laboratory test results will be instructed to suspend further treatment with study drug until the patient becomes eligible for re-treatment (see Section 4.3.6).

The reflex messages will be in effect during the entire study duration. Further details will be provided in the Laboratory Manual.

- Hematology: WBC count (absolute and differential), RBC count, RBC morphology, hemoglobin, hematocrit, quantitative platelet count, and ANC count
- Blood chemistry: AST, ALT, gamma glutamyl transferase, alkaline phosphatase, amylase, lipase, total protein, albumin, cholesterol, total bilirubin (direct and indirect will be performed if total bilirubin is greater than the ULN), uric acid, potassium, sodium, chloride, calcium, phosphorus, LDH, CPK, and triglycerides

- Thyroid function test: Sensitive thyroid-stimulating hormone (TSH) will be tested as outlined in the schedule of activities (see Appendix 1). Thyroid autoantibodies (i.e., thyroid peroxidase antibody, thyroglobulin antibody) will be assayed only at screening.
- Immunologic assessments: Determination of B– and T–cell populations and natural killer cells
- Quantitative Ig levels: Including total Ig, IgG, IgM, and IgA isotypes
- Antibody titers: Measurement of antibody titers to common antigens (mumps, rubella, varicella*, S. pneumoniae*) will be performed.
- ADA: Serum samples will be collected for determination of antibodies against ocrelizumab. Because ocrelizumab concentrations affect the ADA assay, the concentration of ocrelizumab will be measured as well at all timepoints with ADA assessment to enable interpretation of the results (PK sample).

On infusions visits, all samples must be taken prior to the methylprednisolone infusion.

For more information, refer to the schedule of activities (see Appendix 1).

4.5.19.3 Laboratory Tests Performed at Screening

The following laboratory tests will be performed at screening:

- Pregnancy test: A serum pregnancy test will be performed at screening for all females of childbearing potential and will be sent for central laboratory analysis.
- Hepatitis serology: HBcAb, HBsAg, and HepCAb at screening only or if clinically indicated during the trial
- Thyroid function test: sensitive TSH and thyroid autoantibodies (i.e., thyroid peroxidase antibody, thyroglobulin antibody) at screening
- Rapid plasma regain

See also Section 4.1.2.3 (Exclusions Related to Laboratory Findings).

4.5.19.4 Hepatitis Screening and Liver Function Monitoring

Patients with recurrent or chronic hepatitis B or history/presence of hepatitis C infection must be excluded from enrollment into the study. Hepatitis B and C serology will be performed at screening.

A positive result to either HBsAg, total HBcAb associated with positive viral DNA titers as measured by PCR, or a positive result for HepCAb should result in the patient's exclusion.

Patients with evidence of past resolved hepatitis B infection (i.e., positive total HBcAb associated with a negative viral DNA) can be enrolled and will have the hepatitis B viral DNA checked regularly as per the schedule of activities (see Appendix 1).

Patients in whom the viral DNA becomes positive but in whom the quantity is at the lower limit of detection of the assay should have the test repeated as soon as possible. Patients found to have a confirmed viral DNA–positive test should be referred to a hepatologist for immediate assessment. These patients will not receive further ocrelizumab infusions and will enter the SFU period.

Liver function (i.e., ALT, AST, gamma glutamyl transferase, alkaline phosphatase, and total bilirubin) should be reviewed throughout the study. Patients developing evidence of liver dysfunction should be assessed for viral hepatitis and, if necessary, referred to a hepatologist or other appropriately qualified expert. Study drug should be withheld until the diagnosis of viral hepatitis has been excluded.

Patients developing hepatitis B or C should be withdrawn from the study and should enter the SFU period. Should treatment be prescribed, this will be recorded on the eCRF. Patients with viral hepatitis due to other agents, such as hepatitis A, may resume treatment after the patient's recovery.

4.5.19.5 Plasma and Urine Banking for JC–virus

Long-term storage of plasma samples and urine is planned for JC–virus (JCV) DNA and/or other relevant tests for JCV, independent of an occurrence of suspected PML case (see Section 5.1.2.2). Plasma samples (5 mL) and urine samples (10 mL) will be collected as per the schedule of activities (see Appendix 1). As there have been no cases of PML reported with ocrelizumab and a correlation between viremia and onset of PML has not been established for another anti-CD20 therapy, JCV samples will not be used to determine study participation or treatment decisions. The JCV assessments in plasma and urine will be performed if deemed necessary in the future and not on an ongoing basis.

4.5.19.6 Pharmacokinetic/Pharmacodynamic Assessments

Pharmacokinetics

First ocrelizumab dose (Dose 1, Days 1 and 15):

PK samples (2 mL blood for serum) will be collected on the infusion day at Days 1 and 15 at 5–30 minutes before the methylprednisolone infusion and 30 (±10) minutes after the completion of the ocrelizumab infusion.

In addition, during the 24–week dose exploration period, one PK sample each will be collected any time during visits at Weeks 4, 8, 12, 16, and 24 (prior to the next infusion of ocrelizumab for patients continuing in the OOE period).

Subsequent ocrelizumab doses in the OOE period:

A PK sample will also be collected predose before each infusion during the OOE period, until Week 96, at a withdrawal from treatment visit, and during the SFU period as outlined in the schedule of activities (see Appendix 1).

Note: The PK sample must be collected from the arm opposite the arm receiving the IV infusion of ocrelizumab.

Pharmacodynamics

CD19 B–cell count in blood will be performed at baseline; Weeks 2, 4, 8, 12, 16, and 24; and at further timepoints as outlined in the schedule of activities (see Appendix 1).

4.5.19.7 Blood Samples for Biomarker Research

Serum samples will be collected for exploratory research on biomarkers.

These samples will be collected according to the schedule of activities (see Appendix 1) and analysis will include, but may not be limited to neurofilament light chain. Biomarker samples will be sent to one or several central laboratories or to the Sponsor or a designee. Samples may be processed by the Sponsor's laboratory or the Sponsor's qualified designated laboratory (Contract Research Organization and/or academic research laboratory affiliated with the study). Instructions for the collection and handling of biomarker samples, including sampling procedures, storage conditions, and shipment instructions, are provided in the laboratory manual.

Unless the patient and/or their parent(s)/legal guardian(s) gives specific consent for the patient's leftover samples to be stored for optional exploratory research (see Section 4.5.20), biomarker samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient and/or their parent(s)/legal guardian(s) specifically requests that the samples be destroyed, or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

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

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

4.5.20 Optional Samples for Research Biosample Repository

4.5.20.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The

collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent or who have been given specific consent by their parent(s)/legal guardian(s) 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

4.5.20.2 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 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 4.5.20) will not be applicable at that site.

4.5.20.3 Sample Collection

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

- Optional blood collection for DNA
- Leftover blood, serum and plasma

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

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger

dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

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

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

4.5.20.4 Data Protection, Use, and Sharing

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

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

Data generated from RBR samples will be analyzed in aggregate rather than on an individual patient basis. Thus, there will be no identification and reporting of incidental findings to investigators or patients and/or their parent(s)/legal guardian(s). In addition, 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 patient and/or their parent(s)/legal guardian(s), unless required by law, with the exception of data generated from blood samples collected for WGS or WES as described below.

If permitted by local law, a patient and/or their parent(s)/legal guardian(s) may request access to uninterpreted WGS or WES data derived from analysis of the patient's blood sample. If a patient and/or their parent(s)/legal guardian(s) wishes to access these data, the investigator must inform the Sponsor, using the following email address:

global.return-genomics-results@roche.com

The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file, but will not provide any interpretation of the data. The investigator should not include the data file in the patient's medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

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.

4.5.20.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient and/or their parent(s)/legal guardian(s) the objectives, methods, and potential hazards of participation in the RBR. Patients and/or their parent(s)/legal guardian(s) will be told that they are free to choose not to provide optional RBR samples and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature from the patient and/or their parent(s)/legal guardian(s) will be required to document a patient's agreement to provide optional RBR samples. Patients and/or their parent(s)/legal guardian(s) who choose not to provide optional RBR samples will not provide a separate signature. The investigator should document whether or not the patient and/or their parent(s)/legal guardian(s) has given consent to provide optional RBR samples and (if applicable) the date of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

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

4.5.20.6 Withdrawal from the Research Biosample Repository

Patients and/or their parent(s)/legal guardian(s) who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed. 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 and/or their parent(s)/legal guardian(s) wishes to withdraw consent to the testing of the patient's RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient and/or their parent(s)/legal guardian(s)'s wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the Sample Informed Consent/Withdrawal eCRF. If a patient and/or their parent(s)/legal guardian(s) wishes to withdraw consent to the testing of the patient's RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and participant number to the following email address:

global.rcr-withdrawal@roche.com

A patient and/or their parent(s)/legal guardian(s)'s withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a

patient and/or their parent(s)/legal guardian(s)'s withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.20.7 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 an individual's participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Life-threatening (Grade 4) infusion–related event or severe allergic or anaphylactic reaction to an ocrelizumab infusion
- Active hepatitis B or C infection, either new onset or reactivation in the case of hepatitis B
- PML
- Treatment emergent life-threatening (Grade 4) infection

It is important to distinguish between "withdrawal from treatment" and "withdrawal from study." Patients who withdraw from treatment should be encouraged to remain in the study for the full duration of the SFU period (*104* weeks following the last infusion).

A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study.

If the parents/legal guardians or patients insist on withdrawing (their child) from the study, he/she will not be followed for any reason after consent and/or assent withdrawal. The outcome of that discussion should be documented in both the medical records and on the eCRF. If lost to follow-up, the investigator should contact the parents/legal guardians/patient or a responsible relative by telephone followed by registered mail or through a personal visit to establish as completely as possible the reason for the withdrawal.

It should be noted that upon withdrawal from the study, any untested routine samples will be destroyed. However, information already obtained from samples up until the time of withdrawal will not be destroyed.

An excessive rate of withdrawals can render the study non-interpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw, all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible.

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

4.6.2 Patient Discontinuation from Study

Patients who discontinue study participation and withdraw consent or assent, as applicable, will not be required to return for any follow-up assessments.

Parents/legal guardians have the right to withdraw their child from the study at any time for any reason.

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 withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent or assent, as applicable
- Parents/legal guardian withdrawal of consent
- Study termination or site closure
- Investigator or Sponsor determines it is in the best interest of the patient

When applicable, parents/guardians/patients should be informed of circumstances under which their (child's) participation may be terminated by the investigator without parent/guardian/patient consent. The investigator may withdraw patients from the study in the event of intercurrent illness, adverse events, treatment failure, after a prescribed procedure, lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits), or any reason where it is believed by the investigator that it is in the best interest of the patient to be terminated from the study. Any administrative or other reasons for withdrawal must be documented and explained to the patient. If the reason for removal of a patient from the study is an adverse event, the principal specific event will be recorded on the eCRF. If possible, the patient should be followed until the adverse event has resolved.

Every effort should be made to obtain information on patients who withdraw from the study as thoroughly as possible. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study

for safety reasons will not be replaced. Patients who withdraw from the study for reasons other than safety may be replaced in order to ensure that data from at least 6 evaluable patients per each cohort over 24 weeks are available to enable the dose selection decision.

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

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

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:

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Ocrelizumab has not been investigated in children or adolescents with MS. The safety plan in this study is based on clinical experience with ocrelizumab in completed and ongoing studies. The sections below reflect safety data per the current Ocrelizumab Investigator's Brochure.

Parents/legal guardians/patients should be informed of the risks associated with taking ocrelizumab.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. Compliance with the planned dosing schedule of ocrelizumab infusions is required unless an adjustment is necessary for safety reasons. During study visits when the ocrelizumab infusion is

interrupted for toxicity, all other study assessments should be performed as per the schedule of activities (see Appendix 1).

The anticipated important safety risks for ocrelizumab and recommendations for vigilance with signs and symptoms of particular safety events are summarized in the following sections.

Refer to the current version of the Ocrelizumab Investigator's Brochure for a complete summary of safety information.

5.1.1 Identified Risks and Adverse Drug Reactions Associated with Ocrelizumab Use

5.1.1.1 Infusion-Related Reactions

All CD20–depleting agents administered via IV, including ocrelizumab, have been associated with IRRs, which are related to the mechanism of action (i.e., cytokine release and/or other chemical mediators). IRRs may be clinically indistinguishable from Type 1 (IgE-mediated) acute hypersensitivity reactions (see Section 5.1.1.2).

Following the approved administration regimen (which includes the use of premedication prior to treatment with ocrelizumab 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 and parent(s)/legal guardian(s) 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 1 hour after the completion of the infusion for any symptom of IRR. Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact the study physician if he or she develops such symptoms.

Additional caution will be taken in this first study investigating ocrelizumab in children and adolescents by having the first infusion (Day 1 of Dose 1) scheduled in the morning to allow for a hospital stay with medical supervision and monitoring as needed, as long as possible.

For premedication see Section 4.3.3.

Managing Infusion-Related Reactions

Infusion of ocrelizumab is administered under the close supervision of an experienced healthcare professional with access to appropriate medical support to manage severe reactions such as serious IRRs.

Patients who experience severe pulmonary events, such as bronchospasm or asthma exacerbation, must have their infusion interrupted immediately and permanently. After administering symptomatic treatment, monitor the patient until the pulmonary symptoms have resolved because initial improvement of clinical symptoms could be followed by deterioration.

Because transient hypotension may occur during ocrelizumab infusion, patients with low blood pressure should be monitored carefully. Patients with a history of congestive heart failure (New York Heart Association Class III/IV) were not studied.

In case of IRRs during any infusion, see recommendations in Section 4.3.4.

In the event of a suspected anaphylactic reaction during study treatment infusion, please refer to Appendix 6.

5.1.1.2 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%–6%, simplex and zoster) than with comparators (approximately 3%).

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

Serious, opportunistic and fatal infections have occurred in patients with lupus and rheumatoid arthritis 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 current Ocrelizumab Investigator's Brochure.

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

In interventional clinical studies, there were no reports of hepatitis B reactivation in patients with MS treated with ocrelizumab, but was reported in 1 patient with rheumatoid arthritis treated with ocrelizumab. HBV screening should be performed in all patients before initiation of treatment with ocrelizumab as per local guidelines. Patients with active Hepatitis B virus should not be treated with ocrelizumab. Patients with positive serology should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent Hepatitis B reactivation.

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

For PML see Section 5.1.2.

5.1.1.3 Impaired Response to Vaccination

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

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.

In the randomized open-label Study BN29739, the humoral responses to tetanus toxoid, 23-valent pneumococcal polysaccharide (23–PPV), KLH neoantigen, and seasonal influenza vaccines were decreased in patients with RMS treated with ocrelizumab (compared with those patients not treated with ocrelizumab) at all timepoints measured. Nevertheless, patients with RMS who received ocrelizumab and were peripherally B-cell depleted were able to mount humoral responses, albeit decreased, to clinically relevant vaccines (tetanus toxoid, 23–PPV, influenza) and the neoantigen KLH. The results of the study confirm the current recommendation that patients should complete local vaccination requirements 6 weeks prior to initiation of ocrelizumab to obtain full effectiveness of the vaccines. In addition, for seasonal influenza vaccines, it is still recommended to vaccinate patients receiving ocrelizumab, as a humoral response to the vaccine, even if attenuated, can be expected.

Refer to the current Ocrelizumab Investigator's Brochure for details and see Section 3.4.7.2 and 5.1.5.

5.1.1.4 Decrease in Immunoglobulins

Treatment with ocrelizumab resulted in a decrease in total Igs 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 high risk of serious infection cannot be ruled out (see Section 5.1.1.5).

Patients with IgG and IgM below the exclusionary levels per Section 4.1.2.3 at screening will not be enrolled in the study. The investigator should closely monitor the patient's IgG and IgM levels during the study. If their levels decrease below the exclusionary levels following ocrelizumab treatment and require specific medical care or management, repeat dosing may be suspended until resolved or held indefinitely as per the judgement of the treating investigator.

5.1.1.5 Serious Infections Related to Decrease in Immunoglobulins (Particularly in Patients Previously Exposed to Immunosuppressive or Immunomodulatory Drugs or with Preexisting Hypogammaglobulinemia)

Based on additional patient exposure, an association between decrease in Igs and serious infections with ocrelizumab treatment was observed and was most apparent for IgG. There was no difference in the pattern (type, latency, duration, outcome) of the serious infections reported in this subset of patients compared to the overall serious infections profile. In addition, risk factors for a subset of patients at higher risk of serious infections could not be identified.

5.1.1.6 Delayed Return of Peripheral B-cells

Treatment with ocrelizumab leads to rapid depletion of CD19+ B−cells in blood by 14 days post-treatment (first timepoint of assessment) and is an expected pharmacologic effect. This was sustained throughout the treatment period. The longest follow−up time after the last ocrelizumab infusion is from 51 patients in Study WA21493 and indicates that the median time to B−cell repletion (returned to baseline or LLN, whichever occurred first) was 72 weeks (range 27−175 weeks). Patients with prolonged B−cell depletion should be monitored until their B−cells have repleted. See the current Ocrelizumab Investigator's Brochure for further details.

5.1.2 Potential Risks Associated with Ocrelizumab Use

5.1.2.1 Malignancies including Breast Cancer

An increased risk of malignancy with ocrelizumab may exist. In controlled trials in adults with multiple sclerosis, malignancies—including breast cancer—occurred more frequently in ocrelizumab-treated patients. Breast cancer occurred in 6 of 781 females treated with ocrelizumab and none of 668 females treated with Rebif® or placebo. Patients should follow standard breast cancer screening as per local guidelines. The incidence of malignancies was within the background rate expected for an MS population.

Patients with an active malignancy or actively monitored for the recurrence of a malignancy should not be treated with ocrelizumab. For more detailed information and recent analyses, see the current Ocrelizumab Investigator's Brochure.

5.1.2.2 Progressive Multifocal Leukoencephalopathy

JCV infection, resulting in PML has been reported in patients treated with anti−CD20 antibodies, including ocrelizumab, and mostly associated with risk factors, such as patient population or polytherapy with immunosuppressants. The reporting rate with ocrelizumab has been approximately 1 case per 100,000 patients. Since a risk of PML cannot be ruled out, physicians should be vigilant for early signs and symptoms of PML, which can include any new onset, or worsening of neurological signs or symptoms as these can be similar to an MS relapse. If PML is suspected, dosing with ocrelizumab must be withheld. Evaluation of PML, including MRI scan, preferably with contrast

(compared with pre-treatment MRI) confirmatory CSF testing for JCV DNA and repeat neurological assessments, should be considered. If PML is confirmed, ocrelizumab must be discontinued permanently (see Appendix 5).

PML is a potentially fatal neurological condition linked to reactivation of a polyomavirus, JCV, and active viral replication in the brain. Polyomavirus infection is acquired in childhood, and up to 80% of adults demonstrate serologic evidence of past infection. Reactivation of JCV replication with transient viremia or viruria unassociated with clinical symptoms may occur spontaneously in healthy persons. Less frequently, CNS symptoms associated with active viral replication in brain tissue are observed. The clinical syndrome is significantly more frequent among immune-suppressed patients. There is no known treatment or cure for PML. Treatment considerations are discussed in the medical literature (Calabrese et al. 2007).

Physicians should consider the diagnosis of PML in any patient presenting with new and/or progressive neurologic deficits localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, and hemiparesis, and cerebellar symptoms/signs (e.g., gait abnormalities and limb incoordination), at each visit. Guidance for diagnosis of PML is given in Appendix 5.

PML should be reported as a serious adverse event (with all available information) with immediate notification of the Sponsor's Medical Responsible and the Medical Monitor.

In this study, comprehensive neurologic assessments will be performed every 24 weeks at the regular site study visits. Patients will be required to undergo a neurologic examination for calculation of an EDSS score every 24 weeks. This requires that FSS also be determined. The examination to calculate the FSS includes cognitive, visual, and motor assessments; the neurologic systems most often affected by PML; as well as assessments of other neurologic systems.

On the eCRF, the investigator will record the presence or absence of neurological deficits localized to the cerebral cortex (e.g., cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, and hemiparesis) and cerebellar symptoms/signs (e.g., gait abnormalities and limb incoordination) at each visit. Presence of such neurological findings will be recorded as adverse events. If a diagnosis for the deficits is identified, the symptoms should be replaced by the diagnosis in the Adverse Event eCRF.

In addition to the neurologic evaluation performed every 24 weeks at site, there will be regular study visits (site or MN visits, as applicable) in between; furthermore, patients will undergo a telephone interview every 4 weeks between the study visits by site personnel familiar with the patient(s). The purpose of this interview is to identify new or worsening neurological symptoms that warrant an unscheduled visit. Parents/legal guardians of

study patients will be informed on symptoms and signs that may be suggestive of PML and should be instructed to contact the site should any such signs or symptoms appear.

In the event that new or worsening neurological symptoms are considered during the telephone interview or during a study visit (site or MN visit, as applicable), a neurological evaluation will be conducted at the site as quickly as possible. Should a non–MS etiology, such as PML, be considered, further assessments should be done. The evaluation of PML may include a brain MRI scan and CSF analysis per the proposed diagnostic algorithm framework (see Appendix 5).

Refer to the current Ocrelizumab Investigator's Brochure for more details.

5.1.2.3 Neutropenia

During the controlled treatment period, decreased neutrophils were observed in 12% and 15% of patients with MS treated with ocrelizumab in PPMS and RMS, respectively. Most events 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. On the basis of additional patient exposure, an association between neutropenia and serious infections with ocrelizumab treatment was not observed.

In case the ANC decreases below the exclusionary level of $1.5 \times 10^3/\mu L$, further administration of ocrelizumab should be suspended until resolution of this laboratory abnormality or held indefinitely. See Section 4.3.6 for information on criteria for re–treatment with ocrelizumab.

5.1.2.4 Hypersensitivity Reactions

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

5.1.3 Corticosteroids Use

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

5.1.4 Antihistamines Use

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

5.1.5 Pregnancy and Breast Feeding

Female patients of childbearing potential (i.e., those with Tanner Stages ≥2 or post-onset of menarche) should take all appropriate precautions to avoid becoming pregnant during this study. As such, female patients of childbearing potential must agree to either remain completely abstinent or to use reliable means of contraception for the duration of the active treatment period AND for at least 6 months after receiving their last infusion of ocrelizumab. Regular pregnancy tests will be performed during the study.

A female patient/parent/legal guardian must be instructed to immediately inform the investigator if she/the daughter becomes pregnant during the treatment period with ocrelizumab and within 6 months after her last dose of ocrelizumab.

Given that there are insufficient, well-controlled data from studies testing the use of ocrelizumab in pregnant or breastfeeding women, all infusions of ocrelizumab following confirmation of pregnancy must be suspended until the completion of pregnancy and breastfeeding. Patients who are pregnant or breastfeeding should continue to follow the schedule of assessments for the study; however, no infusions will occur. If there is concern with the ability of the patient who is pregnant or breastfeeding to perform all scheduled assessments, the investigator must contact the Medical Monitor for further discussion. Re-start of ocrelizumab treatment following pregnancy and breastfeeding will be decided as a result of a thorough benefit–risk discussion between the patient and investigator (Section 4.3.6). For reporting requirements for pregnancies in female patients, see Section 5.4.2.1.

Reproductive toxicology studies of ocrelizumab conducted in cynomolgus monkeys are described in the Ocrelizumab Investigator's Brochure. B-cell levels in human neonates following maternal exposure to ocrelizumab have not been studied in clinical trials. There are no adequate and well–controlled data from studies in pregnant women; however, transient peripheral B–cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti–CD20 antibodies during pregnancy. It is not known whether ocrelizumab is excreted in breast milk or what effect this might have on the breastfeeding infant. However, since Igs are found in breast milk, breastfeeding mothers are excluded from participation in the study.

As ocrelizumab may cross the placenta and cause B–cell depletion in the neonate, infants born to mothers participating in this study should have an assessment of their lymphocyte counts and be carefully followed until these are within the normal range for the age of the infant. The investigator should counsel the patient as to the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant female patient should continue until conclusion of the pregnancy. Informed consent will be sought in order for the Sponsor to collect information on the health and wellbeing of the infant of a female patient.

For pregnancies occurring in female patients during the treatment period or within 6 months after their last dose of ocrelizumab, pregnancy outcome and the health status of the child will be followed until the child is 1 year of age. Data collection of the health status of the child is voluntary only; it does not include any interventions or invasive procedures. The Pregnancy Outcome and Infant Health Information on First Year of Life questionnaire and the authorization form will be submitted to Health Authorities and IRB/ECs for their approval.

The data will be reported on dedicated paper pregnancy outcome and infant health information pages.

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 of neonates and infants with live or live-attenuated vaccines should be delayed until B−cell levels have recovered. Therefore, measuring CD19+ B-cell levels in neonates and infants prior to vaccination is recommended.

Refer to the current Ocrelizumab Investigator's Brochure for further information.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Adverse events, vital signs, physical and neurological examination, clinical laboratory tests (including pregnancy tests), 12−lead ECG, locally reviewed MRI for safety (non−MS CNS pathology), and data on concomitant medications and diseases will be collected throughout the study.

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

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

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.11
- 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)

New or worsening neurologic symptoms not considered MS-related should be recorded on an Adverse Event eCRF, and the Medical Monitor should be informed.

Adverse events will be recorded on the Adverse Event eCRF. For clinical relapses and IRRs, a Specific Adverse Event eCRF triggered by an appropriate entry on the main Adverse Event eCRF will be used. The reporting requirements will be the same as for any other adverse event.

Further information related to clinical relapses will be recorded only on a prespecified eCRF MS Relapse eCRF. Signs, symptoms, and severity of IRRs will also be recorded on a prespecified IRR eCRF.

B-cell depletion is the expected outcome of ocrelizumab treatment and is not an adverse event. However, patients may be at risk for infections, and particular attention should be directed toward early identification and treatment of infections (see Section 5.1.1.2).

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 5.3.5.12)
- 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 exception to this definition of a serious adverse event is in the event that a patient is hospitalized following an MS relapse, as long as the reason for hospitalization is to receive standard treatment with IV methylprednisolone. The rationale for this exception is that some countries and/or clinical sites routinely hospitalize patients who require administration of methylprednisolone in the event of an MS relapse. Thus, the serious adverse event criteria for "hospitalization" would be met on the basis of local practice and would not reflect the seriousness of the event.

When the MS relapse results in hospitalization for any reason other than for routine treatment of the relapse (such as for a treatment course beyond the standard treatment) or when hospitalization is prolonged, the MS relapse should be considered a serious adverse event.

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 National Cancer Institute Common Terminology Criteria for Adverse Events [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)

Other than the mandated company adverse events of special interest shown below, there are no ocrelizumab-specific adverse events of special interest.

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

- 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 5.3.5.8)

- 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 Sections 5.4–5.6.

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

5.3.1 Adverse Event Reporting Period

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

After informed consent and assent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.1 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported during the study through the end of the SFU period, which is at least *104* weeks after the last infusion but may be extended in patients whose B cells take longer to replete.

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 2 will be used for assessing the severity of adverse events that are not specifically listed in the NCI CTCAE.

Table 2 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

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

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

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

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.1 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 5.4.1 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:

- 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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during the infusion or within 24 hours after study drug administration and are judged to be related to study drug infusion will be captured on a dedicated prespecified Infusion-Related Reaction eForm. This form includes specific fields in order to report all associated signs and symptoms, including severity.

5.3.5.2 Clinical Relapses

Further information related to clinical relapses will be recorded on a prespecified MS Relapse eForm, which will be triggered by an appropriate response on the main Adverse Event eForm.

5.3.5.3 Diagnosis versus Signs and Symptoms

For adverse events other than IRR and MS relapse, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms. 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.

5.3.5.4 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.

5.3.5.5 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.1 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non–serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

5.3.5.6 Abnormal Laboratory Values

B–cell depletion is a PD effect and not an adverse event.

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

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

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

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

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

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

Follow-Up of Abnormal Laboratory Test Values

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established, it should be recorded on the Adverse Event eCRF.

During the study conduct, investigators notified of a patient's critical laboratory test (Section 4.3.6 criteria for re–treatment with ocrelizumab) result will be instructed to suspend further treatment with study drug until the patient can be further evaluated. A repeat laboratory test may be necessary to confirm the results. Patients with values below these critical values should not be re-treated until the re-treatment criteria are met, and these laboratory values have normalized.

5.3.5.7 Abnormal Vital Sign Values

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

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

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5, for details on recording persistent adverse events).

If a clinically significant vital sign abnormality is observed during the infusion of ocrelizumab, the event should be reported on a dedicated Adverse Event eForm, prespecified Infusion-Related Reaction. Associated signs and symptoms, including severity, should be recorded on this dedicated Infusion-Related Reaction eForm (see Section 5.3.5.1). Observation of the same significant vital sign abnormality at any subsequent infusion should be recorded on a dedicated prespecified Infusion-Related Reaction eForm.

5.3.5.8 Abnormal Liver Function Tests

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.1).

5.3.5.9 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 5.4.1). 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 to progression of MS, "multiple sclerosis progression" should be recorded on the Adverse Event eCRF.

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

5.3.5.10 Preexisting Medical Conditions

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

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.11 Lack of Efficacy or Worsening of Multiple Sclerosis

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. Clinical relapses should be captured on the MS Relapse eForm (see Section 5.2.1,). These data will be captured as exploratory assessment data only. 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.

Medical occurrences or symptoms of deterioration that are judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study should be recorded as an adverse event.

5.3.5.12 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
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device 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.

- Hospitalization to receive trial medication, such as infusions of ocrelizumab, unless this is more than 24 hours
- Hospitalization for supervision purposes following completion of ocrelizumab infusion, when not associated with an adverse event
- Hospitalization to receive standard treatment with IV methylprednisolone following an MS relapse

The rationale for this exception is that some countries and/or clinical sites routinely hospitalize patients who require administration of methylprednisolone in the event of an MS relapse. Thus, the serious adverse event criteria for "hospitalization" would be met on the basis of local practice and would not reflect the seriousness of the 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 for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available

5.3.5.13 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded 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 5.4.1).

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

The highest dose tested to date in patients with MS is 2000 mg, administered as two 1000-mg IV infusions separated by 2 weeks (Phase II dose finding study in RRMS). The adverse events were consistent with the safety profile for ocrelizumab in the pivotal clinical studies.

There is no specific antidote in the event of an overdose; interrupt the infusion immediately and observe the patient for IRRs.

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, including serious IRR and serious MS relapse (see Section 5.4.1 for details on reporting requirements)
- Adverse events of special interest (see Section 5.4.1 for details on reporting requirements)
- Pregnancies (see Section 5.4.2 for details on reporting requirements)

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 Emergency Medical Contacts

Investigators will be provided with contact information for the Medical Monitor. An Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators. Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.1.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no

more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.1.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported during the study through the end of the SFU period, which is at least *104* weeks after the last infusion but may be extended in patients whose B cells take longer to replete.

After this period, the investigator should notify the Sponsor of any serious adverse events, all deaths, and any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.4.1.1). These events should be reported through use of the Adverse Event eCRF. A report will be generated and sent to Roche Safety Risk Management by the electronic data capture (EDC) system.

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

Instructions for reporting serious adverse events that occur after the last dose of study drug are provided in Section 5.6.

5.4.2 Reporting Requirements for Pregnancies

5.4.2.1 Pregnancies in Female Patients

Female patients of childbearing potential (and parent[s] or legal guardian, as applicable) will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the treatment period or within 6 months after the last dose of study drug. The investigator should report the pregnancy on the Clinical Trial Pregnancy Reporting Form and submit the form 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.

In the event of pregnancy, all infusions of ocrelizumab must be suspended until the completion of pregnancy and breastfeeding. The Investigator must counsel the patient as to the risks of continuing with the pregnancy and the possible effects on the fetus. Patients who are pregnant or breastfeeding should continue to follow the schedule of assessments for the study until conclusion of the pregnancy; however, no infusions will occur (see Section 4.3.6 and 5.1.5).

Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updatedinformation on the course and outcome of the pregnancy becomes available.

For pregnancies occurring in female patients during treatment with ocrelizumab or within 6 months after their last dose of ocrelizumab, the health status of the child will be followed until the child is 1 year of age (see Section 5.1.5).

5.4.2.2 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 5.4.1).

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 5.4.1). 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.

5.4.2.3 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 5.4.1).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

All pregnancies reported during the study should be followed until pregnancy outcome. In addition, the health status of the child will be followed until the child is 1 year of age. Data collection is voluntary only; it does not include any interventions or invasive procedures (see Section 5.1.5).

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow–up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as at least *104* weeks after the last infusion but may be extended in patients whose B cells take longer to replete), all deaths, regardless of cause, should be reported through use of the Long–Term Survival Follow–Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study drug, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special Situations Form using the fax number or email address provided to investigators.

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

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

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

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the Ocrelizumab Investigator's Brochure. The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Because of the limited number of patients, all statistical analyses are purely descriptive and exploratory, and no formal hypothesis testing will be performed.

6.1 DETERMINATION OF SAMPLE SIZE

The sample size of 6 patients per dose cohort was chosen on the basis of practical considerations and for feasibility.

6.2 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by dose group and/or cohort.

Reasons for premature study withdrawal, enrollment, and major protocol deviations will be listed.

6.3 ANALYSIS POPULATIONS

6.3.1 Pharmacokinetic Analysis Population

Patients will only be excluded from the PK analysis population if they do not meet the inclusion or exclusion criteria, if they deviate significantly from the protocol, or if data are unavailable or incomplete, which may influence the PK analysis. Excluded cases will be documented together with the reason for exclusion.

6.3.2 Safety Analysis Population

All patients who receive at least one dose of study medication will be included in the safety population. Patients will be grouped according to their dose group and/or cohort.

6.4 REPLACEMENT FOR WITHDRAWALS

A minimum of 6 evaluable patients per dose level are required. Patients who are prematurely withdrawn before completion of the 24-week period for reasons other than safety may be replaced (i.e., added to the study and to the data set) in order to have sufficient data to inform the dose selection for the subsequent Phase III study in children and adolescents.

6.5 PHARMACOKINETIC ANALYSES

Individual and mean serum–concentration–versus–time curves will be plotted. Individual PK parameters will be presented by listings and descriptive summary statistics for each dose. PK parameters will be estimated using non–compartmental methods (C_{max},

minimum plasma concentration [C_{trough}]), and a model–based approach (i.e., nonlinear mixed-effects modeling) will be used in addition (AUC). The relationship of selected PK parameters (C_{max} and AUC) with dose will be evaluated to investigate dose linearity, if different dose levels are assessed for the same body weight/age group. The relationship between individual exposure and age and body weight will be investigated. The relationship between individual ocrelizumab exposure and safety, PD (CD19 B–cell count), and exploratory parameters (e.g., ARR, IRRs, infections, adverse events) will be investigated.

6.6 SAFETY ANALYSES

Safety data will be listed individually and summarized descriptively by cohort/dose level for the Dose Exploration period and the OOE. *The exposure period (time at risk) for each safety endpoint is defined as time from the date of the first exposure to the study treatment to the date of study withdrawal or clinical cutoff date, whichever occurs earlier.*

The safety endpoints include, but may not be limited to, the following:

- Incidence of adverse events (overall, by severity, and by relationship to study medication)
- Incidence of serious adverse events
- Incidence of treatment discontinuations due to adverse events
- Change from baseline by time in laboratory parameters and incidence of clinically significant laboratory abnormalities
- Change from baseline by time in vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, body temperature) and incidence of vital sign abnormalities

The incidence count for each adverse event will be defined as the number of patients reporting at least one treatment-emergent occurrence of the event. The incidence rate will be calculated as the incidence count divided by the total number of patients in each cohort as well as total. In addition, the rate per 100 patient-years (along with the 95% confidence interval using the exact method based on the Poisson distribution) will be calculated for all adverse events and serious adverse events.

6.6.1 Adverse Events

The original terms recorded on the eCRF by the investigator for adverse events will be standardized by the Sponsor. Adverse events will be summarized by mapped term and appropriate thesaurus level. Adverse events will also be summarized by severity and relationship to the study drug. Serious adverse events and adverse events leading to treatment discontinuation will be summarized separately.

6.6.2 Clinical Laboratory Test Results

All clinical laboratory data will be stored on the database in the units in which they were reported. Patient listings and summary statistics at each assessment time will be presented using the International System of Units (SI units; Système International d'Unités). Laboratory data not reported in SI units will be converted to SI units before processing.

Laboratory data will be listed for patients with laboratory abnormalities or values outside the normal ranges. In addition, tabular summaries will be used, as appropriate.

6.6.2.1 Standard Reference Ranges and Transformation of Data

Roche standard reference ranges, rather than the reference ranges of the central laboratory, will be used for all parameters. For most parameters, the measured laboratory test result will be assessed directly using the Roche standard reference range. Certain laboratory parameters will be transformed to Roche's standard reference ranges.

A transformation will be performed on certain laboratory tests that lack sufficiently common procedures and have a wide range of investigator ranges (e.g., enzyme tests that include AST, ALT, and alkaline phosphatase and total bilirubin). Because the standard reference ranges for these parameters have a lower limit of zero, only the upper limits of the ranges will be used in transforming the data.

6.6.2.2 Definition of Laboratory Abnormalities

For all laboratory parameters included, there exists a Roche predefined standard reference range. Laboratory values falling outside this standard reference range will be labeled "H" for high or "L" for low in–patient listings of laboratory data.

In addition to the standard reference range, a marked reference range has been predefined by Roche for each laboratory parameter. The marked reference range is broader than the standard reference range. Values falling outside the marked reference range that also represent a defined change from baseline will be considered marked laboratory abnormalities (i.e., potentially clinically relevant). If a baseline value is not available for a patient, the midpoint of the standard reference range will be used as the patient's baseline value for the purposes of determining marked laboratory abnormalities. Marked laboratory abnormalities will be labeled in the patient listings as "HH" for very high or "LL" for very low.

6.6.3 Vital Signs

Vital signs data will be listed for patients with marked abnormalities or values outside the normal ranges.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analyses will include all patients with at least one predose and one postdose ADA assessment, with patients grouped according to treatment received.

6.8 EXPLORATORY ANALYSES

The exploratory endpoints as described in Table 1 will be listed individually and summarized according to the respective dose group. This includes baseline values as well as the changes from baseline.

All numerical variables where a change from baseline can be assessed will be displayed graphically as "spaghetti plots," with "timepoint" (baseline, 24 weeks) on the x–axis and the variable of interest on the y–axis.

Additional exploratory and graphical analyses may be performed if appropriate.

Biomarkers will be assessed at the beginning of the OOE and subsequent timepoints as per schedule of activities. Descriptive or summary statistics will be used to describe biomarker assessments.

6.9 INTERIM ANALYSIS

No formal interim analysis will be performed. Data will be reviewed regularly in an ongoing manner and at specified timepoints by the IMC (Section 9.4). Data will be kept confidential and no stop for efficacy is possible.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

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 on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc 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, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the principal investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. Food and Drug Administration regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trials Directive (2001/20/EC) or Clinical Trials Regulation (526/2014) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as 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/Child's Informed Assent 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.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

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

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

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

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

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators, patients or parents/legal guardian unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

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.

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 3.1.1.4).

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 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.

9.4 ADMINISTRATIVE STRUCTURE

An IMC will review available relevant accumulated data for the 300– and 600–mg dose cohorts in order to 1) make the decision whether another cohort(s) is needed to study either another dose level or different dosing intervals/regimens or more patients at

300 mg and/or 600–mg ocrelizumab to expand the knowledge on ocrelizumab effects and 2) select the appropriate dose of ocrelizumab to be investigated in a subsequent Phase III study in children and adolescents.

In addition, the IMC may also review available safety, tolerability, PK, and PD data on an ad–hoc basis, as deemed necessary by the Study Management Team and IMC members.

The IMC will consist of selected Roche representatives from at least the following departments: Clinical Pharmacology, Clinical Science, Safety Science, Statistics, and Statistical Programming.

A separate IMC Charter documents the roles, responsibilities, membership, as well as scope of activities, time of meetings (predefined milestones or on an ad-hoc basis), and communication plan.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

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

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

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

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

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

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

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

9.6 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

Adelman G, Rane SG, Villa KF. The cost burden of multiple sclerosis in the United States: a systematic review of the literature. J Med Econ 2013;16:639–47.

Avivi I, Stroopinsky D, Katz T. Anti-CD20 monoclonal antibodies: beyond B-cells. Blood Rev 2013;27:217–23.

Azevedo CJ, Overton E, Khadka S, et al. Early CNS neurodegeneration in radiologically isolated syndrome. Neurol Neuroimmunol Neuroinflamm 2015;2:e102.

Banwell BL. Pediatric multiple sclerosis. In: Dulac O, Lassonde M, Sarnat HB, editors. Handbook of clinical neurology: pediatric neurology, part II. The Netherlands: Elsevier, 2013;1263–74.

Banwell BL, Anderson PE. The cognitive burden of multiple sclerosis in children. Neurology 2005;64:891–4.

Banwell BL, Krupp L, Kennedy J, et al. Clinical features and viral serologies in children with multiple sclerosis: a multinational observational study. Lancet Neurol 2007;6:773–81.

Bennett CM, Rogers ZR, Kinnamon DD, et al. Prospective phase 1/2 study of rituximab in childhood and adolescent chronic immune thrombocytopenic purpura. Blood 2006;107:2639–42.

Boiko A, Vorobeychik G, Paty D, et al. Early onset multiple sclerosis: a longitudinal study. Neurology 2002;59:1006–10.

Calabrese LH, Molloy ES, Huang D, et al. Progressive multifocal leukoencephalopathy in rheumatic diseases: evolving clinical and pathologic patterns of disease. Arthritis Rheum 2007;56:2116–28.

[CDC] Centers for Disease Control and Prevention. Recommendations of the Advisory Committee on Immunization Practices (ACIP): use of vaccines and immune globulins in persons with altered immunocompetence. MMWR 1993;42:RR–04.

Charvet LE, O'Donnell EH, Belman AL, et al. Longitudinal evaluation of cognitive functioning in pediatric multiple sclerosis: report from the US Pediatric Multiple Sclerosis Network. Mult Scler 2014;20:1502–10.

Chitnis T. Disease-modifying therapy of pediatric multiple sclerosis. Neurotherapeutics 2013;10:89–96.

Chitnis T, Tenembaum S, Banwell B, et al. Consensus statement: evaluation of new and existing therapeutics for pediatric multiple sclerosis. Mult Scler 2012;18:116–27.

Damal K, Stoker E, Foley JF. Optimizing therapeutics in the management of patients with multiple sclerosis: a review of drug efficacy, dosing, and mechanisms of action. Biologics 2013;7:247–58.

DeLillo 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.

Duchamp M, Sterlin D, Diabate, et al. B-cell subpopulations in children: national reference values. Immun Inflamm Dis 2014;2:131–40.

Ghezzi A, Amato MP, Makhani N, et al. Pediatric multiple sclerosis: Conventional first-line treatment and general management. Neurology 2016;87 (Suppl 2);S97–S102.

Ghezzi A, Deplano V, Faroni J, et al. Multiple sclerosis in childhood: clinical features of 149 cases. Mult Scler 1997;3:43–6.

Ghezzi A, Goretti B, Portaccio E, et al. Cognitive impairment in pediatric multiple sclerosis. Neurol Sci 2010;31(Suppl 2):S215–8.

Gold R, Wolinsky JS, Amato MP, et al. Evolving expectations around early management of multiple sclerosis. Ther Adv Neurol Disord 2010;3:351–67.

Goretti B, Portaccio E, Ghezzi A, et al. Fatigue and its relationships with cognitive functioning and depression in paediatric multiple sclerosis. Mult Scler 2012;18:329–34.

Gorman MP, Healy BC, Polgar-Turcsanyi M, et al. Increased relapse rate in pediatric-onset compared with adult-onset MS. Arch Neurol 2009;66:54–9.

Greulich WW, Pyle SI. Radiologic atlas of skeletal development of the hand and wrist. Stanford: Stanford University Press, 1959.

Harding KE, Liang K, Cossburn MD, et al. Long-term outcome of paediatric-onset multiple sclerosis: a population-based study. J Neurol Neurosurg Psychiatry 2012;0:1–7.

Julian L, Serafin D, Charvet L, et al. Cognitive impairment occurs in children and adolescents with multiple sclerosis: results from a United States network. J Child Neurol 2013;28:102–7.

Kalb TC, DiLorenzo TA, LaRocca NG, et al. The impact of early onset mutliple sclerosis on cognitive and social indices. Int J MS Care 1999;1:1–6.

Kappos L, Bates D, Hartung HP, et al. Natalizumab treatment for multiple sclerosis: recommendations for patient selection and monitoring. Lancet Neurol 2007;6:431–41.

Kappos L, Li D, Calebresi PA, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. Lancet 2011;378:1779–87.

Klein C, Lammens A, Schäfer W, et al. Epitope interactions of monoclonal antibodies targeting CD20 and their relationship to functional properties. mAbs 2013;5:22–33.

Kobelt G, Berg J, Atherly D, et al. Costs and quality of life in multiple sclerosis: a cross-sectional study in the United States. Neurology 2006a;66:1696–702.

Kobelt G, Berg J, Lindgren P, et al. Costs and quality of life in multiple sclerosis in Europe. J Neurol Neurosurg Psychiatry 2006b;77:918–26.

Krupp LB, Tardieu M, Amato MP, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. Mult Scler 2013;19:1261–7.

Labiano-Fontcuberta A, Aladro Y, Martínez-Ginés ML, et al. Psychiatric disturbances in radiologically isolated syndrome. J Psyc Res 2015;68:309–15.

Labiano-Fontcuberta A, Martínez-Ginés ML, Aladro Y, et al. A comparison study of cognitive deficits in radiologically and clinically isolated syndromes. Mult Scler2016;22:250–3.

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. New multiple sclerosis phenotypic classification. Eur Neurol 2014;72(Suppl 1):1–5.

Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. Neurology 1996;46:907–11.

MacAllister WS, Belman AL, Milazzo M, et al. Cognitive functioning in children and adolescents with multiple sclerosis. Neurology 2005;64:1422–5.

MacAllister WS, Christodoulou C, Troxell R, et al. Fatigue and quality of life in pediatric multiple sclerosis. Mult Scler 2009;15:1502–8.

Martin F, Chan AC. B cell immunobiology in disease: evolving concepts from the clinic. Annu Rev Immunol 2006;24:467–96.

Morbach H, Eichhorn EM, Liese JG, et al. Reference values for B cell subpopulations from infancy to adulthood. Clin Exp Immunol 2010;162:271–9.

[MSCCPG] Multiple Sclerosis Council for Clinical Practice Guidelines. Immunization and multiple sclerosis: evidence-based management strategies for immunizations in multiple sclerosis patients. Washington, DC: Paralyzed Veterans of America, 2001.

[MSIF] Multiple Sclerosis International Federation. Atlas of MS 2013: mapping multiple sclerosis around the world [resource on the Internet]. 2013 [cited March 2017]. Available from: https://www.msif.org/about-us/advocacy/atlas/.

Narula S, Hopkins SE, Banwell B. Treatment of pediatric multiple sclerosis. Curr Treat Options Neurol 2015;17:336.

Ontaneda D, Fox RJ. Progressive multiple sclerosis. Curr Opin Neurol 2015;28:237–43.

Pena JA, Lotze TE. Pediatric multiple sclerosis: current concepts and consensus definitions. Autoimmune Dis 2013;2013:673947.

Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69:292–302.

Renoux C, Vukusic S, Mikaeloff Y, et al. Natural history of multiple sclerosis with childhood onset. N Engl J Med 2007;356:2603–13.

Rocca MA, Mezzapesa DM, Falini A, et al. Evidence for axonal pathology and adaptive cortical reorganization in patients at presentation with clinically isolated syndromes suggestive of multiple sclerosis. Neuroimage 2003;18:847–55.

Rojas JI, Patrucco L, Míguez J, et al. Brain atrophy in radiologically isolated syndromes. J Neuroimaging 2015;25:68–71.

Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:309–18.

Simone IL, Carrara D, Tortorella C, et al. Course and prognosis in early-onset MS: comparison with adult onset forms. Neurology 2002;59:1922–8.

Sinay V, Perez Akly M, Zanga G, et al. School performance as a marker of cognitive decline prior to diagnosis of multiple sclerosis. Mult Scler 2015;21:945–52.

Stashenko P, Nadler L, Hardy R, et al. Characterization of a human B lymphocyte-specific antigen. J Immunol 1980;125:1678–85.

Suppiej A, Cainelli E. Cognitive dysfunction in pediatric multiple sclerosis. Neuropsychiatr Dis Treat 2014;10:1385–92.

Tardieu M, Banwell B, Wolinsky JS, et al. Consensus definitions for pediatric MS and other demyelinating disorders in childhood. Neurology 2016;87(Suppl 2):S8–11.

Tanner JM. Normal growth and techniques of growth assessment. Clin Endocrinol Metab 1986;15:411–51.

Tedder TF, Engel P. CD20: a regulator of cell-cycle progression of B lymphocytes. Immunol Today 1994;15:450–4.

Tenembaum SN, Banwell B, Pohl D, et al. Subcutaneous interferon Beta-1a in pediatric multiple sclerosis: a retrospective study. J Child Neurol 2013;28:849–56.

Thomas T, Banwell B. Multiple sclerosis in children. Semin Neurol 2008;28:69–83.

Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17:162–73.

Trisolini M, Honeycutt A, Wiener J, et al. Global economic impact of multiple sclerosis [resource on the Internet]. Multiple Sclerosis International Federation 2010 [cited March 2017]. Available from: https://www.msif.org/resources/.

Trojano M, Paolicelli D, Bellacosa A, et al. Atypical forms of multiple sclerosis or different phases of a same disease? Neurol Sci 2004;25(Suppl 4):323–5.

Tullman MJ. A review of current and emerging therapeutic strategies in multiple sclerosis. Am J Manag Care 2013;19(2Suppl):S21–7.

Waubant E, Chabas D. Pediatric multiple sclerosis. Curr Treat Options Neurol 2009;11:203–10.

Yousry TA, Major EO, Ryschkewitsch C, et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. N Engl J Med 2006;354:924–33.

Appendix 1
Schedule of Activities

Table 1 Schedule of Activities for Dose Exploration Period

	Screening [a] (MN) [a]	Dose Exploration Period (24 Weeks)								Delayed Dosing Visit [h]	Opt Inf Visit for SD [h, i]	Unsched. Site/MN [j]	WD from Trtmt Visit [k]
Site or optional MN visit [c]	1	2	3	4	5	6	7 [b]	8 (MN) opt. [d]	9 [e, f]				
Week	–8 to–1	1	2	4	8	12	16	22 [g]	24				
Study day (±days)	–56 to –1	1	15 (±3)	29 (±4)	57 (±4)	85 (±4)	113 (±4)	155 (±6)	169 (±6)				
Telephone interview (±6 days) [l]							Week 20						
Informed consent and assent [m]	x												
Demographic data	x												
Medical history and baseline conditions	x	x											
Review of eligibility criteria	x	x											
SDMT		x							x	(x)		(x)	x
Visual testing (ETDRS and LCVA charts) [n]		x							x	(x)		(x)	x
Physical examination [o]	x	x	x	x	x	x	x	x	x	x	x	x	x
Weight [p]	x	x							x	(x)			x
Height [q]		x							x	(x)			x
Tanner staging [r]		x								(x)			x
Date of menarche		x	x	x	x	x	x	x	x	(x)			x
Wrist/Hand X–ray [s]	x [s]									(x)			(x) [t]
Brain MRI scan [u]	x					x			x	(x)		x	x
Neurological examination and EDSS [v]	x	x				x			x	(x)		x	x
Concomitant medication [w]		x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [x]	only SAEs	x	x	x	x	x	x	x	x	x	x	x	x
Clinical relapses			x	x	x	x	x	x	x	x	x	x	x

Table 1 Schedule of Activities for Dose Exploration Period (cont.)

	Screening [a] (MN) [a]	Dose Exploration Period (24 Weeks)								Delayed Dosing Visit [h]	Opt Inf Visit for SD [h, i]	Unsched. Site/MN [j]	WD from Trtmt Visit [k]
Site or optional MN visit [c]	1	2	3	4	5	6	7 [b]	8 (MN) opt. [d]	9 [e, f]				
Week	–8 to–1	1	2	4	8	12	16	22 [g]	24				
Study day (±days)	–56 to –1	1	15 (±3)	29 (±4)	57 (±4)	85 (±4)	113 (±4)	155 (±6)	169 (±6)				
Thyroid function tests [y]	x (MN)								x	(x)		(x)	x
Hepatitis screening [z]	x (MN)												
Hepatitis B Virus DNA [z]	x (MN)	(x)			(x)				(x)			(x)	(x)
Rapid plasma reagin	x (MN)												
CD4 percentage	x (MN)							x				(x)	
Total Ig, IgA, IgG, and IgM	x (MN)	x				x		x	x [aa]	(x)		(x)	x
Immunologic assessments (including CD4%) [bb]		x	x	x	x	x	x		x	(x)		(x)	x
Routine safety laboratory [cc]	x (MN)	x	x			x		x	x [aa]	(x)		(x)	x
Pregnancy test [dd]	x (MN)	x	x			x		x	x	x	x	(x)	x
Antibody titers [ee]		x				x			x	(x)		(x)	x
Plasma/Urine banking for JCV [ff]		x							x	(x)		(x)	x
Review of re-treatment criteria [g]			x						x	x	x		
Twelve-lead ECG (predose and postdose) [gg]	x	x	x						x	x	x	x	x
Vital signs [hh]	x	x	x	x	x	x	x	x	x	x	x	x	x
PK samples (predose and postdose) [ii]		x	x	x	x	x	x		x	x	x		x
ADA [jj]		x							x	x			x
Pre-medications [kk]		x	x						x	x	x		
Ocrelizumab administration [g, i, l]		x	x						x	x	x		

Table 1 Schedule of Activities for Dose Exploration Period (cont.)

ADA = anti-drug antibody; AE = adverse event; β–hCG = beta-human chorionic growth hormone; EC = Ethics Committee; eCRF = electronic case report form; EDSS = Expanded Disability Status Scale; ETDRS = Early Treatment Diabetic Retinopathy Study; Gd = gadolinium; HbcAb = hepatitis B core antigen; HbsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HepCAb = hepatitis C antibody; Ig = immunoglobulin; IMC = Internal Monitoring Committee; Inf. = infusion; IRB = Institutional Review Board; IRR = infusion-related reaction; JCV = JC–virus; LCVA = low-contrast visual acuity; LLN = lower limit of normal; MN = mobile nursing; MRI = magnetic resonance imaging; opt = optional; PA = posteroanterior; PCR = polymerase chain reaction; PK = pharmacokinetic; SAE = serious adverse event; SD = split dose; SDMT = Symbol Digit Modalities Test; SFU = safety follow-up period; Trtmt = treatment; Unsched = unscheduled; WD = withdrawal.

Notes:

Marks in parentheses are optional and may be done as appropriate (e.g., if not done at the scheduled dosing visit or if needs to be repeated).

Columns shaded in gray indicate visits that include an ocrelizumab infusion.

(MN) indicates that this visit may be performed as a mobile nursing visit. Note for the screening visit: For the patient's convenience, the mobile nursing service can be requested if any laboratory tests have to be repeated.

For consistency, it is recommended the same examiner will perform the same assessment at each visit using the same instrument in the same patient.

[a] The screening period may be extended but cannot exceed 10 weeks for relevant clinical, administrative, or operational reasons. Note: For the patient's convenience, the optional mobile nursing professional can be requested to collect blood samples and ship them directly to the central laboratory if any laboratory tests have to be repeated.

[b] **In this study, patients will be offered the possibility to continue ocrelizumab treatment in an optional treatment extension period** with the dose (e.g., 300 mg or 600 mg) initially assigned to them until the appropriate dose for the subsequent Phase III study in children/adolescents is selected by the IMC (see Section 3.1.1.3). At that time, patients will be assigned to this selected dose level. In a situation where a subsequent dose of ocrelizumab is higher than the initial dose, that dose must be administered as two infusions of half the dose 14 days apart to mitigate the risk and severity of IRRs. In this case, the second infusion will take place as an optional infusion visit for split dose. For patients continuing the study, the second dose of ocrelizumab will be administered if all re-treatment criteria are met (footnote g). It is recommended that the treating investigator discuss with the parents/legal guardian and patient the benefits and risks of continuing study treatment with ocrelizumab, including treatment options, in advance and prior to any further dosing in order to schedule subsequent visits, accordingly, **see footnotes d, e, and f**.

Table 1 Schedule of Activities for Dose Exploration Period (cont.)

[c] **Optional MN visits**: At applicable sites, for patient convenience, all assessments at visits marked with (MN) may be performed by an MN professional at the patient's home or another suitable location instead of the clinical site (see Section 4.5.3.5). If during a visit the MN professional identifies any change in patient's health status (e.g., new or worsening neurologic symptoms or any other situation that may warrant an unscheduled site visit), the MN professional will contact the site immediately to report and discuss the findings. If required, an unscheduled visit will be scheduled as soon as possible with the site (i.e., within 7 days of symptom onset if possible). At sites where MN visits are not applicable, visits will take place at the clinical site.

[d] **Visit 8** (site or optional MN visit, as applicable) **at Week 22 is only to be scheduled for patients entering the optional ocrelizumab extension period** (footnote b). Assessments performed at this visit will serve to determine if patients meet criteria for re-treatment with ocrelizumab (footnote g) before the next optional infusion of ocrelizumab at Week 24 (Visit 9) (footnote f).

[e] **Visit 9 at Week 24 is mandatory for all patients** who received the first dose of ocrelizumab. **For patients continuing the study in the optional ocrelizumab extension period (footnote b)**, the second dose of ocrelizumab will be administered if all re-treatment criteria are met (footnote g) and all assessments described for Visit 9 will be performed.

Patients who are not continuing the study in the optional ocrelizumab extension period will not receive further treatment with ocrelizumab, assessments corresponding to withdrawal from treatment visit will apply, and these patients will enter the SFU period (see Section 3.1.1.4 and 4.5.3.6).

[f] **At Week 24 (Visit 9), only patients continuing in the optional ocrelizumab extension period (footnote b) will receive an infusion of ocrelizumab** with either the dose (e.g., 300 mg or 600 mg) initially assigned to them or with the dose selected by the IMC for the subsequent Phase III study in children/adolescents, as applicable. In a situation where the second dose of ocrelizumab is higher than the initial treatment regimen, that dose must be administered as two infusions of half the dose 14 days apart to mitigate the risk and severity of IRRs. In this case, the second infusion will take place as an optional infusion visit for split dose. The benefits and risks of continuing study treatment should be discussed by the treating investigator with the parents/legal guardian and patient in advance, and prior to any further dosing. In situations where patients cannot receive their second dose within 24 hours of the Week 24 visit, they should be re-scheduled for a delayed dosing visit (footnotes g and h).

[g] **Prior to re-treatment with ocrelizumab**, patients must be evaluated for the conditions and laboratory abnormalities described in Section 4.3.6 of the protocol. If any of these conditions are present prior to re-dosing, further administration of ocrelizumab should be suspended until resolved or held indefinitely. **A site visit or optional MN visit (as applicable) within 2 weeks prior to a planned or delayed dosing visit will be required to collect blood samples and patient's information to enable the treating investigator to assess whether a patient meets re-treatment criteria at the time of an infusion with ocrelizumab.** Treating investigator must have reviewed all safety laboratory data and ensure that any repeat laboratory tests have been performed, analyzed, and reviewed before administration of ocrelizumab. If these conditions are not met, an unscheduled visit and/or delayed dosing visit must occur.

Table 1 Schedule of Activities for Dose Exploration Period (cont.)

[h] **A delayed dosing** visit will be performed and recorded in the Delayed Dosing Visit eCRF form when dosing cannot be administered at the scheduled dosing visit. Other tests or assessments may be done as appropriate. A site visit or optional MN visit (as applicable) within 2 weeks prior to a delayed dosing visit will be required to collect blood samples and patient's information to enable the treating investigator to assess whether a patient meets criteria for re-treatment with ocrelizumab (footnote g). Note that in situations where the delayed dosing visit occurs more than 4 weeks after the planned infusion date, the dose should be administered as two infusions of half the dose 14 days apart. In this case, the second infusion will take place as an optional infusion visit for split dose.

[i] **Administration of IV ocrelizumab:** The first dose of ocrelizumab must be administered as two infusions of half the dose 14 days apart (e.g., 150 mg on Day 1 and 150 mg on Day 15 for the 300 mg ocrelizumab cohort). It is recommended to schedule the first infusion of ocrelizumab (Day 1 of Dose 1) in the morning to allow the patient to stay at the hospital (or infusion center) with medical supervision and monitoring as required, as long as possible (e.g., until 6 p.m. or 8 p.m. according to the hospital rules), with a minimum of 1 hour after completion of the infusion. Patients may be hospitalized for a 24-hour observation after completion of the infusion at the discretion of the treating investigator. It is also recommended to administer the second infusion (Day 15 of Dose 1) and subsequent infusions in the morning, as patients should remain under observation for at least 1 hour after the completion of the infusion and up to 24 hours at the treating investigator's discretion.
For patients continuing in the optional ocrelizumab extension period (footnote b), subsequent doses will be administered as single infusions (e.g., 300 mg for the 300-mg ocrelizumab cohort). However, whenever the subsequent dose is higher than the previous dose, it should be administered as two infusions of half the dose 14 days apart. In this case, the second infusion will take place as an optional infusion visit for split dose. Prior to subsequent infusion of ocrelizumab, the treating investigator must review the clinical and laboratory re-treatment criteria (footnote g). Patients and their parents/legal guardian will be advised that an IRR can occur until 24 hours after completion of each infusion. A telephone interview will be conducted by site personnel within 24 (± 4) hours after completion of each infusion (footnote l).

[j] Unscheduled site or MN visit: Assessments performed at unscheduled (non-dosing) visits will depend on the clinical needs of the patient. All patients with new neurological symptoms suggestive of relapse should have EDSS performed within 7 days of the onset of the relapse. Other tests/assessments may be done as appropriate.

[k] Withdrawal from treatment visit only takes place if patient discontinues prematurely from treatment (i.e., before Week 288) (see Section 4.5.3.6).

[l] **A telephone interview** will be conducted by site personnel within 24 (± 4) hours after completion of each infusion and every 4 weeks (± 6 days) between any visit (MN or site visit) and throughout the entire SFU period to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit (including new or worsening neurological symptoms or signs of infection) (see Appendix 4).

[m] Informed consent must be signed by parent or legal guardian, with patient assent obtained verbally and when possible, in writing, from all pediatric patients as per local regulation (prior to any study-related procedure).

[n] Determination of the LCVA will include a measure of high-contrast acuity using the ETDRS chart as described in Appendix 3 of the protocol.

Table 1 Schedule of Activities for Dose Exploration Period (cont.)

[o] At screening and baseline, a complete physical examination will be performed and should include an evaluation of the head, eyes, ears, nose, and throat and of the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. At subsequent visits, a limited, symptom-directed physical examination should be performed. Any abnormality identified should be entered either as medical history or AE accordingly.

[p] Body weight is to be determined to the nearest 0.1 kg. For body weight measurements, the patient should wear clothes, without any shoes, outerwear, or accessories.

[q] Height should be measured in a standing position using the same wall-mounted stadiometer for the same individual. Three standing height measurements should be made. The average of the three measurements will be considered to be the true height of the child/adolescent, provided the measurements are within 0.3 cm. The average value will be recorded on the eCRF. Note: Height should be collected from consenting biological mothers and fathers. This information should be entered directly on the eCRF. If both parents are not able to attend the same visit, please collect the missing height at a next clinic visit. If the parents are unknown this assessment will not be applicable.

[r] Tanner staging assessment will be contingent on IRB/EC's approval and written informed consent from the patients' parents/legal guardian and with patient assent (as applicable). Tanner staging will be documented on the eCRF at baseline. During the study conduct, patients will have their Tanner stages documented or assessed yearly until they reach Stage 5 (see Section 4.5.8).

[s] Wrist/Hand X–ray: This radiographic assessment will be contingent on IRB/EC's approval and written informed consent from the patients' parents/legal guardian and with patient assent (as applicable). One combined standard PA radiograph of the left wrist and hand will be obtained within 4 weeks of baseline and repeated yearly (± 4 weeks). If evidence of growth-plate fusion is not demonstrated at baseline but during subsequent X–rays, no further hand/wrist X-rays will be necessary provided that final growth/bone maturation has unequivocally been reached (see Section 4.5.10).

[t] If a prior X-ray was obtained within the last 6 months before the WD visit, the X-ray should not be repeated.

[u] **"Baseline" MRI scan should be performed after the screening visit, but at least 10 days prior to the baseline visit**. Baseline and Week 12 (± 2 weeks) MRI scans will be performed with and without Gd-contrast agent. Subsequent MRI scans will be performed without a Gd-contrast agent at Week 24 (a window of minus 4 weeks can apply) and Weeks 48, 72, 96, 144, 192, 240, and 288 (window of ± 4 weeks of these scheduled visits). Also, MRI scans will be obtained in patients withdrawn from the treatment period (at a withdrawal from study visit), if not performed during the last 4 weeks.

[v] Neurological examination and EDSS: See Sections 4.5.14 and 4.5.15.

[w] Concomitant medications: See Section 4.4.

[x] Adverse events: See Section 5.

[y] Sensitive thyroid-stimulating hormone will be tested at screening and during the treatment period as indicated. Thyroid autoantibodies will be assayed only at screening.

Table 1 Schedule of Activities for Dose Exploration Period (cont.)

[z] Hepatitis screening and monitoring: All patients must have negative HbsAg and negative HepCAb screening test results prior to enrollment. If total HbcAb is positive at screening, HBV DNA measured by PCR must be negative to be eligible. For those patients enrolled with negative hBsAg and positive total HbcAb, HBV DNA (PCR) must be repeated every 12 weeks during the treatment period.

[aa] To be completed on Visit 9 if not done at Visit 8.

[bb] Immunologic assessments: Includes CD19 and other circulating B–cell subsets, T cells, and natural killer cells. On infusion visits, blood samples should be collected prior to the methylprednisolone administration.

[cc] Routine safety laboratory (hematology, chemistry, and urinalysis): On infusion visits, all urine and blood samples should be collected prior to the methylprednisolone administration. At other times, samples will be collected at any time during the visit. For urinalysis, a urine dipstick for blood, protein, nitrite and glucose (using the dipsticks provided) will be performed. If abnormal and applicable a microscopic examination will be performed on site (local laboratory). For more information related to safety laboratory assessments, see Section 4.5.19.1.

[dd] Serum β-hCG must be performed at screening in female patients of childbearing potential (e.g., in Tanner stages ≥ 2 or post-onset of menarche). Subsequently, urine β–hCG (sensitivity of at least 25 mIU/mL) will be performed. On infusion visits, the urine pregnancy test should be performed prior to the methylprednisolone administration in all female patients of childbearing potential. If positive, the patient will not receive the scheduled dose, and confirmation by a serum pregnancy test will be performed.

[ee] Antibody titers: Measurement of antibody titers against common antigens (mumps, rubella, varicella zoster, and *S. pneumoniae*) will be performed.

[ff] Plasma and urine samples for JCV will be collected at specified timepoints and analyzed in batches, if decided by the Sponsor.

[gg] ECG (predose and postdose): At screening, ECG may be taken at any time during the visit. On infusion visits, ECGs should be performed prior to receipt of study drug, prior to vital sign measurements and blood draws. ECG should be taken within 45 minutes prior to the methylprednisolone administration in all patients and within 60 minutes after completion of the ocrelizumab infusion (see Section 4.5.11). Additional ECGs may be taken at the discretion of the treating investigator, as required during an unscheduled visit.

[hh] Vital signs (i.e., pulse rate, systolic and diastolic blood pressure, respiration rate, and temperature). On infusion visits, the vital signs should be taken within 45 minutes prior to the methylprednisolone administration in all patients. In addition, vital signs should be obtained prior to ocrelizumab infusion, then every 15 (± 5) minutes for the first hour, then every 30 (± 10) minutes until 1 hour after the end of the infusion. On non-infusion days, the vital signs may be taken at any time during the visit. Additional vital signs may be taken at the discretion of the treating investigator and should be recorded on the corresponding unscheduled Vital Signs eCRF.

[ii] PK samples (predose and postdose): On infusion visits, two serum samples will be collected, one 5–30 minutes prior to the methylprednisolone administration and the second one 30 (± 10) minutes following the completion of the infusion of ocrelizumab. At other timepoints (non-infusion visits), samples will be collected at any time during the visit.

[jj] ADA: On infusion visits (except on Day 15, and on the optional infusion visit for split dose if applicable), a serum sample is collected 5–30 minutes prior to the methylprednisolone administration.

Table 1 Schedule of Activities for Dose Exploration Period (cont.)

[kk] **All patients will receive <u>prophylactic treatment with an antihistamine and methylprednisolone</u> prior to any infusion of ocrelizumab**.
Methylprednisolone dose (slow IV infusion to be completed approximately 30 minutes before the start of each infusion): adjusted to weight for patients $<$ 40 kg (2 mg/kg methylprednisolone) and for patients $\geq$ 40 kg (100 mg methylprednisolone). In the rare case, when the use of methylprednisolone is contraindicated for the patient, an equivalent dose of an alternative steroid should be used as premedication prior to the infusion of ocrelizumab. IV or oral antihistamine (e.g., diphenhydramine) will be administered 30–60 minutes prior to ocrelizumab. The addition of an analgesic/antipyretic, such as acetaminophen/paracetamol, may also be considered.

Table 2a Schedule of Activities for Optional Ocrelizumab Extension Period (Weeks 36 to 180)

	Optional Ocrelizumab Extension (264 Weeks) [a]																			Delayed Dosing Visit [d]	Opt Inf Visit for SD [d, e]	Unsched. Site/MN [f]	WD from Trtmt Visit [g]
Site or optional MN visit [b]	10(MN)	11(MN)	12	13(MN)	14(MN)	15	16(MN)	17(MN)	18	19(MN)	20(MN)	21	22(MN)	23(MN)	24	25(MN)	26(MN)	27	28(MN)				
Week	36	46 [c]	48	60	70 [c]	72	84	94 [c]	96	108	118 [c]	120	132	142 [c]	144	156	166 [c]	168	180				
Study day (±days)	253 (±6)	323 (±6)	337 (±6)	421 (±6)	491 (±6)	505 (±6)	589 (±6)	659 (±6)	673 (±6)	757 (±6)	827 (±6)	841 (±6)	925 (±6)	995 (±6)	1009 (±6)	1093 (±6)	1163 (±6)	1177 (±6)	1261 (±6)				
Telephone interview [h]	At Weeks 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88, 92, 100, 104, 112, 116, 124, 128, 136, 140, 148, 152, 160, 164, 172, 176 (± 6 days)																						
SDMT			x			x			x			x			x			x		(x)		(x)	x
Visual testing (ETDRS and LCVA charts) [i]			x			x			x			x			x			x		(x)		(x)	x
Physical examination [j]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Weight [k]			x			x			x			x			x			x		(x)			x
Height [l]			x			x			x			x			x			x		(x)			x
Tanner staging [m]			x						x						x					(x)			x
Date of menarche	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	(x)			x
Wrist/Hand X–ray [n]			x						x						x					(x)			(x) [o]
Brain MRI scan [p]			x			x			x						x					(x)		x	x
Neurological examination and EDSS [q]			x			x			x			x			x			x		(x)		x	x
Concomitant medication [r]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [s]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Clinical relapses	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Table 2a Schedule of Activities for Optional Ocrelizumab Extension Period (Weeks 36 to 180) (cont.)

	Optional Ocrelizumab Extension (264 Weeks) [a]																			Delayed Dosing Visit [d]	Opt Inf Visit for SD [d, e]	Unsched. Site/MN [f]	WD from Trtmt Visit [g]
Site or optional MN visit [b]	10(MN)	11(MN)	12	13(MN)	14(MN)	15	16(MN)	17(MN)	18	19(MN)	20(MN)	21	22(MN)	23(MN)	24	25(MN)	26(MN)	27	28(MN)				
Week	36	46 [c]	48	60	70 [c]	72	84	94 [c]	96	108	118 [c]	120	132	142 [c]	144	156	166 [c]	168	180				
Study day (±days)	253 (±6)	323 (±6)	337 (±6)	421 (±6)	491 (±6)	505 (±6)	589 (±6)	659 (±6)	673 (±6)	757 (±6)	827 (±6)	841 (±6)	925 (±6)	995 (±6)	1009 (±6)	1093 (±6)	1163 (±6)	1177 (±6)	1261 (±6)				
Thyroid function tests [t]			x			x			x			x			x			x		(x)		(x)	x
Hepatitis B Virus DNA [u]		(x)			(x)			(x)			(x)			(x)			(x)					(x)	(x)
Total Ig, IgA, IgG, and IgM		x			x			x			x			x			x			(x)		(x)	x
Immunologic assessments (including CD4%) [v]	x	x		x	x		x	x		x	x		x	x		x	x		x	(x)		(x)	x
Routine safety laboratory [w]	x	x	(x)	x	x	(x)	x	x	(x)	x	x	(x)	x	x	(x)	x	x	(x)	x	(x)		(x)	x
Pregnancy test [x]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	(x)	x
Antibody titers [y]			x			x			x			x			x			x		(x)		(x)	x
Plasma/Urine banking for JCV [z]			x			x			x			x			x			x		(x)		(x)	x
Review of re-treatment criteria [c]			x			x			x			x			x			x		x	x		
Twelve-lead ECG (predose and postdose) [aa]			x			x			x			x			x			x		x	x	x	x
Vital signs [bb]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Table 2a Schedule of Activities for Optional Ocrelizumab Extension Period (Weeks 36 to 180) (cont.)

	Optional Ocrelizumab Extension (264 Weeks) [a]																			Delayed Dosing Visit [d]	Opt Inf Visit for SD [d, e]	Unsched. Site/MN [f]	WD from Trtmt Visit [g]
Site or optional MN visit [b]	10(MN)	11(MN)	12	13(MN)	14(MN)	15	16(MN)	17(MN)	18	19(MN)	20(MN)	21	22(MN)	23(MN)	24	25(MN)	26(MN)	27	28(MN)				
Week	36	46 [c]	48	60	70 [c]	72	84	94 [c]	96	108	118 [c]	120	132	142 [c]	144	156	166 [c]	168	180				
Study day (±days)	253 (±6)	323 (±6)	337 (±6)	421 (±6)	491 (±6)	505 (±6)	589 (±6)	659 (±6)	673 (±6)	757 (±6)	827 (±6)	841 (±6)	925 (±6)	995 (±6)	1009 (±6)	1093 (±6)	1163 (±6)	1177 (±6)	1261 (±6)				
PK samples (predose and postdose) [cc]			x			x			x											(x)			(x)
ADA [dd]			x			x			x											(x)			(x)
Pre-medications [ee]			x			x			x			x			x			x		x	x		
Ocrelizumab administration [c, e, h]			x			x			x			x			x			x		x	x		

ADA = anti-drug antibody; AE = adverse event; β–hCG = beta-human chorionic growth hormone; EC = Ethics Committee; eCRF = electronic case report form; EDSS = Expanded Disability Status Scale; ETDRS = Early Treatment Diabetic Retinopathy Study; Gd = gadolinium; HbcAb = hepatitis B core antigen; HbsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HepCAb = hepatitis C antibody; Ig = immunoglobulin; IMC = Internal Monitoring Committee; Inf. = infusion; IRB = Institutional Review Board; IRR = infusion-related reaction; JCV = JC–virus; LCVA = low-contrast visual acuity; LLN = lower limit of normal; MN = mobile nursing; MRI = magnetic resonance imaging; OOE = Optional Ocrelizumab Extension; opt = optional; PA = posteroanterior; PCR = polymerase chain reaction; PK = pharmacokinetic; SAE = serious adverse event; SD = split dose; SDMT = Symbol Digit Modalities Test; SFU = safety follow-up period; Trtmt = treatment; Unsched = unscheduled; WD = withdrawal; wk(s) = week(s).

Notes:

Marks in parentheses are optional and may be done as appropriate (e.g., if not done at the scheduled dosing visit or if needs to be repeated).

Columns shaded in gray indicate visits that include an ocrelizumab infusion.

(MN) indicates that this visit may be performed as a mobile nursing visit. Note for the screening visit: For the patient's convenience, the mobile nursing service can be requested if any laboratory tests have to be repeated.

For consistency, it is recommended the same examiner will perform the same assessment at each visit using the same instrument in the same patient.

[a] **In this study, patients will be offered the possibility to continue ocrelizumab treatment in an optional treatment extension period** with the dose (e.g., 300 mg or 600 mg) initially assigned to them until the appropriate dose for the subsequent Phase III study in children/adolescents is selected by the IMC

Table 2a Schedule of Activities for Optional Ocrelizumab Extension Period (Weeks 36 to 180) (cont.)

(see Section 3.1.1.3). At that time, patients will be assigned to this selected dose level. In a situation where a subsequent dose of ocrelizumab is higher than the initial dose, that dose must be administered as two infusions of half the dose 14 days apart to mitigate the risk and severity of IRRs. In this case, the second infusion will take place as an optional infusion visit for split dose. For patients continuing the study, the second dose of ocrelizumab will be administered if all re-treatment criteria are met (footnote c). It is recommended that the treating investigator discuss with the parents/legal guardian and patient the benefits and risks of continuing study treatment with ocrelizumab, including treatment options, in advance and prior to any further dosing in order to schedule subsequent visits. The OOE period will last 264 weeks, and may be extended until the patient turns 18 years old (or as required per local regulation) or until commercial ocrelizumab is approved for children and available in the country for these patients, whichever occurs first. Initiation of an alternative treatment for MS may be considered by the investigator in which case the patient will enter the SFU period.

[b] **Optional MN visits**: At applicable sites, for patient convenience, all assessments at visits marked with (MN) may be performed by an MN professional at the patient's home or another suitable location instead of the clinical site (see Section 4.5.3.5). If during a visit the MN professional identifies any change in patient's health status (e.g., new or worsening neurologic symptoms or any other situation that may warrant an unscheduled site visit), the MN professional will contact the site immediately to report and discuss the findings. If required, an unscheduled visit will be scheduled as soon as possible with the site (i.e., within 7 days of symptom onset if possible). At sites where MN visits are not applicable, visits will take place at the clinical site.

[c] **Prior to re-treatment with ocrelizumab**, patients must be evaluated for the conditions and laboratory abnormalities described in Section 4.3.6 of the protocol. If any of these conditions are present prior to re-dosing, further administration of ocrelizumab should be suspended until resolved or held indefinitely. **A site visit or optional MN visit (as applicable) within 2 weeks prior to a planned or delayed dosing visit will be required to collect blood samples and patient's information to enable the treating investigator to assess whether a patient meets re-treatment criteria at the time of an infusion with ocrelizumab.** Treating investigator must have reviewed all safety laboratory data and ensure that any repeat laboratory tests have been performed, analyzed, and reviewed before administration of ocrelizumab. If these conditions are not met, an unscheduled visit and/or delayed dosing visit must occur.

[d] **A delayed dosing** visit will be performed and recorded in the Delayed Dosing Visit eCRF form when dosing cannot be administered at the scheduled dosing visit. Other tests or assessments may be done as appropriate. A site visit or optional MN visit (as applicable) within 2 weeks prior to a delayed dosing visit will be required to collect blood samples and patient's information to enable the treating investigator to assess whether a patient meets criteria for re-treatment with ocrelizumab (footnote c). Note that in situations where the delayed dosing visit occurs more than 4 weeks after the planned infusion date, the dose should be administered as two infusions of half the dose 14 days apart. In this case, the second infusion will take place as an optional infusion visit for split dose.

Table 2a Schedule of Activities for Optional Ocrelizumab Extension Period (Weeks 36 to 180) (cont.)

[e] **Administration of IV ocrelizumab:** The first dose of ocrelizumab must be administered as two infusions of half the dose 14 days apart (e.g., 150 mg on Day 1 and 150 mg on Day 15 for the 300 mg ocrelizumab cohort). It is recommended to schedule the first infusion of ocrelizumab (Day 1 of Dose 1) in the morning to allow the patient to stay at the hospital (or infusion center) with medical supervision and monitoring as required, as long as possible (e.g., until 6 p.m. or 8 p.m. according to the hospital rules), with a minimum of 1 hour after completion of the infusion. Patients may be hospitalized for a 24-hour observation after completion of the infusion at the discretion of the treating investigator. It is also recommended to administer the second infusion (Day 15 of Dose 1) and subsequent infusions in the morning, as patients should remain under observation for at least 1 hour after the completion of the infusion and up to 24 hours at the treating investigator's discretion.
For patients continuing in the optional ocrelizumab extension period (footnote a), subsequent doses will be administered as single infusions (e.g., 300 mg for the 300-mg ocrelizumab cohort). However, whenever the subsequent dose is higher than the previous dose, it should be administered as two infusions of half the dose 14 days apart. In this case, the second infusion will take place as an optional infusion visit for split dose. Prior to subsequent infusion of ocrelizumab, the treating investigator must review the clinical and laboratory re-treatment criteria (footnote c). Patients and their parents/legal guardian will be advised that an IRR can occur until 24 hours after completion of each infusion. A telephone interview will be conducted by site personnel within 24 (± 4) hours after completion of each infusion (footnote h).

[f] Unscheduled site or MN visit: Assessments performed at unscheduled (non-dosing) visits will depend on the clinical needs of the patient. All patients with new neurological symptoms suggestive of relapse should have EDSS performed within 7 days of the onset of the relapse. Other tests/assessments may be done as appropriate.

[g] Withdrawal from treatment visit only takes place if patient discontinues prematurely from treatment (i.e., before Week 288) (see Section 4.5.3.6).

[h] **A telephone interview** will be conducted by site personnel within 24 (± 4) hours after completion of each infusion and every 4 weeks (± 6 days) between any visit (MN or site visit) and throughout the entire SFU period to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit (including new or worsening neurological symptoms or signs of infection) (see Appendix 4).

[i] Determination of the LCVA will include a measure of high-contrast acuity using the ETDRS chart as described in Appendix 3 of the protocol.

[j] At screening and baseline, a complete physical examination will be performed and should include an evaluation of the head, eyes, ears, nose, and throat and of the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. At subsequent visits, a limited, symptom-directed physical examination should be performed. Any abnormality identified should be entered either as medical history or AE accordingly.

[k] Body weight is to be determined to the nearest 0.1 kg. For body weight measurements, the patient should wear clothes, without any shoes, outerwear, or accessories.

Table 2a Schedule of Activities for Optional Ocrelizumab Extension Period (Weeks 36 to 180) (cont.)

[l] Height should be measured in a standing position using the same wall-mounted stadiometer for the same individual. Three standing height measurements should be made. The average of the three measurements will be considered to be the true height of the child/adolescent, provided the measurements are within 0.3 cm. The average value will be recorded on the eCRF. Note: Height should be collected from consenting biological mothers and fathers. This information should be entered directly on the eCRF. If both parents are not able to attend the same visit, please collect the missing height at a next clinic visit. If the parents are unknown this assessment will not be applicable.

[m] Tanner staging assessment will be contingent on IRB/EC's approval and written informed consent from the patients' parents/legal guardian and with patient assent (as applicable). Tanner staging will be documented on the eCRF at baseline. During the study conduct, patients will have their Tanner stages documented or assessed yearly until they reach Stage 5 (see Section 4.5.8).

[n] Wrist/Hand X–ray: This radiographic assessment will be contingent on IRB/EC's approval and written informed consent from the patients' parents/legal guardian and with patient assent (as applicable). One combined standard PA radiograph of the left wrist and hand will be obtained within 4 weeks of baseline and repeated yearly (± 4 weeks). If evidence of growth-plate fusion is not demonstrated at baseline but during subsequent X–rays, no further hand/wrist X-rays will be necessary provided that final growth/bone maturation has unequivocally been reached (see Section 4.5.10).

[o] If a prior X-ray was obtained within the last 6 months before the WD visit, the X-ray should not be repeated.

[p] MRI scans will be performed without a Gd-contrast agent at Week 24, Weeks 48, 72, 96, 144, 192, 240, and 288 (window of ± 4 weeks of these scheduled visits). Also, MRI scans will be obtained in patients withdrawn from the treatment period (at a withdrawal from study visit), if not performed during the last 4 weeks.

[q] Neurological examination and EDSS: See Sections 4.5.14 and 4.5.15.

[r] Concomitant medications: See Section 4.4.

[s] Adverse events: See Section 5.

[t] Sensitive thyroid-stimulating hormone will be tested at screening and during the treatment period as indicated.

[u] Hepatitis screening and monitoring: All patients must have negative HbsAg and negative HepCAb screening test results prior to enrollment. If total HbcAb is positive at screening, HBV DNA measured by PCR must be negative to be eligible. For those patients enrolled with negative hBsAg and positive total HbcAb, HBV DNA (PCR) must be repeated every 12 weeks during the treatment period.

[v] Immunologic assessments: Includes CD19 and other circulating B–cell subsets, T cells, and natural killer cells. On infusion visits, blood samples should be collected prior to the methylprednisolone administration.

[w] Routine safety laboratory (hematology, chemistry, and urinalysis): On infusion visits, all urine and blood samples should be collected prior to the methylprednisolone administration. At other times, samples will be collected at any time during the visit. For urinalysis, a urine dipstick for blood, protein, nitrite and glucose (using the dipsticks provided) will be performed. If abnormal and applicable a microscopic examination will be performed on site (local laboratory). For more information related to safety laboratory assessments, see Section 4.5.19.1.

Table 2a Schedule of Activities for Optional Ocrelizumab Extension Period (Weeks 36 to 180) (cont.)

[x] Serum β-hCG must be performed at screening in female patients of childbearing potential (e.g., in Tanner stages ≥ 2 or post-onset of menarche). Subsequently, urine β–hCG (sensitivity of at least 25 mIU/mL) will be performed. On infusion visits, the urine pregnancy test should be performed prior to the methylprednisolone administration in all female patients of childbearing potential. If positive, the patient will not receive the scheduled dose, and confirmation by a serum pregnancy test will be performed.

[y] Antibody titers: Measurement of antibody titers against common antigens (mumps, rubella, varicella zoster, and S. pneumoniae) will be performed.

[z] Plasma and urine samples for JCV will be collected at specified timepoints and analyzed in batches, if decided by the Sponsor.

[aa] ECG (predose and postdose): At screening, ECG may be taken at any time during the visit. On infusion visits, ECGs should be performed prior to receipt of study drug, prior to vital sign measurements and blood draws. ECG should be taken within 45 minutes prior to the methylprednisolone administration in all patients and within 60 minutes after completion of the ocrelizumab infusion (see Section 4.5.11). Additional ECGs may be taken at the discretion of the treating investigator, as required during an unscheduled visit.

[bb] Vital signs (i.e., pulse rate, systolic and diastolic blood pressure, respiration rate, and temperature). On infusion visits, the vital signs should be taken within 45 minutes prior to the methylprednisolone administration in all patients. In addition, vital signs should be obtained prior to ocrelizumab infusion, then every 15 (± 5) minutes for the first hour, then every 30 (± 10) minutes until 1 hour after the end of the infusion. On non-infusion days, the vital signs may be taken at any time during the visit. Additional vital signs may be taken at the discretion of the treating investigator and should be recorded on the corresponding unscheduled Vital Signs eCRF.

[cc] PK samples (predose and postdose): On infusion visits, two serum samples will be collected, one 5–30 minutes prior to the methylprednisolone administration and the second one 30 (± 10) minutes following the completion of the infusion of ocrelizumab. At other timepoints (non-infusion visits), samples will be collected at any time during the visit.

[dd] ADA: On infusion visits (except on Day 15, and on the optional infusion visit for split dose if applicable), a serum sample is collected 5–30 minutes prior to the methylprednisolone administration.

[ee] **All patients will receive prophylactic treatment with an antihistamine and methylprednisolone prior to any infusion of ocrelizumab**. Methylprednisolone dose (slow IV infusion to be completed approximately 30 minutes before the start of each infusion): adjusted to weight for patients < 40 kg (2 mg/kg methylprednisolone) and for patients ≥ 40 kg (100 mg methylprednisolone). In the rare case, when the use of methylprednisolone is contraindicated for the patient, an equivalent dose of an alternative steroid should be used as premedication prior to the infusion of ocrelizumab. IV or oral antihistamine (e.g., diphenhydramine) will be administered 30–60 minutes prior to ocrelizumab. The addition of an analgesic/antipyretic, such as acetaminophen/paracetamol, may also be considered.

Appendix 1: Schedule of Activities

Table 2b Schedule of Activities for Optional Ocrelizumab Extension Period (Weeks 190 to 288)

	Optional Ocrelizumab Extension (264 Weeks)[a]													Delayed Dosing Visit [d]	Opt Inf Visit for SD [d,e]	Unsched. Site/MN [f]	WD from Trtmt Visit [g]
Site or optional MN visit [b]	29 (MN)	30	31 (MN)	32 (MN)	33	34 (MN)	35 (MN)	36	37 (MN)	38 (MN)	39	40 (MN)	41 (MN)				
Week	190 [c]	192	204	214 [c]	216	228	238 [c]	240	252	262 [c]	264	276	288 [c]				
Study day (± days)	1331 (± 6)	1345 (± 6)	1429 (± 6)	1499 (± 6)	1513 (± 6)	1597 (± 6)	1667 (± 6)	1681 (± 6)	1765 (± 6)	1835 (± 6)	1849 (± 6)	1933 (± 6)	2017 (± 6)				
Telephone interview [h]	At Weeks 184, 188, 196, 200, 208, 212, 220, 224, 232, 236, 244, 248, 256, 260, 268, 272, 280, 284 (± 6 days)																
SDMT		x			x			x			x		x	(x)		(x)	x
Visual testing (ETDRS and LCVA charts) [i]		x			x			x			x		x	(x)		(x)	x
Physical examination [j]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Weight [k]		x			x			x			x		x	(x)			x
Height [l]		x			x			x			x		x	(x)			x
Tanner staging [m]		x						x					x	(x)			x
Date of menarche	x	x	x	x	x	x	x	x	x	x	x	x	x	(x)			x
Wrist/Hand X–ray [n]		x						x					x	(x)			(x) [o]
Brain MRI scan [p]		x						x					x	(x)		x	x
Neurological examination and EDSS [q]		x			x			x			x		x	(x)		x	x
Concomitant medication [r]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [s]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Clinical relapses	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Thyroid function tests [t]		x			x			x			x		x	(x)		(x)	x

Table 2b Schedule of Activities for Optional Ocrelizumab Extension Period (Weeks 190 to 288) (cont.)

	Optional Ocrelizumab Extension (264 Weeks)[a]													Delayed Dosing Visit [d]	Opt Inf Visit for SD [d, e]	Unsched. Site/MN [f]	WD from Trtmt Visit [g]
Site or optional MN visit [b]	29 (MN)	30	31 (MN)	32 (MN)	33	34 (MN)	35 (MN)	36	37 (MN)	38 (MN)	39	40 (MN)	41 (MN)				
Week	190 [c]	192	204	214 [c]	216	228	238 [c]	240	252	262 [c]	264	276	288 [c]				
Study day (± days)	1331 (± 6)	1345 (± 6)	1429 (± 6)	1499 (± 6)	1513 (± 6)	1597 (± 6)	1667 (± 6)	1681 (± 6)	1765 (± 6)	1835 (± 6)	1849 (± 6)	1933 (± 6)	2017 (± 6)				
Hepatitis B Virus DNA [u]	(x)			(x)			(x)			(x)			(x)			(x)	(x)
Total Ig, IgA, IgG, and IgM	x			x			x			x			x	(x)		(x)	
Immunologic assessments (including CD4%) [v]	x		x	x		x	x		x	x		x	x	(x)		(x)	x
Routine safety laboratory [w]	x	(x)	x	x	(x)	x	x	(x)	x	x	(x)	x	(x)	(x)		(x)	x
Pregnancy test [x]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	(x)	x
Antibody titers [y]		x			x			x			x		x	(x)		(x)	x
Plasma/Urine banking for JCV [z]		x			x			x			x		x	(x)		(x)	x
Serum biomarker [aa]		x						x					x				(x)
Optional RBR DNA [bb]		x															
Review of re–treatment criteria [c]		x			x			x			x			x	x		
Twelve-lead ECG (predose and postdose) [cc]		x			x			x			x			x	x	x	x
Vital signs [dd]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Table 2b Schedule of Activities for Optional Ocrelizumab Extension Period (Weeks 190 to 288) (cont.)

	Optional Ocrelizumab Extension (264 Weeks)[a]													Delayed Dosing Visit [d]	Opt Inf Visit for SD [d, e]	Unsched. Site/MN [f]	WD from Trtmt Visit [g]
Site or optional MN visit [b]	29 (MN)	30	31 (MN)	32 (MN)	33	34 (MN)	35 (MN)	36	37 (MN)	38 (MN)	39	40 (MN)	41 (MN)				
Week	190 [c]	192	204	214 [c]	216	228	238 [c]	240	252	262 [c]	264	276	288 [c]				
Study day (± days)	1331 (± 6)	1345 (± 6)	1429 (± 6)	1499 (± 6)	1513 (± 6)	1597 (± 6)	1667 (± 6)	1681 (± 6)	1765 (± 6)	1835 (± 6)	1849 (± 6)	1933 (± 6)	2017 (± 6)				
Pre-medications [ee]		x			x			x			x			x	x		
Ocrelizumab administration [c, e, h]		x			x			x			x			x	x		

ADA = anti-drug antibody; AE = adverse event; β–hCG = beta-human chorionic growth hormone; EC = Ethics Committee; eCRF = electronic case report form; EDSS = Expanded Disability Status Scale; ETDRS = Early Treatment Diabetic Retinopathy Study; Gd = gadolinium; HbcAb = hepatitis B core antigen; HbsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HepCAb = hepatitis C antibody; Ig = immunoglobulin; IMC = Internal Monitoring Committee; Inf. = infusion; IRB = Institutional Review Board; IRR = infusion-related reaction; JCV = JC–virus; LCVA = low-contrast visual acuity; LLN = lower limit of normal; MN = mobile nursing; MRI = magnetic resonance imaging; OOE = Optional Ocrelizumab Extension; opt = optional; PA = posteroanterior; PCR = polymerase chain reaction; RBR = Research Biosample Repository; SAE = serious adverse event; SD = split dose; SDMT = Symbol Digit Modalities Test; SFU = safety follow-up period; Trtmt = treatment; Unsched = unscheduled; WD = withdrawal; wk(s) = week(s).

Notes:

Marks in parentheses are optional and may be done as appropriate (e.g., if not done at the scheduled dosing visit or if needs to be repeated).

Columns shaded in gray indicate visits that include an ocrelizumab infusion.

(MN) indicates that this visit may be performed as a mobile nursing visit. Note for the screening visit: For the patient's convenience, the mobile nursing service can be requested if any laboratory tests have to be repeated.

For consistency, it is recommended the same examiner will perform the same assessment at each visit using the same instrument in the same patient.

Table 2b Schedule of Activities for Optional Ocrelizumab Extension Period (Weeks 190 to 288) (cont.)

[a] **In this study, patients will be offered the possibility to continue ocrelizumab treatment in an optional treatment extension period** with the dose (e.g., 300 mg or 600 mg) initially assigned to them until the appropriate dose for the subsequent Phase III study in children/adolescents is selected by the IMC (see Section 3.1.1.3). At that time, patients will be assigned to this selected dose level. In a situation where a subsequent dose of ocrelizumab is higher than the initial dose, that dose must be administered as two infusions of half the dose 14 days apart to mitigate the risk and severity of IRRs. In this case, the second infusion will take place as an optional infusion visit for split dose. For patients continuing the study, the second dose of ocrelizumab will be administered if all re-treatment criteria are met (footnote c). It is recommended that the treating investigator discuss with the parents/legal guardian and patient the benefits and risks of continuing study treatment with ocrelizumab, including treatment options, in advance and prior to any further dosing in order to schedule subsequent visits. The OOE period will last 264 weeks, and may be extended until the patient turns 18 years old (or as required per local regulation) or until commercial ocrelizumab is approved for children and available in the country for these patients, whichever occurs first. Initiation of an alternative treatment for MS may be considered by the investigator in which case the patient will enter the SFU period.

[b] **Optional MN visits**: At applicable sites, for patient convenience, all assessments at visits marked with (MN) may be performed by an MN professional at the patient's home or another suitable location instead of the clinical site (see Section 4.5.3.5). If during a visit the MN professional identifies any change in patient's health status (e.g., new or worsening neurologic symptoms or any other situation that may warrant an unscheduled site visit), the MN professional will contact the site immediately to report and discuss the findings. If required, an unscheduled visit will be scheduled as soon as possible with the site (i.e., within 7 days of symptom onset if possible). At sites where MN visits are not applicable, visits will take place at the clinical site.

[c] **Prior to re-treatment with ocrelizumab**, patients must be evaluated for the conditions and laboratory abnormalities described in Section 4.3.6 of the protocol. If any of these conditions are present prior to re-dosing, further administration of ocrelizumab should be suspended until resolved or held indefinitely. **A site visit or optional MN visit (as applicable) within 2 weeks prior to a planned or delayed dosing visit will be required to collect blood samples and patient's information to enable the treating investigator to assess whether a patient meets re-treatment criteria at the time of an infusion with ocrelizumab.** Treating investigator must have reviewed all safety laboratory data and ensure that any repeat laboratory tests have been performed, analyzed, and reviewed before administration of ocrelizumab. If these conditions are not met, an unscheduled visit and/or delayed dosing visit must occur.

[d] **A delayed dosing** visit will be performed and recorded in the Delayed Dosing Visit eCRF form when dosing cannot be administered at the scheduled dosing visit. Other tests or assessments may be done as appropriate. A site visit or optional MN visit (as applicable) within 2 weeks prior to a delayed dosing visit will be required to collect blood samples and patient's information to enable the treating investigator to assess whether a patient meets criteria for re-treatment with ocrelizumab (footnote c). Note that in situations where the delayed dosing visit occurs more than 4 weeks after the planned infusion date, the dose should be administered as two infusions of half the dose 14 days apart. In this case, the second infusion will take place as an optional infusion visit for split dose.

Table 2b Schedule of Activities for Optional Ocrelizumab Extension Period (Weeks 190 to 288) (cont.)

[e] **Administration of IV ocrelizumab:** The first dose of ocrelizumab must be administered as two infusions of half the dose 14 days apart (e.g., 150 mg on Day 1 and 150 mg on Day 15 for the 300 mg ocrelizumab cohort). It is recommended to schedule the first infusion of ocrelizumab (Day 1 of Dose 1) in the morning to allow the patient to stay at the hospital (or infusion center) with medical supervision and monitoring as required, as long as possible (e.g., until 6 p.m. or 8 p.m. according to the hospital rules), with a minimum of 1 hour after completion of the infusion. Patients may be hospitalized for a 24-hour observation after completion of the infusion at the discretion of the treating investigator. It is also recommended to administer the second infusion (Day 15 of Dose 1) and subsequent infusions in the morning, as patients should remain under observation for at least 1 hour after the completion of the infusion and up to 24 hours at the treating investigator's discretion.
For patients continuing in the optional ocrelizumab extension period (footnote a), subsequent doses will be administered as single infusions (e.g., 300 mg for the 300-mg ocrelizumab cohort). However, whenever the subsequent dose is higher than the previous dose, it should be administered as two infusions of half the dose 14 days apart. In this case, the second infusion will take place as an optional infusion visit for split dose. Prior to subsequent infusion of ocrelizumab, the treating investigator must review the clinical and laboratory re-treatment criteria (footnote c). Patients and their parents/legal guardian will be advised that an IRR can occur until 24 hours after completion of each infusion. A telephone interview will be conducted by site personnel within 24 ($\pm$ 4) hours after completion of each infusion (footnote h).

[f] Unscheduled site or MN visit: Assessments performed at unscheduled (non-dosing) visits will depend on the clinical needs of the patient. All patients with new neurological symptoms suggestive of relapse should have EDSS performed within 7 days of the onset of the relapse. Other tests/assessments may be done as appropriate.

[g] Withdrawal from treatment visit only takes place if patient discontinues prematurely from treatment (i.e., before Week 288) (see Section 4.5.3.6).

[h] **A telephone interview** will be conducted by site personnel within 24 ($\pm$ 4) hours after completion of each infusion and every 4 weeks ($\pm$ 6 days) between any visit (MN or site visit) and throughout the entire SFU period to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit (including new or worsening neurological symptoms or signs of infection) (see Appendix 4).

[i] Determination of the LCVA will include a measure of high-contrast acuity using the ETDRS chart as described in Appendix 3 of the protocol.

[j] At screening and baseline, a complete physical examination will be performed and should include an evaluation of the head, eyes, ears, nose, and throat and of the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. At subsequent visits, a limited, symptom-directed physical examination should be performed. Any abnormality identified should be entered either as medical history or AE accordingly.

[k] Body weight is to be determined to the nearest 0.1 kg. For body weight measurements, the patient should wear clothes, without any shoes, outerwear, or accessories.

Table 2b Schedule of Activities for Optional Ocrelizumab Extension Period (Weeks 190 to 288) (cont.)

[l] Height should be measured in a standing position using the same wall-mounted stadiometer for the same individual. Three standing height measurements should be made. The average of the three measurements will be considered to be the true height of the child/adolescent, provided the measurements are within 0.3 cm. The average value will be recorded on the eCRF. Note: Height should be collected from consenting biological mothers and fathers. This information should be entered directly on the eCRF. If both parents are not able to attend the same visit, please collect the missing height at a next clinic visit. If the parents are unknown this assessment will not be applicable.

[m] Tanner staging assessment will be contingent on IRB/EC's approval and written informed consent from the patients' parents/legal guardian and with patient assent (as applicable). Tanner staging will be documented on the eCRF at baseline. During the study conduct, patients will have their Tanner stages documented or assessed yearly until they reach Stage 5 (see Section 4.5.8).

[n] Wrist/Hand X–ray: This radiographic assessment will be contingent on IRB/EC's approval and written informed consent from the patients' parents/legal guardian and with patient assent (as applicable). One combined standard PA radiograph of the left wrist and hand will be obtained within 4 weeks of baseline and repeated yearly (± 4 weeks). If evidence of growth-plate fusion is not demonstrated at baseline but during subsequent X–rays, no further hand/wrist X–rays will be necessary provided that final growth/bone maturation has unequivocally been reached (see Section 4.5.10).

[o] If a prior X-ray was obtained within the last 6 months before the WD visit, the X-ray should not be repeated.

[p] MRI scans will be performed without a Gd-contrast agent at Week 192, 240, and 288 (window of ± 4 weeks of these scheduled visits). Also, MRI scans will be obtained in patients withdrawn from the treatment period (at a withdrawal from study visit), if not performed during the last 4 weeks.

[q] Neurological examination and EDSS: See Sections 4.5.14 and 4.5.15.

[r] Concomitant medications: See Section 4.4.

[s] Adverse events: See Section 5.

[t] Sensitive thyroid-stimulating hormone will be tested at screening and during the treatment period as indicated.

[u] Hepatitis screening and monitoring: All patients must have negative HbsAg and negative HepCAb screening test results prior to enrollment. If total HbcAb is positive at screening, HBV DNA measured by PCR must be negative to be eligible. For those patients enrolled with negative hBsAg and positive total HbcAb, HBV DNA (PCR) must be repeated every 12 weeks during the treatment period.

[v] Immunologic assessments: Includes CD19 and other circulating B–cell subsets, T cells, and natural killer cells. On infusion visits, blood samples should be collected prior to the methylprednisolone administration.

[w] Routine safety laboratory (hematology, chemistry, and urinalysis): On infusion visits, all urine and blood samples should be collected prior to the methylprednisolone administration. At other times, samples will be collected at any time during the visit. For urinalysis, a urine dipstick for blood, protein, nitrite and glucose (using the dipsticks provided) will be performed. If abnormal and applicable a microscopic examination will be performed on site (local laboratory). For more information related to safety laboratory assessments, see Section 4.5.19.1.

Table 2b Schedule of Activities for Optional Ocrelizumab Extension Period (Weeks 190 to 288) (cont.)

[x] Serum β–hCG must be performed at screening in female patients of childbearing potential (e.g., in Tanner stages ≥ 2 or post-onset of menarche). Subsequently, urine β–hCG (sensitivity of at least 25 mIU/mL) will be performed. On infusion visits, the urine pregnancy test should be performed prior to the methylprednisolone administration in all female patients of childbearing potential. If positive, the patient will not receive the scheduled dose, and confirmation by a serum pregnancy test will be performed.

[y] Antibody titers: Measurement of antibody titers against common antigens (mumps, rubella, varicella zoster, and S. pneumoniae) will be performed.

[z] Plasma and urine samples for JCV will be collected at specified timepoints and analyzed in batches, if decided by the Sponsor.

[aa] Blood to be drawn for serum prior to dosing at the indicated timepoints. A single serum sample will be collected if patients withdraw from treatment prior to Week 192 (at the withdrawal from treatment visit).

[bb] A single RBR DNA blood sample to be collected for research purposes if patient and/or parents/legal guardian agrees to separate optional RBR consent. This collection can be drawn at any subsequent visit if missed.

[cc] ECG (predose and postdose): At screening, ECG may be taken at any time during the visit. On infusion visits, ECGs should be performed prior to receipt of study drug, prior to vital sign measurements and blood draws. ECG should be taken within 45 minutes prior to the methylprednisolone administration in all patients and within 60 minutes after completion of the ocrelizumab infusion (see Section 4.5.11). Additional ECGs may be taken at the discretion of the treating investigator, as required during an unscheduled visit.

[dd] Vital signs (i.e., pulse rate, systolic and diastolic blood pressure, respiration rate, and temperature). On infusion visits, the vital signs should be taken within 45 minutes prior to the methylprednisolone administration in all patients. In addition, vital signs should be obtained prior to ocrelizumab infusion, then every 15 (±5) minutes for the first hour, then every 30 (±10) minutes until 1 hour after the end of the infusion. On non-infusion days, the vital signs may be taken at any time during the visit. Additional vital signs may be taken at the discretion of the treating investigator and should be recorded on the corresponding unscheduled Vital Signs eCRF.

[ee] **All patients will receive prophylactic treatment with an antihistamine and methylprednisolone prior to any infusion of ocrelizumab**. Methylprednisolone dose (slow IV infusion to be completed approximately 30 minutes before the start of each infusion): adjusted to weight for patients < 40 kg (2 mg/kg methylprednisolone) and for patients ≥ 40 kg (100 mg methylprednisolone). In the rare case, when the use of methylprednisolone is contraindicated for the patient, an equivalent dose of an alternative steroid should be used as premedication prior to the infusion of ocrelizumab. IV or oral antihistamine (e.g., diphenhydramine) will be administered 30–60 minutes prior to ocrelizumab. The addition of an analgesic/antipyretic, such as acetaminophen/paracetamol, may also be considered.

Table 3 Safety Follow-Up (including Prolonged B-Cell Monitoring if Required)

	Safety Follow-Up (at least *104* weeks from the date of last infusion of ocrelizumab) [a]									Prolonged B–Cell Monitoring [b]	End of Observation or WD from SFU	Unscheduled Site or optional MN visit [o]
Site Visits (weeks from the withdrawal from treatment visit) (± 7 days) [a]		24		48		*72*		*96*	*104*	Visits every 24 weeks (± 7 days)		
Site or opt mobile nursing visits (weeks from the withdrawal from treatment visit) (± 7 days) [a]	12		36		*60*		*84*					
Urine pregnancy test [c]	x	x										x
Routine safety laboratory [d]	x	x	x	x	*x*	*x*	*x*	*x*	*x*	x	x	x
Immunologic assessments [e]	x	x	x	x	*x*	*x*	*x*	*x*	*x*	x	x	(x)
Total Ig, IgA, IgG, IgM		x		x		*x*		*x*	*x*	x	x	(x)
ADA		x		x		*x*		*x*	*x*	x	x	
PK samples		x		x		*x*		*x*	*x*	x	x	
Plasma/Urine banking for JCV		x		x		*x*		*x*	*x*	x	x	(x)
Antibody titers		x		x		*x*		*x*	*x*	x	x	(x)
Hepatitis B Virus DNA [f]	(x)	(x)	(x)	(x)	*(x)*	*(x)*	*(x)*	*(x)*	*(x)*	(x)	(x)	
Vital signs	x	x	x	x	*x*	*x*	*x*	*x*	*x*	x	x	x
Neurological examination and EDSS		x		x		*x*		*x*	*x*	x	x	x
Physical examination [g]	x	x	x	x	*x*	*x*	*x*	*x*	*x*	x	x	x
SDMT		x		x		*x*		*x*	*x*	x	x	(x)
Visual testing (ETDRS and LCVA charts) [h]		x		x		*x*		*x*	*x*	x	x	(x)

Table 3 Safety Follow-Up (including Prolonged B-Cell Monitoring if Required) (cont.)

	Safety Follow-Up (at least *104* weeks from the date of last infusion of ocrelizumab) [a]									Prolonged B–Cell Monitoring [b]	End of Observation or WD from SFU	Unscheduled Site or optional MN visit [o]
Site Visits (weeks from the withdrawal from treatment visit) (± 7 days) [a]		24		48		*72*		*96*	*104*	Visits every 24 weeks (± 7 days)		
Site or opt mobile nursing visits (weeks from the withdrawal from treatment visit) (± 7 days) [a]	12		36		*60*		*84*					
Weight		x		x		*x*		*x*	*x*	x	x	
Height [i]		x		x		*x*		*x*	*x*	yearly	x	
Tanner staging [j]				x		*x*		*x*	*x*	yearly	x	
Date of menarche	x	x	x	x	*x*	*x*	*x*	*x*	*x*	x	x	
Wrist/Hand X–ray [k] (yearly)		(x)		(x)		*(x)*		*(x)*		yearly	x	
Potential relapses recording	x	x	x	x	*x*	*x*	*x*	*x*	*x*	x	x	x
Adverse events	x	x	x	x	*x*	*x*	*x*	*x*	*x*	x	x	x
Concomitant medication	x	x	x	x	*x*	*x*	*x*	*x*	*x*	x	x	x
Brain MRI [l]		x		x		*x*		*x*	*(x)*	yearly	x	(x)
Telephone interview [m]	Weeks: 4, 8, 16, 20, 28, 32, 40, 44*, 52, 56, 64, 68, 76, 80, 88, 92 and 100*									Every 12 weeks [n]		

ADA = anti-drug antibody; AE = adverse event; β–hCG = beta-human chorionic growth hormone; eCRF = electronic case report form; EDSS = Expanded Disability Status Scale; EDTRS = Early Treatment Diabetic Retinopathy Study; Gd = gadolinium; HbcAb = hepatitis B core antigen; HbsAg = hepatitis B surface antigen; HBV =∗ hepatitis B virus; Ig = immunoglobulin; JCV = JC–virus; LCVA = low-contrast visual acuity; MRI = magnetic imagining resonance; MS = multiple sclerosis; opt = optional; PA = posteroanterior; PK = pharmacokinetic; SDMT = Symbol Digit Modalities Test; SFU = safety follow-up period; WD = withdrawal.

Table 3 Safety Follow-Up (including Prolonged B-Cell Monitoring if Required) (cont.)

Note: Marks in parentheses are optional and may be done as appropriate (e.g., if needs to be repeated).

[a] SFU will be carried out for at least 104 weeks starting from the date of last infusion of ocrelizumab.

Visits will be performed at 12-week intervals starting from the date of the patient's withdrawal from treatment visit or from the date of the Week 288 visit. At applicable sites, site visits will alternate with mobile nursing visits. SFU applies to study patients who have completed the treatment period (i.e., up to Week 288) and to patients who withdraw early from treatment. If B cells have returned to normal levels at the end of this SFU period, then the last scheduled SFU visit will become the end-of-observation visit, and the patient will have completed the study. Patients who receive alternative MS therapies that may change B-cell levels will only be followed up for a period of 104 weeks; they will not be entered into the prolonged B-cell monitoring period thereafter. A dedicated SFU visit directly prior to the start of an alternative MS treatment is required in order to assess patient's clinical status and safety.

[b] Patients whose B cells have not returned to normal levels after 104 weeks of SFU will continue with site visits every 24 weeks (± 7 days) until B-cell repletion. Once B cells have returned to normal levels, patient will be scheduled for an end-of-observation visit, and the patient will have completed the study. Patients who begin during the prolonged B-cell monitoring period, alternative MS therapies that may change B-cell levels will only be followed up until the point they initiate this alternative MS therapy; an end-of-observation visit will be scheduled, and patients will have completed the study.

[c] Urine β-hCG (sensitivity of at least 25 mIU/mL) test will be performed until 24 weeks after the last dose of ocrelizumab. Female patients of childbearing potential (e.g., in Tanner stages ≥ 2 or post-onset of menarche) must agree to remain completely abstinent or to use reliable means of contraception for 24 weeks after the last dose of ocrelizumab as described in Section 5.1.5). Confirmation by a serum pregnancy test will be performed for positive urine pregnancy test.

[d] Routine safety laboratory: hematology, chemistry, and urinalysis. For urinalysis, a urine dipstick for blood, protein, nitrite and glucose (using the dipsticks provided) will be performed. If abnormal and applicable a microscopic examination will be performed on site (local laboratory). For more information related to safety laboratory assessments see Section 4.5.19.1.

[e] Immunologic assessments including CD19 and other circulating B-cell subsets, T cells, and natural killer cells.

[f] Hepatitis to be monitored only in patients with screening results of HbsAg negative, hBcAb positive, and HBV DNA negative, inclusive.

[g] A limited, symptom-directed physical examination should be performed. Any abnormality identified should be entered either as medical history or AE accordingly.

[h] Assessment of the LCVA will include a measure of high−contrast acuity using the ETDRS chart as described in Appendix 3.

[i] Height should be measured in a standing position using the same wall-mounted stadiometer for the same individual. Three standing height measurements should be made. The average of the three measurements will be considered to be the true height of the child, provided the measurements are within 0.3 cm. The average value will be recorded on the eCRF.

Table 3 Safety Follow-Up (including Prolonged B-Cell Monitoring if Required) (cont.)

[j] Patients will have their Tanner stages documented or assessed yearly until they reach Stage 5. Afterwards no further hand/wrist X-rays will be necessary provided that final growth/bone maturation has unequivocally been reached (see Section 4.5.10). For patients who have discontinued from treatment early and did not have a yearly X-ray (because the last one was performed within the last 6 months before that WD visit), an X-ray may have to be performed at the SFU Week 24 visit. From this point, subsequent X-rays will be performed yearly.

[l] Brain MRI scans will be performed without a Gd-contrast agent with a window of ± 4 weeks of a scheduled visit. MRI scans will be obtained in patients withdrawn from the SFU period (at a withdrawal from SFU visit), if not performed during the last 4 weeks. *MRI scan at SFU Week 104 may be acquired if clinically indicated.* For patients who begin an alternative treatment for MS during the SFU period or while in the B-cell monitoring period, an MRI scan will be performed within the time window of 1 month prior to the start of the alternative MS treatment (unless MRI has already been performed within prior 8 weeks).

[m] A telephone interview will be performed by site personnel every 4 weeks (± 6 days) between visits until *104* weeks after the last infusion to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit (including new or worsening neurological symptoms, signs of infection). If prolonged B-cell monitoring is required beyond *104* weeks after the last infusion, telephone interviews will be done every 12 weeks (± 6 days) between visits.

[n] For patients who undergo an alternative MS treatment while in B-cell monitoring period, telephone interview will continue to be performed every 4 weeks.

[o] Unscheduled site or mobile nursing visit: Assessments performed at unscheduled visits will depend on the clinical needs of the patient. All patients with new neurological symptoms suggestive of relapse should have EDSS performed within 7 days of the onset of the relapse. Other tests/assessments may be done as appropriate.

[k] Two radiographs; one combined standard PA radiograph of the left wrist and hand and a similar combined radiograph of the right wrist and hand will be obtained yearly ± 4 weeks until evidence of growth-plate fusion is demonstrated.

Appendix 2 Tanner Staging

Male puberty stage:

Stages Description:

Stage 1 Preadolescent. Testes, scrotum, and penis are about the same size and proportion as those in early childhood.

Stage 2 Scrotum and testes have enlarged, and there is a change in the texture of scrotal skin and some reddening of scrotal skin.

Stage 3 Growth of the penis has occurred, at first mainly in length but with some increase in breadth. There has been further growth of the testes and the scrotum.

Stage 4 The penis is further enlarged in length and breadth, with development of glans. The testes and the scrotum are further enlarged. There is also further darkening of scrotal skin.

Stage 5 Genitalia are adult in size shape. No further enlargement takes place after stage 5 is reached.

Female puberty stage:

Stages Description:

Stage 1 Preadolescent; only papillae are elevated.

Stage 2 Breast bud and papilla are elevated and a small amount is present; areola diameter is enlarged.

Stage 3 Further enlargement of breast mound, increased palpable glandular tissue.

Stage 4 Areola and papilla are elevated to form a second mound above the level of the rest of the breast.

Stage 5 Adult mature breast; recession of areola to the mound of breast tissue, rounding of the breast mound, and projection of only the papilla are evident.

Appendix 3
Low-Contrast Visual Acuity

A measure of high-contrast visual acuity will be performed using the Early Treatment Diabetic Retinopathy Study (ETDRS) charts and the low-contrast visual acuity test will be performed using the Sloan chart 2.5% contrast.

All charts will be provided for this study.

Patients should be placed at a distance of 2 meters from each chart during the examination.

The same settings (i.e., same charts and same distance) must be used at each examination.

For consistency, it is recommended the same examiner perform the tests at each visit for the same patient.

Both monocular (right eye, then left eye) and binocular (right and left eyes) testing should be performed using each chart wall-mounted at a distance of 2 meters, as follows:

- The right eye will be tested on the high−contrast ETDRS chart, followed by the left eye, then both eyes, and then move to the 2.5% low-contrast Sloan chart following the same sequence.

These charts are scored by the number of letters read correctly (out of 70), and numbers will be entered on the visual acuity evaluation forms provided, which will serve as a source document before being entered on the electronic case report form.

Appendix 4
Telephone Interview

The purpose of this interview is to identify and collect information on any changes in the patient's health status (i.e., new or worsening neurological symptoms, signs of infection, any unusual signs or symptoms since patient left the clinic after the infusion) that warrant an unscheduled visit.

The telephone interview will be conducted by site personnel familiar with the patient(s) within 24 hours after completion of each infusion of ocrelizumab, and every 4 weeks between the study visits (with exemption of patients in the prolonged B-cell Monitoring Period without alternative treatment for MS when telephone interviews need to be performed every 12 weeks). The date of the telephone interview, or if the site was unable to contact the patient, will be recorded on the electronic case report form.

This form should be used and kept with the patient's records.

Please ask the following questions during the Telephone Interview. Read aloud and record patient's answers to the following questions:

1. Since your last visit or telephone interview, have you had any new or worsening medical problems that have persisted more than 1 day such as (select Yes or No):

1a)	Sudden changes in your thinking	☐ Yes	☐ No
1b)	Alterations in your behavior	☐ Yes	☐ No
1c)	Visual disturbances	☐ Yes	☐ No
1d)	Extremity weakness	☐ Yes	☐ No
1e)	Limb coordination problems	☐ Yes	☐ No
1f)	Gait abnormalities	☐ Yes	☐ No
1g)	Any other symptoms	☐ Yes	☐ No

If yes, specify _____

2. Since your last visit or telephone interview, have you noticed any of the following signs of an infection such as (select Yes or No):

2a)	Fever	☐ Yes	☐ No
2b)	Sweat	☐ Yes	☐ No
2c)	Chills	☐ Yes	☐ No
2d)	Low body temperature	☐ Yes	☐ No
2e)	Peeing less than normal	☐ Yes	☐ No
2f)	Rapid pulse	☐ Yes	☐ No
2g)	Rapid breathing	☐ Yes	☐ No

2h) Malaise ☐ Yes ☐ No

2i) Nausea and vomiting ☐ Yes ☐ No

2j) Diarrhea ☐ Yes ☐ No

2k) Any other signs ☐ Yes ☐ No
If yes, specify_____

3. Questions relating to signs of infusion-related reaction within 24 hours post-infusion: Since you have left the hospital have you experienced any symptoms such as:

3a) Itching of the skin ☐ Yes ☐ No

3b) Rash ☐ Yes ☐ No

3c) Throat irritation ☐ Yes ☐ No

3d) Pain ☐ Yes ☐ No

3e) Flushing (reddening of the skin) ☐ Yes ☐ No

3f) Headache ☐ Yes ☐ No

3g) Fever ☐ Yes ☐ No

3h) Hives ☐ Yes ☐ No

3i) Chills ☐ Yes ☐ No

3j) Fatigue ☐ Yes ☐ No

3k) Nausea ☐ Yes ☐ No

3l) Vomiting ☐ Yes ☐ No

3m) Abnormally low blood pressure ☐ Yes ☐ No

3n) Rigors (sudden feeling of being cold with shivers) ☐ Yes ☐ No

3o) Bronchospasm ☐ Yes ☐ No

3p) Any other signs ☐ Yes ☐ No
If yes, specify_____

4. Since your last visit or telephone interview, have you had any other new or worsening medical problems or conditions (including pregnancy), surgery, or hospitalization? ☐ Yes ☐ No
If yes, specify _____

5. Since your last visit or telephone interview, did you miss school or work? ☐ Yes ☐ No
If yes, specify the reason_____

6. Since your last visit or telephone interview, have you taken any new medicines (including medicines to treat cancer or MS, any steroid medicines other than for the

treatment of a recent relapse)? ☐ Yes ☐ No
If yes, specify _____

If the patient answered YES to any question, contact the Investigator and review the patient's answers. The Investigator can determine if an unscheduled visit is required and if any adverse event should be reported.

Record any pertinent comments made by the patient during the interview:

_____

_____

_____

Name and date of staff completing the telephone interview:

NAME: _____ Date: _____

Below is a sample list of medications that can weaken the immune system and should not be used concomitantly to ocrelizumab.

Examples of Immunosuppressants, Antineoplastics, and Immunomodulators

Approved MS Therapies (approved in at least 1 country):

- Glatiramer acetate (Copaxone®) Interferon beta-1a (Rebif®, AVONEX®) Interferon beta-1b (Betaseron®) Mitoxantrone (Novantrone®) Natalizumab (Tysabri®)
- Fingolimod (Gilenya®)
- Alemtuzumab (Lemtrada®) Teriflunomide (Aubagio®)
- Dimethyl fumarate (Tecfidera®)

Immunosuppressants/Antineoplastics:

- Azathioprine (Imuran®, Azasan®) Cladribine (Leustatin®) Cyclophosphamide (Cytoxan®, Neosar®) Cyclosporine (Sandimmune®, Neoral®) Fludarabine phosphate (Fludara®) Leflunomide (Arava®)
- Mercaptopurine (Purinethol®)
- Methotrexate (Methotrex®, Rheumatrex®, Trexall®) Mycophenolate mofetil (CellCept®)
- Pemetrexed (Alimta®)

Additional Immunomodulators and Immunosuppressants:

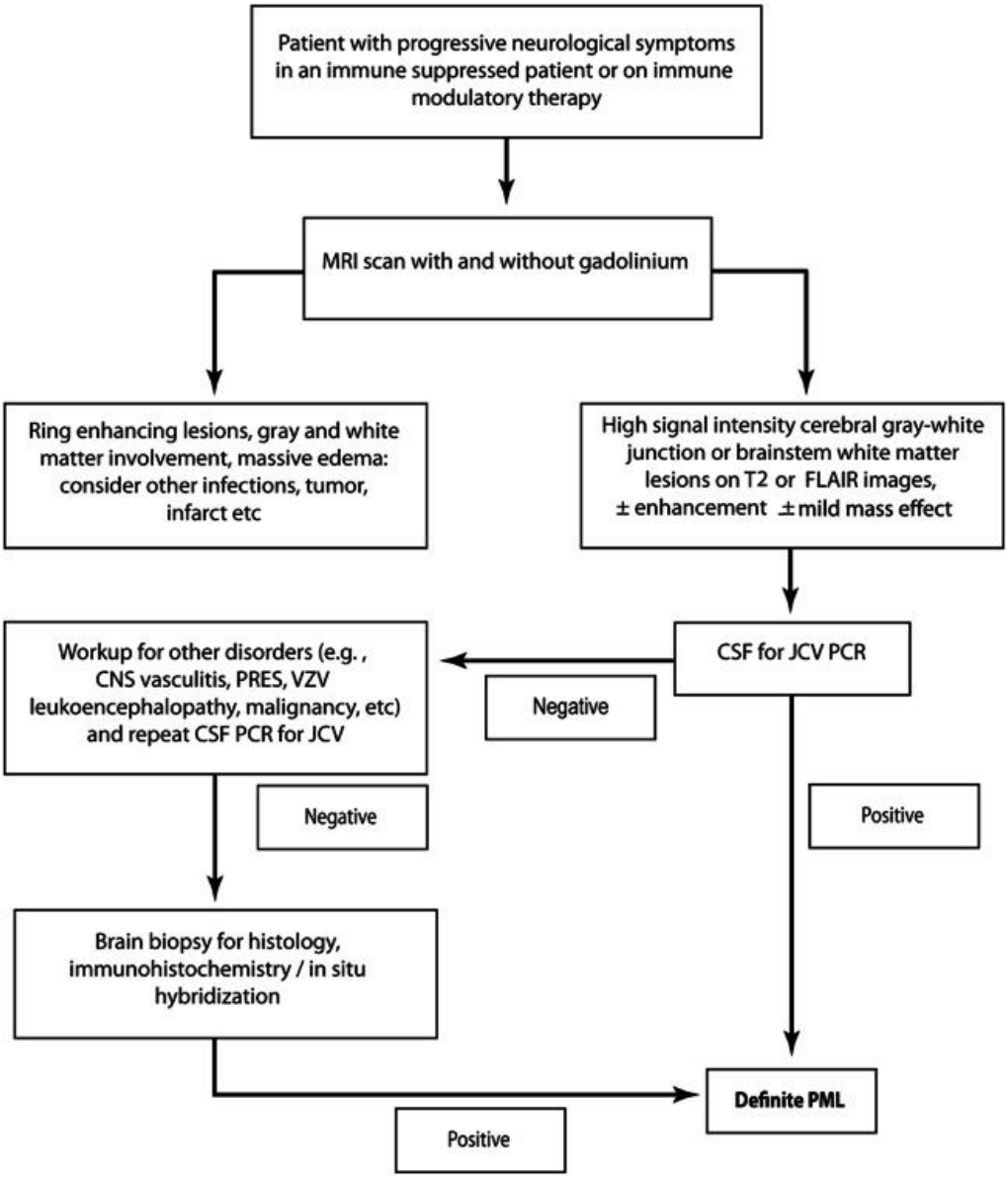
- Other interferons (Actimmune®, Infergen®, Intron® A, Pegasys®, PEG-Intron®, Rebetron®, Roferon®-A) Adalimumab (Humira®)
- Alefacept (Amevive®) Anakinra (Kineret®) Daclizumab (Zenapax®) Efalizumab (Raptiva®)
- Etanercept (Enbrel®)
- Infliximab (Remicade®)
- Intravenous immunoglobulin (IVIG) Ofatumumab (Arzerra®)
- Rituximab (Rituxan/MabThera®) Trastuzumab (Herceptin®)

This list does not include all drugs that can suppress the immune system.
Patients should notify the study team of any new medications taken during the course of the study.

Appendix 5
Guidance for the Diagnosis of Progressive Multifocal Leukoencephalopathy

The following safety monitoring algorithm will be implemented in this study (see Figure 1).

Figure 1 Diagnostic Algorithm Framework for Progressive Multifocal Leukoencephalopathy (Berger et al. 2013)



CSF = cerebrospinal fluid; FLAIR = fluid-attenuated inversion recovery; JCV = JC–virus; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; PML = progressive multifocal leukoencephalopathy; PRES = posterior reversible encephalopathy syndrome; VZV = varicella zoster virus.

THE FOLLOWING CLINICAL GUIDANCE IS PROVIDED:

- As in all multiple sclerosis (MS) studies, new or recurrent neurological symptoms occurring in study patients should prompt careful clinical evaluation.
- Given the occurrence of progressive multifocal leukoencephalopathy (PML) in immunocompromised patients who had received rituximab, PML should be considered in patients who develop worsening neurological signs or symptoms.
- There are no pathognomonic signs or symptoms that distinguish MS from PML, but there are certain clinical features that may help differentiate between the two conditions (see Table 1).
- In addition to PML and MS, other CNS conditions (e.g., stroke, migraine) should be considered when evaluating a patient with new neurological changes.
- Relapses should be managed according to the study protocol.
- Corticosteroid treatment should only be considered for cases in which PML is unlikely on clinical grounds and when the severity of the relapse warrants such treatment. Lack of response to corticosteroids should trigger further investigation.

ACTION STEPS IF PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY IS SUSPECTED

- If the clinical presentation is suggestive of PML, further investigations should include brain magnetic resonance imaging (MRI) evaluation as soon as possible. If MRI evaluation reveals lesions suspicious for PML (see Table 2), a lumbar puncture with evaluation of the cerebrospinal fluid (CSF) for the detection of JC–Virus (JCV) DNA should be undertaken. A diagnosis of PML can potentially be made by evaluating clinical and MRI findings plus the identification of JCV in the CSF.

Please note: In the event that PML is highly suspected but JCV testing is negative in the CSF, additional plasma, urine, and CSF samples should be obtained for JCV analysis (see Figure 1).

CSF samples will be analyzed upon receipt, and the results will be provided directly to the investigational site and to the Sponsor. The additional plasma and urine samples will be stored together with the routine JCV samples. Storage conditions and shipment instructions will be provided.

For details, refer to the most up–to–date laboratory manual providing storage conditions and shipment instructions.

MAGNETIC RESONANCE IMAGING ASSESSMENT

- Although there are no pathognomonic findings that differentiate PML from MS, a brain MRI scan that includes fluid-attenuated inversion recovery (FLAIR) and T2weighted 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.

CEREBROSPINAL FLUID ASSESSMENT

- The detection of JCV DNA in the CSF of a patient with clinical and MRI features suggestive of PML establishes the diagnosis of PML.
- If JCV DNA is not detected in CSF and if clinical suspicion of PML remains high, a repeat lumbar puncture should be performed.

If diagnosis remains uncertain and suspicion of PML remains high, a brain biopsy may be considered to establish a definitive diagnosis.

Table 1 Clinical Features to Distinguish between MS Relapse and PML

	MS Relapse	PML
Onset	Acute	Subacute
Evolution	Over hours to days	Over weeks
	Normally stabilizes	Progressive
	Resolves spontaneously or with treatment	
Clinical presentation	Optic neuritis	Cortical signs and symptoms
	Incomplete myelopathy or partial myelitis	Behavioral and neuropsychological alterations
		Retrochiasmal visual deficits
		Hemiparesis

MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy.
Adapted from Kappos et al. 2007.

Table 2 MRI Lesion Characteristics Typical of PML and MS

Feature	MS (Relapse)	PML
Location of new lesions	Mostly focal; affects 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

Table 2 MRI Lesion Characteristics Typical of PML and MS (cont.)

Feature	MS (relapse)	PML
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

FLAIR = fluid-attenuated inversion recovery; MRI = magnetic resonance imaging; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy.
Adapted from Yousry et al. 2006.

REFERENCES

Berger JR, Aksamit AJ, Clifford DB, et al. PML diagnostic criteria: consensus statement from the AAN Neuroinfectious Disease Section. Neurology 2013;80:1430−8.

Kappos L, Bates D, Hartung HP, et al. Natalizumab treatment for multiple sclerosis: recommendations for patient selection and monitoring. Lancet Neurol 2007;6:431−41.

Yousry TA, Major EO, Ryschkewitsch C, et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. N Engl J Med 2006;354:924−33.

Appendix 6
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.
7. Collect serum samples for immunogenicity testing.

Appendix 7
Investigational and Auxiliary Medicinal Product Designations (for Use in European Economic Area)

Table 1 Investigational, Authorized Auxiliary, and Unauthorized Auxiliary Medicinal Product Designations for European Economic Area

Product Name	IMP/AxMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Ocrevus (ocrelizumab)/ RO4964913	IMP (test product)	Authorized	Yes
Methylprednisolone	AxMP (other[a])	Authorized	Yes
Antihistamine for systemic use[b]	AxMP (other[c])	Authorized	Yes
Acetaminophen	AxMP (other[d])	Authorized	Yes

AxMP = auxiliary medicinal product; EEA = European Economic Area; IMP = investigational medicinal product, IRR = infusion-related reaction.

[a] Methylprednisolone administered as premedication.

[b] Antihistamines for systemic use may include but not limited to diphenhydramine, cetirizine, clemastine, clorphenamine.

[c] Antihistamine for systemic use administered as premedication or as treatment for IRR events.

[d] Acetaminophen administered as treatment for IRR events.

Signature Page for Protocol - WA39085 - OCREVUS - v3 - Global/Core - Published
System identifier: RIM-CLIN-520134

Approval Task	[redacted] 31-Jan-2024 21:44:07 GMT+0000