Official Title: A Phase III Multicenter, Randomized, Double-blind, Double-dummy Study to Evaluate Safety and Efficacy of Ocrelizumab in Comparison with Fingolimod in Children and Adolescents with Relapsing-Remitting Multiple Sclerosis

NCT Number: NCT05123703

Document Date: Protocol Amendment Version 7: 23-Mar-2026

PROTOCOL

TITLE:	**A PHASE III MULTICENTER, RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY STUDY TO EVALUATE SAFETY AND EFFICACY OF OCRELIZUMAB IN COMPARISON WITH FINGOLIMOD IN CHILDREN AND ADOLESCENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS**
PROTOCOL NUMBER:	WN42086
STUDY NAME	Operetta 2
VERSION NUMBER:	7
TEST PRODUCT:	Ocrelizumab (RO4964913)
STUDY PHASE:	Phase III
REGULATORY AGENCY IDENTIFIERS:	IND Number: 100593 EU CT Number: 2023-506516-40-00 EUDRACT Number: 2020-004128-41 NCT Number: NCT05123703
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4058 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocols		
Version	**Date Final**	**Country**	**Version**	**Date Final**
7	See electronic date stamp on the final page of this document.	—	—	—
6	6 May 2024	—	—	—
5	27 September 2023	—	—	—
4	28 March 2023	Germany	4	14 April 2023
3	26 April 2022	Germany	3	17 May 2022
2	27 April 2021	Germany	2	23 March 2022
		Portugal	2	1 December 2021
		Italy	2	19 October 2021
		France	2	15 October 2021
1	30 July 2020	—	—	—

PROTOCOL AMENDMENT, VERSION 7: RATIONALE

Protocol WN42086 has been amended primarily to update the lists of identified and potential risks for ocrelizumab, in alignment with the Ocrelizumab Investigator's Brochure, Version 24. Additionally, the list of risks associated with fingolimod has been updated, in alignment with the latest fingolimod Summary of Product Characteristics (SmPC). Substantive changes to the protocol, along with the rationale for each change, are summarized below:

- Collection of demographic data, including information on race and ethnicity, is of importance to the future interpretation of results from the clinical trial. A rationale for collection of information on race and ethnicity has been provided (Section 3.4.7).
- The timing of laboratory samples to assess eligibility to the open-label extension (OLE) period Dose 1 Day 1 ocrelizumab infusion has been clarified (Section 4.1.3 and Appendix 1 [Table 2]).
- The timing of laboratory samples to assess retreatment criteria for the OLE Dose 1 Day 15 ocrelizumab infusion for patients initially randomized to fingolimod (Group B) has been clarified (Section 4.3.3 and Appendix 1 [Table 2]).
- It has been clarified that a brain magnetic resonance imaging (MRI) scan is to be performed at the OLE Day 1 visit for patients randomized to ocrelizumab if an MRI scan was not performed during the previous 4 weeks (Section 4.6.5 and Appendix 1 [Table 2]).
- The roles of the investigator and Sponsor during study conduct have been clarified (Section 4.7.1).
- In alignment with the Ocrelizumab Investigator's Brochure, liver injury has been added as a new identified risk for ocrelizumab (Section 5.1.1.1.7), and management guidelines have been provided (Section 5.1.6.2.2).
- In alignment with the Ocrelizumab Investigator's Brochure, non-infectious colitis has been added as a new potential risk for ocrelizumab (Section 5.1.1.2.5).
- In alignment with the latest fingolimod SmPC, progressive multifocal leukoencephalopathy and immune reconstitution inflammatory syndrome have been added as new risks associated with fingolimod (Section 5.1.2).
- The following changes have been made to the schedule of activities (Appendix 1):
  - The timing of biomarker serum sample collection during the OLE period has been corrected to include Dose N Day 22 (Table 2).
  - The timing of routine safety laboratory sample collection during the OLE period has been updated to occur as appropriate at Dose 1 Day 15 (Table 2).

- The requirements for JC–virus (JCV) plasma and urine sampling during the OLE phase have been restricted to the Dose 1 Day 1 visit (Table 2) and removed during the safety follow-up period (Table 3). As JCV titers have not been identified as a risk factor for progressive multifocal leukoencephalopathy with ocrelizumab, continued sample collection for JCV assessment is no longer required.

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III MULTICENTER, RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY STUDY TO EVALUATE SAFETY AND EFFICACY OF OCRELIZUMAB IN COMPARISON WITH FINGOLIMOD IN CHILDREN AND ADOLESCENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS**
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TEST PRODUCT:	Ocrelizumab (RO4964913)
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III MULTICENTER, RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY STUDY TO EVALUATE SAFETY AND EFFICACY OF OCRELIZUMAB IN COMPARISON WITH FINGOLIMOD IN CHILDREN AND ADOLESCENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS**
REGULATORY AGENCY IDENTIFIERS:	IND Number: 100593 EU CT Number: 2023-506516-40-00 EUDRACT Number: 2020-004128-41 NCT Number: NCT05123703

STUDY RATIONALE

Multiple sclerosis (MS) is a serious, disabling disease, which is the leading medical cause of acquired neurological disability in young adults. Preventing the accrual of irreversible neurological impairment is a key goal of MS therapy. It is particularly important in pediatric patients where the onset of the disease is much earlier, and patients reach higher Expanded Disability Status Scale (EDSS) milestones at a younger age than in adult-onset MS. The purpose of this study is to evaluate the safety and efficacy of ocrelizumab compared to fingolimod in children and adolescents with relapsing-remitting multiple sclerosis (RRMS) aged $\geq$ 10 and $<$ 18 years. The prompt initiation of therapies in children and adolescents is supported by the International Pediatric Multiple Sclerosis Study Group. 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.

OBJECTIVES AND ENDPOINTS

This double-blind, double-dummy study will evaluate the safety and efficacy of ocrelizumab compared with fingolimod in children and adolescents with RRMS ages $\geq$ 10 to $<$ 18 years over a flexible duration. The double-blind period will last until after the last patient randomized has completed 24 weeks.

Specific objectives and corresponding endpoints for the study are outlined below. All comparisons will be made in the hypothetical situation that patients do not withdraw from the study treatment.

Primary Efficacy Objective	Corresponding Endpoint
• To demonstrate non-inferiority of ocrelizumab compared with fingolimod	• Protocol-defined annualized relapse rate (ARR), as measured through the rate ratio in counts during the double-blind period.
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To demonstrate non-inferiority of ocrelizumab compared with fingolimod	• Based on the number of new or enlarging T2-hyperintense lesions (T2 lesions) as detected by brain magnetic resonance imaging (MRI) during the double-blind period
• To demonstrate the superiority of ocrelizumab versus fingolimod on the basis of the following endpoints	• Number of T1 Gd lesions at Week 12 • Number of new or enlarging T2 lesions during the double-blind period • Protocol-defined ARR during the double-blind period

Safety Objectives	Corresponding Endpoints
• To evaluate the safety of ocrelizumab administered by IV infusion every 24 weeks compared with fingolimod administered once a day (QD) by mouth (PO)	• Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0) • Change from baseline in targeted vital signs and clinical significant abnormalities in ECG following study treatment administration • Change from baseline in targeted clinical laboratory test results
Pharmacokinetic Objectives	**Corresponding Endpoints**
• Assess the pharmacokinetics of ocrelizumab in all children/adolescents enrolled	• Serum concentration of ocrelizumab at specified timepoints
Pharmacodynamic Objectives	**Corresponding Endpoints**
• Assess the pharmacodynamics in all children/adolescents enrolled	• Levels of CD19 + B-cell count in blood
Immunogenicity Objectives	**Corresponding Endpoints**
• To evaluate the immune response to ocrelizumab	• Prevalence of ADAs at baseline and incidence of ADAs during the study

ADA = anti-drug antibodies; ARR = annualized relapse rate; ECG = electrocardiogram; Gd = gadolinium

Primary and selected secondary objectives for the study are expressed using the estimand framework in accordance with the International Conference on Harmonization E9 (R1) statistical principles for clinical trials (ICH 2020) in Section 2.

OVERALL DESIGN AND STUDY POPULATION

This Phase III randomized, double-blind, double-dummy, multicenter study will evaluate the safety and efficacy of ocrelizumab administered by IV infusion every 24 weeks compared with fingolimod taken PO QD, in children and adolescents with RRMS aged ≥ 10 and < 18 years.

This study consists of the following study periods: a screening period, a double-blind period, an optional OLE period, and a safety follow-up (SFU) period. The study duration will vary for each patient.

Patients will be treated in the double-blind period until the primary analysis, which will be conducted after the last randomized patient has completed 24 weeks.

The study plans to enroll approximately 171 patients in a 1:1 randomization (ocrelizumab:fingolimod), globally. Randomization will be performed through an interactive voice and web-based response system (IxRS) and will be stratified by region (United States vs. rest of world [ROW]), pre-pubertal status (yes vs. no), and presence of T1 Gd lesions at baseline (yes vs. no).

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

Phase:	Phase III	**Population Type:**	Children and adolescents
Control Method:	Active comparator	**Population Diagnosis or Condition:**	Relapsing-remitting multiple sclerosis
Interventional Model:	Parallel	**Population Age:**	Aged ≥10 and <18 years
Test Product{s}:	ocrelizumab fingolimod	**Site Distribution:**	Multicenter, multi-region
Active Comparator:	fingolimod	**Study Treatment Assignment Method:**	Randomization and Stratification
Number of Arms:	2	**Number of Participants to Be Enrolled:**	171 patients

STUDY TREATMENT

The investigational medicinal products (IMPs) for this study are ocrelizumab and fingolimod.

During the double-blind treatment period, all patients will take a daily capsule of fingolimod or fingolimod placebo. In addition, they will be administered an IV infusion of ocrelizumab or ocrelizumab placebo on Day 1 and Day 15 and every 24 weeks thereafter.

Patients will receive ocrelizumab or ocrelizumab placebo by IV infusion every 24 weeks at a dose of 300 mg for patients < 35kg and 600 mg for patients ≥ 35 kg.

The first dose of ocrelizumab or ocrelizumab placebo will be administered as two IV infusions of half the dose given 14 days apart (i.e., 2 x 150 mg for a total dose of 300 mg, and 2 x 300 mg for a total dose of 600 mg).

Patients initially assigned to 300mg dose and who reach a body weight of ≥ 35 kg during the study should be switched to the 600mg dose at their next infusion visit. This subsequent dose will be administered as two infusions of half the dose 14 days apart.

Patients will also receive fingolimod or fingolimod placebo orally once a day as per the prescribing information (i.e. 0.25 mg for patients with a body weight ≤40 kg and 0.5 mg for patients > 40kg).

DURATION OF PARTICIPATION

The total length of the study for patients, from screening to the end of the safety follow-up, will vary from patient to patient because of the flexible duration of the double-blind treatment period, which depends on each patient's time point of inclusion during the enrollment period.

COMMITTEES

Independent Committees:	Independent Data Monitoring Committee Independent Pediatric Multiple Sclerosis Review Committee
Other Committees:	Steering Committee

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
β-hCG	beta-human chorionic growth hormone
ADA	anti-drug antibody
ADEM	acute disseminated encephalomyelitis
AQP-4	aquaporin-4
ANC	absolute neutrophil count
ARR	annualized relapse rate
AUC	area under the concentration–time curve
AV	atrioventricular
BUN	blood urea nitrogen
CaGI-C	Caregiver Global Impression of Change
CD	cluster of differentiation
CDI	confirmed disability improvement
CDP	confirmed disability progression
C_{max}	maximum concentration
COVID-19	coronavirus disease 2019
CSF	cerebrospinal fluid
CSR	Clinical Study Report
DBP	double-blind treatment period
DIS	dissemination in space
DIT	dissemination in time
DMC	Data Monitoring Committee
DMT	disease-modifying therapy
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EDSS	Expanded Disability Status Scale
FDA	(U.S.) Food and Drug Administration
FS	Functional System
GA	glatiramer acetate
Gd	gadolinium
GGT	γ-glutamyl transferase
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

Abbreviation	Definition
HRQL	Health-Related Quality Of Life
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IFN	interferon
IMP	investigational medicinal product
IND	Investigational New Drug
IPMSRC	Independent Pediatric Multiple Sclerosis Review Committee
IPMSSG	International Pediatric Multiple Sclerosis Study Group
IRB	Institutional Review Board
IRR	infusion-related reaction
IxRS	interactive voice or web-based response system
JCV	JC–virus
LLN	lower limit of normal
LPLV	last patient, last visit
MAb	monoclonal antibody
MN	mobile nurse
MOG	myelin oligodendrocyte glycoprotein
MRI	magnetic resonance imaging
MS	multiple sclerosis
NAb	neutralizing antibody
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NfL	neurofilament light
ObsRO	observer reported outcome
OCT	optical coherence tomography
OLE	open-label extension
PCR	polymerase chain reaction
PDCO	Pediatric Committee
PedsQL™	Pediatric Quality of Life Inventory™
PerfO	performance outcome
PD	pharmacodynamic
PGIC	Patient Global Impression of Change
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PO	by mouth; orally
POMS	pediatric onset multiple sclerosis

Abbreviation	Definition
PPMS	primary-progressive multiple sclerosis
PRO	patient reported outcome
QD	once a day
QTc	corrected QT interval
RBR	Research Biosample Repository
RMS	relapsing multiple sclerosis
ROW	rest of world
RPR	rapid plasma reagin
RRMS	relapsing-remitting multiple sclerosis
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SDMT	Symbol Digit Modalities Test
SFU	safety follow-up
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, demyelinating, and degenerative disease of the CNS that affects approximately 2.8 million people worldwide (MSIF 2020). MS is primarily a disease of young adults, with patients usually diagnosed between the ages of 20 and 40 years (Calandri et al. 2019), with a mean age of diagnosis of approximately 30 years (GBD et al. 2017). Overall, women are affected at least twice as often as men, except individuals with the primary progressive form of the disease, which has no difference in gender prevalence (Goodin 2014; MSIF 2020).

Multiple sclerosis is a serious, disabling disease, which is the leading medical cause of acquired neurological disability in young adults (Hauser and Oksenberg 2006; Tullman 2013). The clinical signs in MS can occur in isolation or in combination, and can include weakness, spasticity, gait and coordination disturbances, sensory dysfunction, visual loss, sexual dysfunction, fatigue, depression, chronic pain, sleep disorders, and cognitive impairment (Tanasescu et al. 2014). Prognosis is highly variable, and if left untreated, half of patients with MS would require constant assistance to walk within 15 years of disease onset (Expanded Disability Status Scale [EDSS] score $\geq$6.0). Multiple sclerosis also imposes a substantial economic burden on patients, their families, and society as a whole (Trisolini et al. 2010; Adelman et al. 2013). 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).

MS is classified into three clinical phenotypes: relapsing remitting (RRMS), secondary progressive (SPMS), and primary progressive (PPMS) (Lublin et al. 2014). Each of these three phenotypes can be assessed as being active or non-active, based on the presence or absence of clinical relapses and new, enlarging, or gadolinium (Gd)-enhancing lesions on a magnetic resonance imaging (MRI) scan. The term "Relapsing MS" (RMS) comprises both RRMS and early stages of SPMS where patients still experience relapses (Lublin et al. 2014).

1.1.1 Features of Pediatric Multiple Sclerosis

Pediatric onset multiple sclerosis (POMS) is rare, with between 3%–5% of patients with MS experiencing their first symptom before reaching the age of 18 years (Chitnis et al. 2012). Its incidence varies according to countries and is estimated around 0.66 to 1.66/100 000 children less than 16 to 18 years old. Most POMS patients are diagnosed during adolescence, and are thus "pediatric" for only a few years. Like in adult onset MS, a female predominance is observed in POMS, except in children younger than 10 to 12 years, which may suggest hormonal interferences during puberty (Deiva 2019).

As compared with adult onset MS, where approximately 85% of patients start their disease with a relapsing-remitting course, more than 95% of pediatric patients have RRMS (Boiko et al. 2002; Banwell et al. 2007), and PPMS is exceedingly rare in children

(Ghezzi et al. 1997; Boiko et al. 2002; Simone et al. 2002; Waubant and Chabas 2009; Waldman et al. 2016).

Several studies have demonstrated that individuals with POMS 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. 2013). 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 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, later in adult life, is ultimately younger (Boiko et al. 2002).

Pediatric onset MS appears to have more inflammatory activity with a higher relapse rate than that observed in adults (annualized relapse rate [ARR]: 1.12–2.76 vs. 0.35–1.78, respectively), especially during the first two years (Gorman et al. 2009).

The patho-biological processes in pediatric MS at onset involve inflammation and neuronal and axonal loss, with highly active MRI features such as high T2 lesion burden, Gd-enhancing T1-weighted lesions occurring early and reduced brain volume (Bar-Or 2008). A higher T2 lesion load with a higher rate of new MRI lesions was observed in children compared to adults (Waubant et al. 2009). In addition, cerebral atrophy may be present from the very beginning of the disease, even involving the deep gray matter (Aubert-Broche et al. 2011; Aubert-Broche et al. 2014). Onset of MS during childhood and adolescence limits age expected primary brain growth and leads to subsequent brain atrophy, implicating early neurodegeneration (Waber et al. 2007; Aubert-Broche et al. 2014). Bartels et al. have reported reduced brain volumes at first presentation and brain growth failure, with increased disease activity associated with more severe brain volume loss (Bartels et al. 2019). Gray matter volume loss has also been observed in pediatric MS indicating that the expected resilience to CNS injury and greater repair potential are not sufficient to prevent gray matter atrophy (Mesaros et al. 2008; De Meo et al. 2019).

While the clinical onset of MS is defined by clinical attack, the biological onset of the disease predates clinical disease expression.

Evidence supporting this contention includes baseline imaging demonstrating focal areas of permanent tissue loss, so called "black holes," and a high volume of T2 bright clinically silent lesions with variable enhancement—suggestive of differential lesion age (Banwell 2019).

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). Children tend to experience their second clinical exacerbation more rapidly than adults do.

The disability as measured by the EDSS score is often not informative, as children recover well after their relapses and rarely would present with an EDSS score ≥ 4 during their follow-up. On the other hand, cognitive difficulties with psychosocial and academic consequences can be observed. 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 Multiple Sclerosis 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 (DIT) and dissemination in space (DIS) criteria to diagnose MS at the time of the initial clinically isolated syndrome. It has been proposed to incorporate in IPMSSG criteria the 2010 McDonald criteria for MS for children of all ages, when MRI-defined DIT and DIS 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). Recently the 2010 McDonald criteria for MS have been revised by the International Panel on Diagnosis of Multiple Sclerosis: 2017 revision of the McDonald criteria (Thompson et al. 2018). These criteria can be used in children more than 11 years old if the first attack is not an ADEM presentation (Thompson et al. 2018).

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. Based on experience in adults, glucocorticoids are standard first-line treatments (usually IV methylprednisolone), with IV Ig as a second-line therapy for children who either fail to respond to glucocorticoids or have contraindications to their administration (Yeshokumar and Banwell 2017).

Until recent years, injectables such as interferon (IFN)-β and glatiramer acetate were frequently used as first-line treatment for pediatric patients with MS (Ghezzi et al. 2016). The three IFN-β agents (two IFN β-1a and one IFN β-1b) are approved in the European Union for the use in adolescent patients with RMS aged 12 years and older on the basis of studies suggesting that the safety profile in adolescents is similar to that seen in adults.

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).

With the availability of more potent disease-modifying therapies (DMTs) during the last decade, the ultimate therapeutic goal in POMS, similar to adult MS, is 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 (Narula et al. 2015; Thompson et al. 2018).

Accordingly, a large cohort study from the United States Pediatric MS Network indicates that a treatment shift from injectables to newer MS treatments approved for adult MS has been observed, with newer DMTs often being used in pediatric patients with MS off label (Krysko et al. 2018).

Clinical trials with these newer MS treatments are planned or ongoing in pediatric patients with MS, and some studies have been completed showing similar short-term safety, tolerability, and side effect profiles as in adults.

- The Focus study was an open-label Phase II study in 22 children and adolescents with RRMS aged 10 to 17 years with RRMS to evaluate the safety, efficacy and pharmacokinetics of dimethyl fumarate. The study showed dimethyl fumarate treatment was associated with a reduction in MRI activity in pediatric patients and that pharmacokinetics and safety profiles were consistent with those in adults (Alroughani et al. 2018).
- Another open-label Phase II study with natalizumab was recently completed in 13 children and adolescents with RRMS aged 10 to 17 years. This study showed that natalizumab pharmacokinetic (PK)/pharmacodynamic (PD) parameters and safety profile were similar in adults and pediatric patients in the short term (Ghezzi et al. 2019).
- In 2018, the United States Food and Drug Administration and European Commission approved Gilenya® (fingolimod) to treat RMS in children and

adolescents aged 10 years and older following the completion of the first randomized controlled trial in pediatric patients with MS, on the basis of level 1A evidence of superiority of fingolimod versus interferon (Chitnis et al. 2018), and establishing it as the new standard of care in this indication.

- In 2020, preliminary results of a 2-year, randomized, double-blind, placebo-controlled, parallel-group Phase 3 study of teriflunomide in children and adolescents aged 10–17 years with relapsing forms of MS were presented at the 6th Congress of the European Academy of Neurology. The study missed its primary endpoint (median time to first confirmed relapse), but showed significant benefit in a pre-specified sensitivity analysis of median time to first disease activity as well as in key secondary outcomes. As of April 2021, the full results of the double blind period have not been published.

1.2 BACKGROUND ON OCRELIZUMAB

Ocrelizumab is a recombinant humanized monoclonal antibody (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.

Ocrelizumab has been developed for the treatment of both relapsing and primary progressive forms of MS. The double-blinded control periods of the Phase III Studies WA21092, WA21093, and WA25046 in adult patients with MS have been completed, and the respective open-label extension (OLE) periods of these studies are ongoing. Phase IIIb and Phase IV studies are planned or ongoing.

The Ocrelizumab Investigator's Brochure summarizes the nonclinical data and the current clinical experience with ocrelizumab in the context of the ocrelizumab MS development program. For details, see the current Ocrelizumab Investigator's Brochure.

1.2.1 Nonclinical Information

Repeat-dose toxicology studies of ocrelizumab at doses of up to 100 mg/kg, administered as two doses every 2 weeks (Days 1 and 15), four doses weekly (Days 1, 8, 15, and 22), or eight 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 15,000 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 in the study (2 of 24 animals), 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 was 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 when 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 in the 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. 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 hemocyanin, 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 observed adverse-effect level, which provides the following safety factors over the estimated exposures in the proposed pediatric trial:

- Maximum concentration observed (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 at 20 mg/kg was 13-fold above projected AUC at steady state in pediatric trial.

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 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 RMS, treatment with ocrelizumab 600 mg (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 ocrelizumab 600 mg 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 patients (~1%) tested positive for treatment-emergent ADAs during the controlled treatment period, and 2 of these patients tested positive for neutralizing antibodies (NAbs). The impact of treatment

emergent ADAs on efficacy and safety endpoints could not be determined given the low incidence of ADAs across studies.

1.2.4 Current Clinical Development in Adults with Multiple Sclerosis

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 pivotal 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 OLE period of each study.

Recently, participants who completed the OLE of Studies WA21092, WA21093 and WA25046 were allowed to roll over in Study MN43964 (OLERO) to continue treatment with ocrelizumab and for continuation 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 Phase Ib and Phase IIIb studies are ongoing. Refer to the current Ocrelizumab Investigator's Brochure for the latest information.

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 β-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 β-1a 44 μg SC, ocrelizumab 600 mg demonstrated:

- Relative reductions of 46% and 47% for the primary endpoint of protocol-defined 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 Gd-enhancing lesions in Studies WA21092 and WA21093, respectively (both $p < 0.0001$)
- Relative reductions of 77% and 83% in the 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 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 Short Form-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.

In addition to the robust efficacy data of ocrelizumab observed in the RMS studies, the results from the pivotal Phase III PPMS study WA25046 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 Timed 25-Foot Walk ($p = 0.0404$)
- 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 Week 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 β-1a: 826 patients; ocrelizumab: 825 patients).

The safety profile in the IFN β-1a treatment group was consistent with the labeled safety information available for IFN β-1a. Compared with results from the Phase II study in RRMS (Study 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 β-1a: 4141 adverse events; ocrelizumab: 4194 adverse events) were well balanced between the two treatment groups; the majority of adverse events were of Grade 1 or 2 intensity. The proportion of patients who experienced a serious adverse event (IFN β-1a: 8.7% vs. ocrelizumab: 6.9%) was similar between treatment groups.

A total of 725 patients in the Phase III PPMS (Study WA25046) 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 of Grade 1 or 2 intensity. The proportion of patients who experienced a serious adverse event (placebo: 22.2% vs. ocrelizumab: 20.4%) was similar in both groups.

Infusion-Related Reactions

Infusion-related reactions (IRRs) are known to occur with the administration of MAbs. In the RMS (Studies WA21092 and WA21093) and PPMS (Study WA25046) 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 (WA21092 and WA21093), 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 β-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 of Grade 1 or 2.

In the placebo-controlled PPMS clinical trial (WA25046), the incidence of IRRs was also highest during Dose 1, Infusion 1 (27.4%) and decreased with subsequent doses to $<10\%$ at Dose 4. In this study, where each dose of ocrelizumab was administered as two infusions of ocrelizumab 300 mg 14 days apart, 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 Grade 1 or 2.

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 (Studies WA21092 and WA21093) and PPMS (Study WA25046) 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 β-1a or placebo).

By contrast, respiratory tract infections and herpes infections were more frequently reported in the ocrelizumab treatment arm of the RMS (Studies WA21092 and WA21093) and PPMS (Study WA25046) trials. Respiratory tract infections were predominately of Grade 1 or 2 intensity and consisted mostly of upper respiratory tract infections (including nasopharyngitis) and bronchitis.

- In the RMS trials (WA21092 and WA21093), herpes infections were reported more frequently in ocrelizumab-treated patients than IFN β-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 of Grade 1 or 2 in intensity and patients recovered with treatment by standard therapies. There were no reports of disseminated herpes.

- In the PPMS trial (WA25046), a higher proportion of patients with oral herpes (2.7% vs. 0.8%) was 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 β-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.

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.

In the two 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 β-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 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 during SFU in the ocrelizumab treatment group.

For detailed information and most recent analyses of the safety of ocrelizumab, refer to the current Ocrelizumab Investigator's Brochure.

Laboratory Data

Immunoglobulins

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

In the RMS studies (WA21092 and WA21093), the proportion of patients at baseline with IgG, IgA and IgM below 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 with IgG, IgA, and IgM below 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 with successive dosing. There was no association between sustained decreases in Ig (defined as IgG, IgA, or IgM levels below LLN for at least two consecutive visits) and infection rates.

In the PPMS study (WA25046), the proportion of patients at baseline with IgG, IgA and IgM below 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. There was no association between sustained decreases in Ig (defined as IgG, IgA, IgG, or IgM levels below LLN for at least two consecutive visits) and infection rates.

CD19+ B Cells

In the RMS studies (WA21092 and WA21093), 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 cell/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 the PPMS study (WA25046), 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 indicated 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 RMS studies (WA21092 and WA21093), decreased neutrophils were observed in 14.7% of patients treated with ocrelizumab compared with 40.9% of patients treated with

IFN β-1a. In the PPMS study (WA25046), 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 of Grades 1 and 2 in intensity. Overall, approximately 1% of the patients in the ocrelizumab treatment group had Grade 3 or 4 neutropenia, which was not temporally associated with an infection.

Antibody Titers

In the RMS studies (WA21092 and WA21093), ocrelizumab did not appear to have an effect on specific humoral immunity to common bacterial and viral antigens over the 96–week controlled treatment 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 the PPMS study (WA25046), no effect on specific humoral immunity to common bacterial and viral antigens was observed with ocrelizumab during the controlled treatment period at Week 120 (*Streptococcus pneumoniae*, mumps, rubella, and varicella zoster). The proportions of patients with positive antibody titers against rubella, mumps, and varicella at Week 120 were similar in both groups.

Anti-Drug Antibodies

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, 3 patients (0.4%) 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 postbaseline 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.

1.2.5 Current Clinical Development in Pediatric Patients with Multiple Sclerosis

The pediatric clinical development plan is a post-approval commitment with Pediatric Committee (PDCO) and U.S. Food and Drug Administration (FDA) to conduct two clinical trials, a Phase II study and a Phase III study in children and adolescents with RRMS aged ≥ 10 to < 18 years.

The first pediatric study with ocrelizumab is an open-label, parallel-group Phase II study (WA39085) to evaluate safety, tolerability, pharmacokinetics, and PD effects of ocrelizumab in children and adolescents with RRMS aged ≥ 10 to < 18 years. This study is designed to characterize the ocrelizumab PK profile and to explore the relationship between drug exposure and pharmacodynamics (CD19+ B-cell count).

The first patient in Study WA39085 was enrolled on 9 January 2020 and the study is currently ongoing in Italy, Poland, and the United States. The study recruitment was completed on 20 April 2023. As of 5 October 2023, twenty-three patients were recruited, as follows:

- Six patients weighing <40 kg had received 300 mg of ocrelizumab including 2 patients with a body weight below 30 kg). All patients completed the 24–week dose exploration period. Median number of doses was 4.5 (range: 2–8).
- Seventeen patients weighing ≥ 40 kg had received 600 mg of ocrelizumab. All patients completed the 24-week dose exploration period. Median number of doses was 6 (range: 5–9).

Based on the available PK, PD, and safety data from these patients, the Internal Monitoring Committee, held on 13 December 2023, confirmed that for pediatric patients 10 years of age and older weighing less than 35 kg, the recommended dosage of ocrelizumab is 300 mg intravenous infusion every 6 months, and that for pediatric patients 10 years of age and older weighing ≥35 kg, the recommended dosage of ocrelizumab is 600 mg intravenous infusion every 6 months.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Preventing the accrual of irreversible neurological impairment is a key goal of MS therapy. It 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. 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.

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.

The adult 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 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 (WA21092 and WA21093) show that compared with IFN β-1a, ocrelizumab significantly reduced protocol-defined ARR, and 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. MRI findings provide additional evidence of suppression of 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. In addition, ocrelizumab also showed consistent effects on markers of neurodegeneration, by reducing new T1-hypointense brain lesions, and rate of brain volume loss compared with IFN β−1a, a well-characterized and established pediatric MS therapy.

These data from the Phase III program in adults are further supported by the results from the Phase II study (WA21493). In this study, statistically significant reductions in the total number of Gd-enhancing T1 lesions at Weeks 12, 16, 20, and 24 (primary endpoint) were obtained in both ocrelizumab arms (300 mg $\times$ 2 and 1000 mg $\times$ 2, followed by a single ocrelizumab infusion of 600 mg or 1000 mg) compared with patients who received placebo (0.6 and 0.2 vs. 5.6, respectively; $p \leq 0.0001$ for both comparisons).

The total number of new and/or enlarging T2 lesions at Weeks 4, 8, 12, 16, 20, and 24 was reduced in patients who received either 600 mg or 1000 mg of ocrelizumab compared with those who received placebo (0.9 and 1 vs. 7.5, respectively; $p < 0.0001$ for both comparisons).

The efficacy results from this Phase III program in RMS and in PPMS have generated compelling evidence that in addition to acting on ARR, ocrelizumab has consistent efficacy in slowing disability progression.

Regarding safety, in adults, ocrelizumab demonstrates a favorable overall safety profile over multiple doses. The most frequent risks associated with treatment were IRRs, which were manageable by appropriate measures, and infections, both mostly of Grade 1 or 2 in intensity, which are consistent with the MAb nature and mechanism of action of ocrelizumab. As the pathophysiology of MS in children and adolescents 10 years or older is similar to adults and the safety profile of DMTs in pediatric MS is consistent to what was observed in adults (Alroughani et al. 2018; Chitnis et al. 2018; Ghezzi et al. 2019), the favorable benefit−risk profile of ocrelizumab observed in adult patients with RMS is expected to be similar in children and adolescents with RRMS aged ≥ 10 to < 18 years.

The pediatric Phase II study with ocrelizumab (WA39085) completed its recruitment on 20 April 2023. The study is ongoing.

Five serious adverse events related to ocrelizumab have been reported up to the clinical cutoff date of 5 October 2023 (end of Dose Exploration Period), with no new safety signals or treatment discontinuations due to adverse events.

All patients are clinically stable (no relapses since start of ocrelizumab treatment, with stable EDSS). IRRs were observed in 17 patients at Grade 1 (10 patients), Grade 2 (6 patients) and Grade 3 (1 patient), and the IRR symptoms match the established safety profile observed in adult MS patients. Overall, the safety profile of pediatric patients with MS recruited in the Phase II study is similar so far to the safety profile observed in adult patients with MS.

Patients with ≥40 kg body weight treated with 600 mg ocrelizumab showed exposure within the adult exposure range observed at 600 mg administered every 6 months in the Phase III studies in adults.

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 et al. 2006) and suggest the pattern of peripheral blood B-cell depletion and repletion in children and adolescents to be similar to that in young adults. The PK/PD relationship for the mechanism of action of ocrelizumab (i.e., B-cell depletion) was expected to be comparable in adults and children/adolescents with MS.

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 range: 38–170 kg). MAbs are not metabolized via CYP450s or renally excreted (factors that are known to be different between children and adults), and therefore, body weight is also expected to be the most relevant covariate for individual exposure in children and adolescents aged 10 to 17 years.

The population PK model was used for the Phase II Study WA39085 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 to 17 years). Based on this model, children and adolescent patients with a body weight in the range of the adult Phase III study population (i.e., ≥40 kg) were expected to show exposure at a dose of ocrelizumab 600 mg similar to the adult exposure range observed at 600 mg

administered every 6 months in the Phase III studies in adults. PK data from the currently ongoing Phase II Study WA39085 has confirmed this hypothesis. The exposure after administration of 600 mg ocrelizumab in pediatric patients with a body weight ≥40 kg is well within the exposure range observed at 600 mg in the three pivotal studies of adult patients with MS.

Therefore, a dose of ocrelizumab 600 mg every 6 months (24 weeks) has been selected for this Phase III Study WN42086 for children and adolescents with a body weight >40 kg.

Based on the review of PK, PD, safety and efficacy data with a clinical cutoff date of 05 October 2023, the WA39085 Internal Monitoring Committee established the following recommendations:

1. For pediatric patients 10 years of age and older weighing less than 35 kg, the recommended dosage of ocrelizumab is 300 mg intravenous infusion every 6 months. For pediatric patients 10 years of age and older weighing ≥35 kg, the recommended dosage of ocrelizumab is 600 mg intravenous infusion every 6 months
2. Patients of body weight reaching 35.0 kg and higher will switch to the 600 mg dosage at 1st body weight measurement at an infusion visit. The first dose of ocrelizumab/ocrelizumab placebo will be administered as two IV infusions of half the dose given 14 days apart (Section 4.3.2.1)

Enrollment of patients ≤40kg will now be allowed by the interactive voice and web-based response system (IxRS).

1.3.2 Benefit–Risk Assessment of the Conduct of the Study during the COVID-19 pandemic

A benefit–risk assessment was conducted to determine whether there would be any impact of the coronavirus disease-2019 (COVID-19) pandemic on the conduct of this study. Based on this assessment, no impact is anticipated, and the existing information on identified and potential risks, safety monitoring, management guidelines, and risk mitigation measures provided in the study protocol are considered adequate.

The available safety data from patients diagnosed with MS treated with ocrelizumab to date suggests that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection follows a similar course in these patients as in the general population, with risk factors for severe infection that are similar among the general population, the overall MS population, and in those patients treated with ocrelizumab (Hughes et al. 2021).

In summary, protocol-mandated safety monitoring and management guidelines, study eligibility criteria, and the ocrelizumab re-treatment criteria are considered adequate in the context of conducting the study during the COVID-19 pandemic. Investigators

should manage SARS-CoV-2 infection in the same way (with respect to the protocol) as infections caused by any other pathogen, as per local guidelines.

1.3.3 Benefit–Risk Assessment for the Concomitant Use of Severe Acute Respiratory Syndrome Coronavirus-2 Vaccines

A benefit–risk assessment was conducted to determine whether there is any impact on the concomitant use of COVID-19 vaccines on the conduct of this study. Based on this assessment, no impact is anticipated to affect the safety and efficacy in patients enrolled in clinical trials with ocrelizumab. Existing information on identified risks, safety monitoring, and risk mitigation measures related to administration of vaccines (including those for SARS-CoV-2 infection) provided in the study protocol (namely immunization concomitant therapy and impaired response to vaccination; see Section 4.4.4) are considered adequate.

As described in Section 5.1.1.1.3, data from the pivotal Phase III studies of ocrelizumab in patients with RRMS and PPMS show that preexisting humoral immunity to common viral and bacterial antigens is not affected by ocrelizumab treatment. The vaccination study (BN29739, VELOCE) showed that patients diagnosed with MS treated with ocrelizumab were able to mount a humoral immune response to non-live vaccines and new antigens. The humoral immune response was considered protective, albeit with reduced levels of antibodies compared with controls. In this study, vaccines were given as early as 12 weeks after the first ocrelizumab infusion (as early as 10 weeks after the second ocrelizumab infusion of the first dose). Booster doses were given at least 4 weeks before the next dose of ocrelizumab. Other immune responses such as cellular responses were not investigated in Study BN29739.

Roche is continually collecting evidence from clinical and biological sources to better understand immune response mechanisms of the COVID-19 vaccines in ocrelizumab-treated patients.

As with any other medication or vaccine, COVID-19 vaccines should be reported as concomitant medication by using the standard fields in the clinical database (see Section 4.4). See Section 5.1.1 for information on anticipated risks for ocrelizumab and risk mitigation measures, including guidelines for managing adverse events associated with ocrelizumab.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of ocrelizumab may be found in the Ocrelizumab Investigator's Brochure.

2. OBJECTIVES AND ENDPOINTS

This double-blind, double-dummy study will evaluate the safety and efficacy of ocrelizumab compared with fingolimod in children and adolescents with RRMS aged ≥10

to < 18 years over a flexible duration. The double-blind period will last until after the last patient randomized has completed 24 weeks.

Specific objectives and corresponding endpoints for the study are outlined below. Except where stated, baseline refers to assessments performed at the Day 1 visit.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to demonstrate non-inferiority of ocrelizumab compared with fingolimod on the basis of the following endpoint:

- Protocol-defined annualized relapse rate (ARR, defined in Section 6.4.1)

  The comparison of interest is the difference of protocol-defined ARR, as measured through the rate ratio in counts during the double-blind period. The primary comparison will be made in the hypothetical situation that patients do not withdraw from the study treatment.

2.1.2 Secondary Efficacy Objectives

The secondary efficacy objectives for this study are the following:

- To demonstrate non-inferiority of ocrelizumab compared with fingolimod based on the number of new or enlarging T2-hyperintense lesions (T2 lesions) as detected by brain MRI during the double-blind period
- To demonstrate the superiority of ocrelizumab versus fingolimod on the basis of the following endpoints:
  - Number of T1 Gd lesions at Week 12
  - Number of new or enlarging T2 lesions during the double-blind period
  - Protocol-defined ARR during the double-blind period

All comparisons will be made in the hypothetical situation that patients do not withdraw from the study treatment.

2.1.3 Exploratory Efficacy Objectives

The exploratory efficacy objective for this study is to evaluate the efficacy of ocrelizumab compared with fingolimod on the basis of the following endpoints:

- Time to the first relapse (Kaplan-Meier proportion of relapse-free patients)
- Time to the first new or enlarging T2 lesions (Kaplan-Meier proportion of patients free of new or enlarging T2 lesions)
- Change in total T2 lesion volume from baseline to Weeks 24, 48 and 96
- Change in total T1-hypointense lesion (T1 lesion) volume from baseline to Weeks 24, 48, and 96
- Change in the Symbol Digit Modalities Test (SDMT) from baseline to Weeks 48 and 96

- Time to 24-week confirmed 4-point worsening in the SDMT
- Change from baseline in the EDSS at each scheduled visit during the double-blind period
- Time to confirmed disability progression over the treatment period, defined as an increase of ≥ 1.0 point from baseline EDSS when the baseline score is ≤ 5.5. EDSS will be confirmed at a regular scheduled visit at least 12 weeks or 24 weeks after the initial documentation of neurological worsening.
- Change in patient- and caregiver-reported Pediatric Quality of Life Inventory™ (PedsQL™) Generic Core Scale, Version 4.0, from baseline to Weeks 48 and 96
- Change in patient-reported fatigue, as measured by the PedsQL Multidimensional Fatigue Scale (domain scores and total score) from baseline to Week 48 and 96
- Change in EQ-5D-5L from baseline to Weeks 48 and 96
- Patient Global Impression of Change (PGIC) for fatigue, cognition, and overall MS symptoms at Weeks 48 and 96
- Caregiver Global Impression of Change (CaGI-C) for fatigue, cognition, and overall MS symptoms at Weeks 48 and 96
- Change in MS symptom severity and impact assessed by patient and caregiver interviews at Weeks 48 and 96

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of ocrelizumab administered by IV infusion every 24 weeks compared with fingolimod administered once a day (QD) by mouth (PO); including exploratory, long-term safety, and tolerability in those patients entering the OLE period on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Change from baseline in targeted vital signs and clinical significant abnormalities in ECG following study treatment administration
- Change from baseline in targeted clinical laboratory test results

2.3 PHARMACOKINETIC AND PHARMACODYNAMIC OBJECTIVES

The PK and PD objectives are as follows:

- Assess the pharmacokinetics of ocrelizumab in all children/adolescents enrolled in this study
- Assess the pharmacodynamics in all children/adolescents enrolled in this study, as measured by blood B-cell count

2.4 IMMUNOGENICITY OBJECTIVE

The immunogenicity objective for this study is to evaluate the immune response to ocrelizumab on the basis of the following endpoint:

- Prevalence of ADAs at baseline and incidence of ADAs during the study

The relationship between ADA status and pharmacokinetics, pharmacodynamics, efficacy, and safety may also be explored

2.5 BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to ocrelizumab (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to ocrelizumab, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of ocrelizumab activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety on the basis of the following endpoints:

- Level of neurofilament light (NfL) before and after ocrelizumab dosing at indicated timepoints (see Appendix 1)
- Relationship between biomarkers in serum (see Section 4.6.19) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This Phase III randomized, double-blind, double-dummy, multicenter study will evaluate the safety and efficacy of ocrelizumab administered by IV infusion every 24 weeks compared with fingolimod taken PO QD, in children and adolescents with RRMS aged $\geq$10 and $<$18 years.

This study consists of the following study periods: a screening period, a double-blind period, an optional OLE period, and a SFU period. The study duration will vary for each patient, as described in Figure 1 and Table 1.

Patients will be treated in the double-blind period until the primary analysis, which will be conducted after the last randomized patient has completed 24 weeks.

The study plans to enroll approximately 171 patients in a 1:1 randomization (ocrelizumab:fingolimod), globally. Randomization will be performed through an IxRS and will be stratified by region (United States vs. rest of world [ROW]), pre-pubertal status (yes vs. no), and presence of T1 Gd lesions at baseline (yes vs. no).

- Patients will receive ocrelizumab or ocrelizumab placebo by IV infusion every 24 weeks at a dose of 300 mg for patients < 35kg and 600 mg for patients ≥ 35 kg.

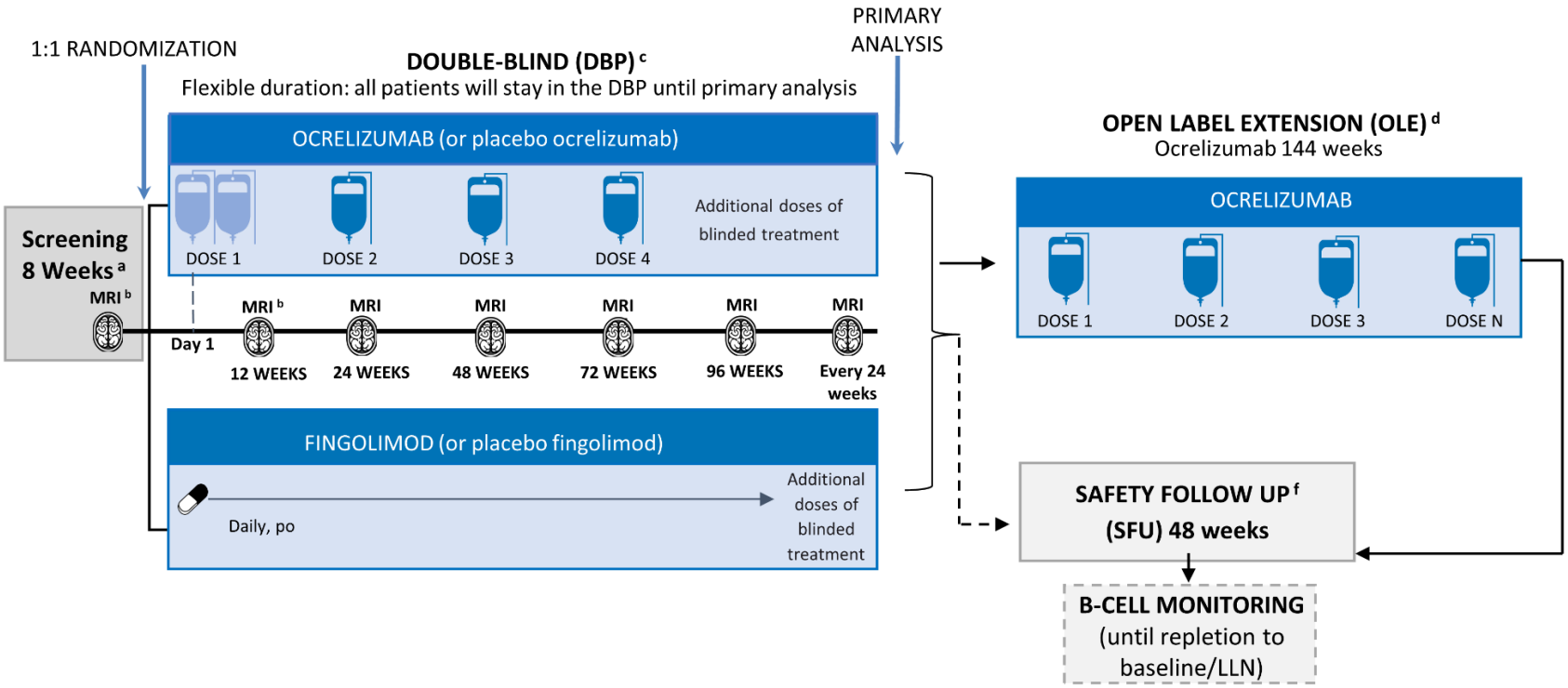
  The first dose of ocrelizumab or ocrelizumab placebo will be administered as two IV infusions of half the dose given 14 days apart (i.e., 2 x 150 mg for a total dose of 300 mg, and 2 x 300 mg for a total dose of 600 mg) (Section 4.3.2.1).

  Patients initially assigned to 300mg dose and who reach a body weight of ≥ 35 kg during the study should be switched to the 600mg dose at their next infusion visit. This subsequent dose will be administered as two infusions of half the dose 14 days apart (Section 4.3.2.1).
- Patients will also receive fingolimod or fingolimod placebo PO QD as per the prescribing information (i.e. 0.25 mg for patients with a body weight ≤40 kg and 0.5 mg for patients > 40kg).

An independent Data Monitoring Committee (iDMC) will be employed to monitor and evaluate safety data throughout the study, until the primary analysis is completed (see Section 3.1.6.3).

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1. Table 1 provides an overview of the treatment assignment.

Figure 1 Study Schema



DBP = double-blind period; Gd = gadolinium; LLN = lower limit of normal; MRI = magnetic resonance imaging; OLE = open-label extension; SFU = safety follow-up.

[a] The screening period may be extended for relevant clinical, administrative, or operational reasons, but cannot exceed 10 weeks.

[b] Brain MRI with and without a Gd-contrast agent should be performed at Baseline and Week 12. Subsequent brain MRIs should be performed without Gd-contrast agent only. Please refer to the Schedule of Activities in Appendix 1 Table 2 regarding brain MRIs during the OLE.

[c] The double-blind period will continue for all patients until primary analysis (Section 3.1.2). The primary analysis will be conducted after the last patient randomized has completed 24 weeks since first blinded ocrelizumab/ocrelizumab placebo infusion.

[d] Following database lock of the DBP, patients should continue to receive blinded treatment, as per Schedule of Assessments (Table 1), until the primary analysis is completed and the decision to start the OLE phase is communicated by the Sponsor. The OLE period will last for at least

144 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 (see Section 3.1.3).

[e] Patients in Group B switching from fingolimod to ocrelizumab must meet the eligibility criteria as per Section 4.1.3. The first dose of ocrelizumab will be administered as two half-dose IV infusions 14 days apart, and subsequent IV doses will be administered as single infusions every 24 weeks.

[f] Safety follow-up period will start after the double-blind period or the OLE period and last for at least 48 weeks, counting from the final ocrelizumab dose received (see Section 3.1.4).

Table 1 Overview of Treatment Assignment

Group	Double-Blind Period [a]						OLE Period [b]			SFU [c]
	Flexible Duration						At Least 144 Weeks			48 Weeks
	1st Dose		2nd Dose	3rd Dose	4th Dose	Additional Treatment Dose N (Every 24 Weeks)	Open-Label Treatment Dose 1, 2, …, N (Every 24 Weeks)			
	Day 1 Infusion	Day 15 Infusion	Week 24 Infusion	Week 48 Infusion	Week 72 Infusion	Week 96+ Infusions	Day 1 Infusion	Day 15 Infusion	Week 24+ Infusion	
A Ocrelizumab	Ocrelizumab	Ocrelizumab	Ocrelizumab	Ocrelizumab	Ocrelizumab	Ocrelizumab	Ocrelizumab	–	Ocrelizumab	–
	Placebo Fingolimod Daily	Placebo Fingolimod Daily	Placebo Fingolimod Daily	Placebo Fingolimod Daily	Placebo Fingolimod Daily	Placebo Fingolimod Daily				
B Fingolimod	Fingolimod Daily	Fingolimod Daily	Fingolimod Daily	Fingolimod Daily	Fingolimod Daily	Fingolimod Daily		Ocrelizumab		
	Placebo Ocrelizumab	Placebo Ocrelizumab	Placebo Ocrelizumab	Placebo Ocrelizumab	Placebo Ocrelizumab	Placebo Ocrelizumab				

OLE = open-label extension; SFU = safety follow-up.

[a] The double-blind period will continue for all patients until primary analysis (see Section 3.1.2).

[b] Patients in Group B switching from fingolimod to ocrelizumab must meet the eligibility criteria as per Section 4.1.3. The first dose of ocrelizumab will be administered as two half-dose IV infusions 14 days apart, and subsequent IV doses will be administered as single infusions every 24 weeks. The OLE period will last for at least 144 weeks, or 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 (see Section 3.1.3).

[c] SFU period will start after the double-blind period or the OLE period and last for at least 48 weeks, counting from the final ocrelizumab dose received (see Section 3.1.4).

3.1.1 Screening and Re-screening

Consenting patients will enter the 8-week screening period to be evaluated for eligibility. The screening period can be shorter if all eligibility criteria are met and the patient is ready to be enrolled. The screening period may be extended for relevant clinical, administrative, or operational reasons, but cannot exceed 10 weeks.

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for two re-screening opportunities (for a total of three screenings per participant) at the investigator's discretion. Patients are not required to re-sign the consent form if they are re-screened within 90 days after previously signing the consent form, unless instructed otherwise by the Sponsor based on specific situations. The investigator will record reasons for screen failure in the screening log. The re-screening process will be detailed in a separate document and sites will be trained accordingly.

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.

3.1.2 Double-Blind Period: Flexible Duration

The double-blind period is planned to continue for all patients until the results from the primary analyses have been communicated by the Sponsor. The primary analysis will be conducted after the last patient randomized has completed 24 weeks since first ocrelizumab/ocrelizumab placebo infusion (see Table 1 for dosing regimen of the treatment period).

The total length of the double-blind period for an individual patient will vary depending on that patient's time point of inclusion during the enrollment phase of the study.

The Sponsor may choose to conduct one interim efficacy analysis to avoid unnecessary long exposure to some patients. Section 6.9 outlines the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed. If there is a potential for the double-blind period to be stopped for positive efficacy as a result of the interim analysis, patients will have the opportunity to continue in the OLE period (Section 3.1.3).

Randomization (Day 1) will occur only after the patient has met all inclusion, none of the exclusion criteria (see Section 4.1), and MS diagnosis has been confirmed by the Independent Pediatric MS Review Committee. Patients will be randomized to either the ocrelizumab (Group A) or fingolimod (Group B) group as described below.

Group A (Ocrelizumab)

Ocrelizumab will be administered by IV infusion every 24 weeks. The first dose is given as dual infusions of half the dose of ocrelizumab on Days 1 and 15 and subsequent doses are given as single infusions of ocrelizumab every 24 weeks.

Patients randomized to Group A (active ocrelizumab group) will also receive a placebo of fingolimod (administered as QD capsule).

Group B (Fingolimod)

Fingolimod will be taken PO QD as per the prescribing information provided with fingolimod. Patients randomized to Group B (active fingolimod group) will also receive a placebo of ocrelizumab (administered as IV infusions on Days 1 and 15, and every 24 weeks thereafter).

Placebos of ocrelizumab and fingolimod will be similar in appearance and administration to the active product.

All patients will follow the same schedule of activities regardless of their treatment assignment. To confirm re-treatment criteria are met, a visit will be required within 2 weeks prior to any planned administration of IV ocrelizumab/ocrelizumab placebo to collect blood samples and patient information.

The first administration of study treatment and placebo (i.e., ocrelizumab/ocrelizumab placebo or fingolimod/fingolimod placebo) should occur within 24 hours of randomization. In exceptional cases where all Day 1 assessments cannot be completed within 24 hours, the first administration of study treatments may be administered within 48 hours of randomization provided the investigator ensures that all inclusion and none of the exclusion criteria are still met on the day of dosing. In particular, there should be no evidence of an ongoing infection at the time of dosing, based on results, clinical findings, and treating investigator judgment.

Efficacy and safety assessments will be collected as outlined in Table 1 of Appendix 1.

Patients who prematurely withdraw from study treatments during the double-blind period will remain (blinded) in the double-blind period (regardless if they start receiving alternative MS medication) and continue to be followed up for both efficacy and safety with the schedule of assessments as outlined in Table 4 of Appendix 1, until the end of the double-blind period, i.e., until the time of the primary analysis (as defined in the Statistical Analysis Plan [SAP]).

Patients, parents/legal guardians, investigators and the sponsor will remain blinded to the original (randomized) treatment allocation of all patients until the primary analysis is completed and the primary results are available and communicated by the Sponsor (see Section 4.2.2), to enable ongoing treatment decisions.

3.1.3 Optional Open-Label Extension Period with Ocrelizumab: At Least 144 Weeks

Patients who complete the double-blind period will be offered the possibility to enter an optional OLE treatment period with ocrelizumab.

Following database lock of the Double Blinded Period, patients should continue to receive blinded treatment, as per Schedule of Assessments (Table 1), until the primary analysis is completed and the decision to start the OLE phase is communicated by the Sponsor.

At this time, treatment allocated during the double-blind period will be unblinded.

Patients in Group A (ocrelizumab) will be instructed to stop the daily treatment with fingolimod placebo and will continue in the OLE period with ocrelizumab if in the opinion of the investigator patients will benefit from continuing with their initial treatment.

These patients will continue on the same dosing schedule with ocrelizumab administered as single infusions every 24 weeks (see Section 4.3.2.1.3). A visit will be required within 2 weeks prior to the next scheduled dosing visit after the OLE has commenced, to collect blood samples and patient information to confirm re-treatment criteria are met. The treating investigator must ensure patients meet criteria for re-treatment with ocrelizumab, as defined under Section 4.3.3, and this visit will serve as the screening visit of the OLE.

For subsequent dosing visits with ocrelizumab in OLE, a visit will be required within 2 weeks prior to any planned dosing visit to collect blood samples and patient information to confirm re-treatment criteria are met (Section 4.3.3).

Patients in Group B (fingolimod) will be instructed to have their next study visit onsite, and continue fingolimod until at least their next on-site visit when a decision will be made concerning patient's eligibility for OLE. Fingolimod should not be discontinued at home without supervision. Patients will continue in the OLE period and switch to ocrelizumab if in the opinion of the investigator, patients will benefit from switching from fingolimod to ocrelizumab (see Section 4.1.3 for OLE eligibility criteria).

There is a risk of disease rebound after discontinuation of fingolimod (Fingolimod Prescribing Information; Nagy et al. 2020; Hatcher et al. 2016). Several publications (Bigaut et al, 2021, Fragoso et al, 2019) advocate that the fingolimod treatment-free period must be defined on an individual basis due to the risk of disease rebound (relapse) and a long treatment interruption should be avoided.

However, a rapid therapy switch without considering lymphocyte recovery could be associated with an increased risk of infections due to possibly overlapping pharmacodynamic effects.

A careful evaluation of the benefit-risk of switching study treatment from fingolimod to ocrelizumab treatment must be performed for each patient by the treating investigator, based on:

- The radiological and clinical MS disease course under fingolimod treatment during the double-blind period.
- Patient medical history, comorbidity and concomitant medications, and
- Potentially social environment conditions.

The treating investigator should discuss the benefits and risks of entering the OLE period with the parents or a legal guardian and patient in advance.

Patients who are willing to participate in the OLE period will enter the OLE Screening period (Appendix 1, Table 2). Eligibility as per Section 4.1.3 must be confirmed by the investigator. Due to the potential fingolimod short washout window (at least 5 days), local laboratories are allowed for fast laboratory parameter review to determine patient's eligibility but local laboratory data will not be collected in the eCRF. However, central laboratory tests should still be performed in parallel for analysis purposes. If within 8 weeks after the discontinuation of fingolimod, patient is still not eligible to enter the OLE, patient should be permanently discontinued from the study. A further extension of these 8 weeks could be granted (based on clinical, administrative, or operational reasons) with prior approval from the sponsor.

The first dose of ocrelizumab will be administered as two half-dose IV infusions 14 days apart, and subsequent IV doses will be administered as single infusions every 24 weeks (see Section 4.3.2.1.3).

For subsequent dosing visits with ocrelizumab, a visit will be required within 2 weeks prior to any planned dosing visit to collect blood samples and patient information to confirm re-treatment criteria are met. The treating investigator (see Section 4.2.3) must ensure patients meet criteria for re-treatment with ocrelizumab, as defined under Section 4.3.3, before each subsequent infusion.

For all patients entering the OLE period, efficacy and safety assessments will be collected as outlined in Table 2 of Appendix 1.

The OLE period will last for at least 144 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.

Note: Patients randomized to ocrelizumab (Group A) who are not entering the OLE period, and patients discontinuing from the OLE period at any time for any reason will enter the SFU period (see Section 3.1.4). Patients randomized to fingolimod (Group B) who are not entering the OLE period will discontinue the study and perform an end of study visit (see Appendix 1).

3.1.4 Safety Follow-Up Period: 48 Weeks

The SFU period will last for at least 48 weeks, counting from the last ocrelizumab dose received.

Patients will enter the SFU period under the following conditions:

- They were randomized to ocrelizumab (Group A) and they have completed the double-blind period but they are not entering the OLE period.
- They were randomized to ocrelizumab (Group A) and they have discontinued treatment in the double-blind period but they have not yet reached 48 weeks after last dose of ocrelizumab received. These patients will be followed for the remainder of the required 48-week SFU.
- They have discontinued from OLE period (see Section 3.1.3)
- They have completed the OLE period (i.e., 144 weeks, or longer if the OLE is extended (see Section 3.1.3).

Patients initially treated with fingolimod (Group B) who are not entering the OLE period will not enter the SFU period and will perform an end of study visit.

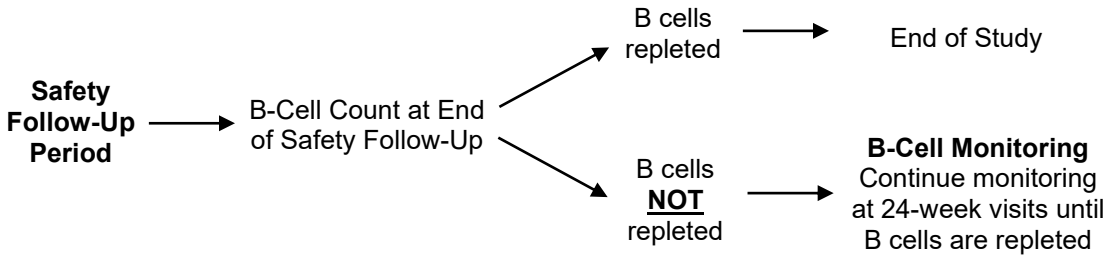
SFU visits will be performed at 12-week intervals starting from the date of the last infusion of ocrelizumab. Efficacy and safety assessments will be collected as outlined in Table 3 of Appendix 1.

If after the SFU, the peripheral blood B-cells remain depleted, the patient should continue to be monitored at 24-week intervals until the B-cell count has returned to the baseline value or to the age-specific 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, see Section 3.1.5 for recommendation.

Patients who receive MS therapies that may change B-cell levels during the SFU period will not enter into the prolonged B-cell monitoring period thereafter (Figure 2).

Figure 2 Safety Follow-Up (including B cell monitoring)



Note: Patients who receive multiple sclerosis therapies that may change B-cell levels during the safety follow-up will not enter into the prolonged B-cell monitoring period thereafter.

3.1.5 Use of Alternative Multiple Sclerosis Treatment after Study Treatment Discontinuation

The decision to initiate an alternative treatment for MS (including commercial ocrelizumab and commercial fingolimod) after study treatment discontinuation will be at the discretion of the treating investigator.

Patients initiating an alternative MS treatment during the double-blind period will remain in the double-blind period and will continue to be followed up for both efficacy and safety with the schedule of assessments as outlined in Table 4 of Appendix 1, until the end of the double-blind period (see Section 3.1.2). Patient level data will be kept blinded until completion of the primary analysis, as indicated above.

Patients discontinuing study treatment during the OLE period will enter the SFU period, where the initiation of an alternative treatment may be decided at the discretion of the treating investigator (see Section 3.1.4).

When switching from ocrelizumab or from fingolimod to another immune-modulating or immunosuppressive alternative treatment for MS, the duration of ocrelizumab and fingolimod effects and their mode of action should be considered to avoid unintended additive immunosuppressive effects.

Since sufficient data are not available to inform risks associated with switching from ocrelizumab to other products, caution is advised while patients remain B-cell depleted. There is an unknown safety risk of administering DMTs for MS after discontinuation of ocrelizumab. Therefore, certain treatments for MS such as lymphocyte-depleting agents or lymphocyte-trafficking blockers (e.g., alemtuzumab, natalizumab, fingolimod, dimethyl fumarate, cyclophosphamide, and azathioprine) are strongly discouraged for as long as the patient remains B-cell depleted due to unknown effects on the immune system (e.g., increased risk, incidence, or severity of infection).

Severe increase in disability accompanied by multiple new lesions on MRI has been reported in the post-marketing setting after discontinuation of fingolimod.
Patients should be monitored for development of severe increase in disability following discontinuation of fingolimod and begin appropriate treatment as needed. Refer to the prescribing information of fingolimod for more details, and to Section 3.1.3.

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

3.1.6 Study Committees

3.1.6.1 Independent Pediatric Multiple Sclerosis Review Committee

An independent review to confirm the diagnosis of pediatric RRMS will be performed by independent experts prior to any enrollment. The detail of this review process will be described in a charter.

3.1.6.2 Steering Committee

An external Steering Committee will provide general guidance, assist with liaison to Investigators, and oversee any external communication of the results of the study. The detail of this committee will be described in a charter. The external Steering Committee will stay blinded to all data until the primary analysis and communication from the Sponsor.

3.1.6.3 Independent Data Monitoring Committee

An external iDMC will be instituted to further protect the well-being of patients in the study. The iDMC will review safety data throughout the study until completion of the primary analysis, and review the interim analyses if an interim efficacy analysis is conducted. After the Sponsor is unblinded for the primary analysis, iDMC involvement in safety monitoring throughout the OLE period is no longer needed. The conduct of the iDMC will be detailed in the iDMC Charter.

3.1.7 Patient Input into Study Design

Representatives from the patient community (teenage patients and their caregivers) and an organization within the patient community were interviewed, attended an advisory board meeting and/or attended a focus group meeting. The representatives were asked to provide feedback on the following aspects of the study:

- Study design, including number and length of visits, study assessments (e.g. MRI, PROs/ObsROs, blood draws) and study drug administration requirements (IV infusion and oral capsule, and frequency of administration)
- Recruitment and retention aspects, including potential recruitment challenges, possible retention challenges, how to support study participation (such as mobile nursing), study branding design and messaging to patients

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 or B-cell monitoring period of the SFU, whichever is later, or when the Sponsor decides to discontinue the study or development program in pediatric MS.

The total length of the study for patients, from screening to the end of the SFU, will vary from patient to patient because of the flexible duration of the double-blind treatment period, which depends on each patient's time point of inclusion during the enrollment period.

3.3 DURATION OF PARTICIPATION

The total length of the study for patients, from screening to the end of the SFU, will vary from patient to patient because of the flexible duration of the double-blind treatment period, which depends on each patient's time point of inclusion during the enrollment period.

3.4 RATIONALE FOR STUDY DESIGN

3.4.1 Rationale for the Use and Choice of Active Comparator

There is consensus in the MS community that the use of placebo in Phase III studies of pediatric patients with MS is ethically indefensible, due to the availability of effective therapies approved in adult patients with MS used off-label in the pediatric population (Rose and Müller 2016; Waubant et al. 2019).

Furthermore, the registration of fingolimod on the basis of level 1A evidence demonstration of its superiority vs. interferon in pediatric MS (Chitnis et al. 2018) has effectively closed the option to use placebo as comparator in pediatric MS studies, making fingolimod a natural active comparator of choice for future development in this indication.

3.4.2 Rationale for Flexible Duration of the Double-Blind Treatment Period

Pediatric trials can take an inordinate amount of time to complete because much of the time is spent in the enrollment phase. A fixed duration study design, where all patients are followed up for the same amount of time, will require both a large sample size and consequently longer total study duration.

In a flexible study duration setting, where all patients stay in the study until the primary data read-out (from double-blind, double-dummy comparative treatment period), the trial will gain more statistical power to test the treatment effect, and thus require a smaller sample size and shorter total study duration. A shorter trial ensures that the research question the trial has been designed to test can be answered quicker and new treatments could be offered to patients sooner.

Furthermore, a flexible duration study design will enable collection of long-term safety and efficacy data from individual patients.

From a patient perspective, the only difference between a flexible duration design and a fixed duration design is in the duration of the double-blind, double-dummy comparative treatment period, which will last longer for most of the patients (i.e., up to 3 years for the first recruited patients in case of a 30-month recruitment period). However, since the study drug, ocrelizumab, is only administered every 24 weeks, and the active comparator, fingolimod, is an oral daily treatment, the inconvenience for patients resulting from a longer double-dummy period duration is anticipated to be minor.

3.4.3 Rationale for Optional Open-Label Extension Period

MS is a disease that requires chronic DMT in order to control disease activity and reduce disability progression. The OLE period will assess longer-term safety and tolerability and further explore efficacy of ocrelizumab (comparison of patients treated with ocrelizumab during the double-blind treatment period with patients switching to ocrelizumab only after the end of the double-blind treatment period) in this young population with RRMS.

3.4.4 Rationale for Safety Follow-Up 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 SFU period for 48 weeks after stopping ocrelizumab. Patients 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 for at least 48 weeks and 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.

3.4.5 Rationale for B cells as Pharmacodynamic Marker

Ocrelizumab selectively depletes CD20 expressing B cells; therefore, blood CD19-expressing B-cell count will be measured as the PD marker of action.

3.4.6 Rationale for Biomarker Assessments

Neurofilament light chain, an acute neuronal injury marker, has been correlated with Gd–enhancing MRI lesions and clinical relapses (Burman et al. 2014) and with response to drug treatment in progressive multiple sclerosis (PMS) and RMS (Gunnarsson et al. 2011; Axelsson et al. 2014, Kuhle et al. 2019). NfL can be detected in the blood, and blood levels are correlated with cerebrospinal fluid level, making NfL an attractive non-invasive biomarker to assess neuronal injury in MS (Disanto et al. 2017). In addition, NfL is prognostic for worse disability outcome in RMS and PPMS (Bar-Or A et al. 2019; Kuhle et al. 2019).

NfL, in addition to other possible markers, may be used to assess the patient's disease activity, and/or as a PD, prognostic, or predictive biomarker(s) for disease progression and/or to assess drug activity, efficacy, safety, or MS pathogenesis.

3.4.7 *Rationale for Collection of Information on Race and Ethnicity*

Data pertaining to participant race and ethnicity represents a component of the broad demographic profile of the study population. Collection of demographic data, including information on race and ethnicity, is of importance to the future interpretation of results from the clinical trial, including identification of potential differences in efficacy, safety, and pharmacokinetics among participants. Collection of race and ethnicity data may enable investigation of potential relationships between biomarkers and race or ethnicity, including determination of whether race or ethnicity could be a prognostic factor. Collection of these data may also contribute to a better understanding of the distribution of MS according to race or ethnicity.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately one hundred and seventy-one patients with RRMS are planned to be enrolled in this 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 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 (e.g., SDMT or questionnaires) due to physical/disease limitations will not be excluded from the study.
- Age between $\geq$ 10 to $<$ 18 years at randomization
- Body weight $\geq$ 25 kg
- Children and adolescents must have received all childhood vaccinations as per local and/or national recommendations for childhood vaccination against infectious diseases.
- Patients negative for serological testing for varicella zoster (Section 4.1.2.5) will have the full course of the vaccine for chickenpox completed before study starts, except patients who have already received the full course of the vaccine for chickenpox, depending on local regulations.
- 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/ocrelizumab placebo and for 2 months after the final dose of fingolimod/fingolimod placebo (see Section 5.1.5). Adherence to local requirement, if more stringent, is required.

A female is considered to be of childbearing potential if she is postmenarchal 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 Multiple Sclerosis

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, or McDonald criteria 2017 (or the most current revision of the IPMSSG criteria or McDonald criteria at the time of study start)
- Confirmation of the diagnosis of Pediatric RRMS by the Independent Pediatric MS Review Committee prior to randomization
- EDSS at screening: 0–5.5, both inclusive
- Disease activity, as defined by the following:

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

- For all countries except Germany: At least one relapse during the year prior to screening or two relapses in the previous two years prior to screening or evidence of at least one Gd-enhancing lesion on MRI within 6 months prior to randomization (including screening MRI)

  Note: If a new MRI is required for re-screening, a new or enlarging T2 lesion compared to the previous screening MRI is sufficient to fulfill the inclusion criteria of recent disease activity even without gadolinium enhancement, provided that both MRIs are done within 6 months prior to randomization.

- For Germany: Highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy, or patients with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with at least one Gadolinium enhancing lesion on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI

4.1.2 Exclusion Criteria

While participating in this 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 neurological (other than MS), somatic, or metabolic condition that could interfere with brain function or normal cognitive or neurological development
- In case of an ADEM like appearance of the first MS relapse, a second relapse with clear MS like features is required.
- Patients that are aquaporin-4 (AQP-4) positive and/or myelin oligodendrocyte glycoprotein (MOG) antibody positive at screening

- Clinical or laboratory findings at first presentation not typically for MS, such as signs of infection; signs of encephalopathy such as confusion, convulsion, reduced state of consciousness.
- Abnormal findings in the cerebrospinal fluid (CSF) at first MS presentation. Protein >100 mg/dL. Pleocytosis >50 cells/mm^3. Presence of neutrophils or eosinophils above the normal reference range per local laboratory, or atypical cells.

  Note: CSF sampling is not mandated at screening and may be performed at investigator discretion to confirm diagnosis of pediatric RRMS.
- 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 uncontrolled somatic diseases or any other significant condition that may preclude patient 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 Day 1 visit or oral anti-infective agents within 2 weeks prior to Day 1 visit
- History or known presence of recurrent or chronic infection (e.g., HIV, syphilis, tuberculosis)
- Receipt of any type of vaccine (e.g., live or live-attenuated, non-live) within 6 weeks prior to treatment allocation. The patient's vaccination record and a need for immunization should be carefully reviewed (scheduled vaccinations, as per local guidelines, should be completed at least 6 weeks prior to receiving ocrelizumab).
- History or laboratory (local laboratory test) evidence of clinically significant coagulation disorders (e.g., any coagulation disorder requiring medical treatment).
- 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, claustrophobia, hypersensitivity to gadolinium, cochlear implants, presence of foreign substances in the eye, or intracranial vascular clips)
- Teeth braces interfering with MRI acquisition (see Section 4.6.5 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 Exclusion Criteria Related to General Health Specific to Fingolimod Treatment

Patients who meet any of the following criteria related to general health specific to fingolimod treatment will be excluded from study entry (for more information also refer to the prescribing information):

- History of symptomatic bradycardia, recurrent syncope, significant QT prolongation (corrected QT interval [QTc] $>$460 msec [pediatric female] or $>$450 msec [pediatric male]), patients having risk factors for QT prolongation such as hypokalemia or congenital QT prolongation, and uncontrolled hypertension
- Patients who in the previous 6 months had myocardial infarction, unstable angina pectoris, stroke/transient ischemic attack, decompensated heart failure (requiring inpatient treatment), or New York Heart Association Class III/IV heart failure
- Patients with severe cardiac arrhythmias requiring anti-arrhythmic treatment with Class Ia or Class III anti-arrhythmic medicinal products.
- Patients with second-degree Mobitz type II atrioventricular (AV) block or third−degree AV block, sick-sinus syndrome, or sinoatrial heart block
- Patients with a baseline QTc interval $\geq$500 msec
- Presence of macular edema
- Presence of any pulmonary conditions, as determined by the investigator, including severe asthma defined as per the 2010 WHO uniform definition on severe asthma (Bousquet et al. 2010)
- History of any type of epileptic seizure(s) as well as psychogenic non-epileptic seizure(s) during the past 12 months before screening
- Patients with any of the following hepatic conditions
  - Chronic liver or biliary disease, acute or chronic pancreatitis, with the exception of Gilbert's syndrome
  - Liver enzymes, as per criteria listed in Section 4.1.2.5.

4.1.2.3 Exclusion Criteria 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 well 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
- Previous treatment with any other immunomodulatory or immunosuppressive medication not already listed above without appropriate washout as described in the applicable local label (washout to be completed prior to baseline). If the washout requirements are not described in the applicable local label, then the wash out period must be at least five times the half-life of the medication. The PD effects of the previous medication must also be considered when determining the required time for washout.
- Treatment with natalizumab within 12 months prior to randomization
- Treatment with teriflunomide within 24 weeks prior to treatment allocation of patients who have not completed an accelerated washout procedure or treatment with teriflunomide within 4 weeks prior to treatment allocation of patients who have completed an accelerated washout procedure and do not have confirmation of drug plasma level of <0.02 mg/L
- Previous treatment with fingolimod
- 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 intravenous immunoglobulin within 12 weeks prior to treatment allocation
- Treatment with plasmapheresis within 4 weeks prior to treatment allocation
- Completion of systemic corticosteroid therapy within 7 days prior to treatment allocation

4.1.2.4 Exclusion Criteria Related to Medications Specific to Fingolimod Treatment

Patients who meet any of the following criteria related to medications specific to fingolimod treatment will be excluded from study entry (for more information also refer to the prescribing information):

- History of a severe allergic reaction or known hypersensitivity to any component of fingolimod tablet
- Patients treated with heart-rate-lowering drugs (e.g., beta blockers); heart-rate lowering calcium channel blockers (e.g., verapamil, diltiazem, or ivabradine)
- Patient treated with digoxin, anticholinesteratic agents, pilocarpine
- For all countries except Germany: Patients treated with anti-arrhythmic drugs of Class Ia (e.g., quinidine, disopyramide) and III (e.g., amiodarone, sotalol) due to their association with torsade de pointes in patients with bradycardia.

- For all countries except Germany: Patients treated with medication that may prolong QTc interval and who have relevant risk factors, such as hypokalemia or congenital QT prolongation
- For Germany: Patients treated with drugs that may prolong the QTc interval and those patients who have relevant risk factors for QTc prolongation and torsade de pointes arrhythmias, such as hypokalemia or congenital QT prolongation. Class IA (e.g., quinidine or disopyramide) and class III (e.g., sotalol or amiodarone) antiarrhythmics, among others, are at high risk of prolonging the QTc interval. It is the duty of the study physicians to check the respective product information for any concomitant medication to see whether the concomitant medication is associated with such a risk.

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.

4.1.2.5 Exclusion Criteria 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
- Positive serological testing for MOG antibody
- Positive serological testing for AQP-4 antibody
- Positive serological testing for HIV (except where national or local regulations do not allow this testing)
- Positive serological testing for tuberculosis (active or latent) (except where national or local regulations do not allow this testing)
- Negative serological testing for varicella zoster (in case of a negative test, vaccination should be considered for study eligibility, except patients who have already received the full course of the vaccine for chickenpox, depending on local regulation)
- Percentage of CD4 $<$ 30% (central laboratory age-specific reference range %CD4: 35%–57%).
- 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 (or 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
- Liver enzymes:

  ALT, AST, alkaline phosphatase, γ-glutamyl transferase (GGT): $> 2 \times$ upper limit of normal (ULN; as per central laboratory for age- and sex-specific reference range) range for age (for pre-pubertal patients $> 1 \times$ ULN or $> 2 \times$ ULN if currently treated with interferon or GA). Elevations of alkaline phosphatase should not be used in isolation to exclude subjects, and would require investigator discretion.

  Bilirubin elevations not in the context of Gilberts Syndrome: Total and conjugated bilirubin $> 1.5 \times$ ULN (for pre-pubertal patients $> 1 \times$ ULN or $> 1.5 \times$ ULN if currently treated with interferon or GA).

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

4.1.3 Eligibility Criteria for Optional Open-Label Extension Period

Patients who complete the double-blind period will be offered the possibility to enter an optional OLE period with ocrelizumab (Section 3.1.3).

Patients who have discontinued from the study during the double-blind period are not eligible for the OLE period.

Patients in Group A (ocrelizumab in the DBP) who meet the following criteria may participate in the OLE period:

- Must have completed the double-blind period with study treatment (ocrelizumab), and who, in the opinion of the investigator, may benefit from continuing treatment with ocrelizumab
- Be willing to comply with the contraception requirements as described in Sections 4.1.1 and 5.1.5
- Meet re-treatment criteria with ocrelizumab (Section 4.3.3)

Patients in Group B (fingolimod in the DBP) who meet the following criteria may participate in the OLE period:

- Must have completed the double-blind period with study treatment (fingolimod) and who, in the opinion of the investigator, may benefit from switching to ocrelizumab. As per Section 3.1.3, a careful evaluation of the benefit-risk of switching study

treatment from fingolimod to ocrelizumab treatment must be performed for each patient by the treating investigator based on:

  - the radiological and clinical MS disease course under fingolimod treatment during the double-blind period
  - prior patient medical history, comorbidity, and concomitant medications
  - social environment conditions

- This should be discussed with the parents or a legal guardian and patient in advance to allow sufficient time for a final decision.
- Absence of active infection and no signs of alternative causes for low lymphocyte count (other than fingolimod treatment). Of note, prior blinded lymphocytes count (incl. CD4) during the double-blind period will be unblinded and be made available to the treating investigator.
- The following laboratory-related eligibility criteria:
  - Lymphocyte count > 0.2 x 10^3 cells/μL
  - ANC (or neutrophil count) ≥ 1.5 x 10^3/μL
  - 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

The laboratory samples to assess eligibility to OLE Dose 1 Day 1 ocrelizumab infusion should be collected within 4 weeks from the OLE Dose 1 Day 1 infusion visit, to ensure that the laboratory samples reflect the current condition of the patients. Similarly, the re-treatment criteria for OLE Dose 1 Day 15 infusion should be assessed based on laboratory samples that are collected within 4 weeks from the OLE Dose 1 Day 15 infusion visit. This is in line with the way visit windows were defined during the double-blind treatment period.

As long as the above criteria are met, the treating investigator will decide when the best timing is to initiate ocrelizumab treatment (with a minimum of 5 days washout after discontinuation of fingolimod).

The above criteria can be re-evaluated. If within 8 weeks after the discontinuation of fingolimod, patient is still not eligible to enter the OLE, patient should be permanently discontinued from the study. A further extension of these 8 weeks could be granted (based on clinical, administrative, or operational reasons) with prior approval from the sponsor.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a randomized, double-blind study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and

eligibility has been confirmed for a patient, the study site will obtain the patient's identification number and treatment assignment from an IxRS. Eligible patients must be randomized through IxRS prior to receiving any study medication. Patients who discontinue treatment for any reason will not be replaced. Patients will be randomly assigned to one of two treatment arms: ocrelizumab plus fingolimod placebo (Group A) or fingolimod plus ocrelizumab placebo (Group B) (see Section 3.1.2). Randomization will occur in a 1:1 ratio using a permuted-block randomization method to ensure a balanced assignment to each treatment arm.

Randomization will be stratified according to the following factors:

- Region (United States or ROW)
- Pre-pubertal status (yes vs. no)
- T1 Gd lesions at baseline (yes or no)

Note: Pre-pubertal status is defined as a Tanner stage score <2.

4.2.2 Blinding

This study will be performed in a double-blind, double-dummy fashion. Randomization and blinding will be employed to minimize bias in treatment assignment and to provide the basis for valid statistical inference. The randomization list will be blinded and will remain blinded until the end of the double-blind period, i.e., until the time of the primary analysis (as defined in the SAP).

Patients, parents/legal guardians, investigators, and the sponsor will remain blinded to the original (randomized) treatment allocation of all patients until the primary analysis is completed and the primary results are available and communicated by the Sponsor. See Sections 4.2.3, 4.6.5, and 4.6.18 for additional measures.

To maintain integrity of the trial results and to prevent potential unblinding of the assigned arm during the double-blind period as a result of adverse events or changes to laboratory results, several additional measures will be implemented until the time of the primary analysis, including a "dual assessor approach" (i.e., two blinded investigators per site: a treating investigator and an examining investigator) and an independent physician for the supervision of the first administration of study treatments; see Section 4.2.3 for details and definitions. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, IxRS service provider, iDMC members and sample handling staff at the external analytical laboratory facilities (not at sites).

Note: While PK and ADA samples will be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK and ADA assay

results for these patients are generally not needed for the safe conduct or proper interpretation of this study. Therefore PK and ADA samples from patients assigned to the comparator arm will not be analyzed except on request (e.g., to evaluate a possible error in dosing).

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

Prior to provision of treatment allocation information after the primary analysis, if the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly prior to unblinding. The investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to patient unblinding, the investigator will be able to break the treatment code by contacting the IxRS.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the investigator, patient, parent/legal guardian, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

4.2.3 Conduct of Procedures during the Double-Blind, Double-Dummy Treatment Period

This is an assessor blinded study.

To maintain the blind throughout the double-blind, double-dummy period, each site will have three independent physicians: a blinded independent physician, a blinded principal or treating investigator, and a blinded examining investigator or rater. These physicians should keep the same predefined role during the double-blind period for all patients enrolled at their site (refer to the study site blinding plan for more details). These roles are distinct and must be performed by three different physicians.

During the double-blind period, treating investigator/site staff at a single site may not be a treating investigator for some patients and an examining investigator for others.

- **The independent physician** is not involved in patient care; his or her role is to supervise the first dose of study treatments, i.e., fingolimod/fingolimod placebo and ocrelizumab/ocrelizumab placebo to ensure that blinding is not compromised by the

known lowering of the heart rate on fingolimod treatment initiation and the occurrence of IRR with the first doses of ocrelizumab (see Section 4.3.2.2.3).

This role will also apply at fingolimod/placebo re-start or if the oral dose of fingolimod/placebo is increased.

The independent physician should be experienced in making clinical decisions based on ECG interpretations and will be responsible for the clinical monitoring of the patient until discharge, including review and recording of vital signs, ECG findings, and adverse events. Although the assessments may be performed by a delegate (e.g., study nurse), review and interpretation of assessments must be performed by the physician. The independent physician will determine patient suitability for discharge and/or decide whether additional monitoring is needed (see Section 4.3.2.2.3).

The independent physician must ensure that the patient, parents/legal guardian, and treating investigator do not have access to or are informed of events occurring at first dose and at fingolimod/fingolimod placebo re-start to avoid unblinding of the patient, parents/legal guardian, or site personnel, unless this is medically warranted.

To maintain the blind, the independent physician can be supported by site staff (e.g., a nurse or other health care professional as appropriate) who are not otherwise involved in the patient care.

To help maintain the blind throughout the double-blind period, a site blinding plan is available and should be carefully read before the study starts.

- **The treating investigator**, who may be the Principal Investigator, is the physician responsible for the patient care and should be a neurologist experienced in the care of pediatric patients with MS. The treating investigator is responsible for patient clinical care and management throughout the study, with the exception of first dose monitoring and re-initiation of fingolimod/fingolimod placebo treatment. The treating investigator will have access to safety and blinded efficacy data, will perform the neurologic examination, and will make treatment decisions based on the patient's clinical response and laboratory findings (see Section 4.6.5 and Section 4.6.18).
- **The examining investigator** should be a neurologist or other health care practitioner experienced in the care of pediatric patients with MS and must be trained and certified in administering the Neurostatus Functional System (FS) scores and EDSS examination prior to study start.

  The examining investigator will perform and document the FS scores, and assess EDSS scores independently (Section 4.6.3). The examining investigator or a qualified designee will also be responsible for performing and documenting results from the SDMT (Section 4.6.15). They will only have access to data from the assessments listed above (i.e. EDSS and SDMT). Results of the neurologic examination (or anything related to patient health) and EDSS scores will not be shared between the treating and examining investigator.

Every effort will be made to ensure that there is no change in the EDSS rater throughout the course of the study for any individual patient. Whenever possible, the same person should perform the examination for the full study duration.

All efforts should be made to keep the examining investigator blinded to the treatment assignment during the double-blind, double-dummy treatment period. Patients and parents/legal guardians will be instructed not to discuss any symptoms related to the study treatment with the examining investigator; the examining investigator should remind the patient at the start of the examination. In view of the extended duration of this study, it is recommended to identify a primary and back-up for the treating and examining investigator.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are ocrelizumab/ocrelizumab placebo and fingolimod/fingolimod placebo.

The non-investigational medicinal products (NIMPs) for this study will include premedications for ocrelizumab/ocrelizumab placebo infusion, as follow:

- Mandatory methylprednisolone (or an equivalent)
- Mandatory antihistamine drug (e.g., diphenhydramine)
- Recommended oral analgesic/antipyretic (e.g., acetaminophen)

Refer to Section 4.3.2.1.5 for further details on premedication administration.

Appendix 6 identifies all IMPs and auxiliary medicinal products for this study.

4.3.1 Study Treatment Formulation and Packaging

During the double-blind treatment period, all patients will take a daily capsule of fingolimod or fingolimod placebo. In addition, they will be administered an IV infusion of ocrelizumab or ocrelizumab placebo on Day 1 and Day 15 and every 24 weeks thereafter.

Study drug packaging will be overseen by the Roche clinical trial supplies department and bear a label with the identification required by local law, the protocol number, drug identification and dosage.

The packaging and labeling of the study medication will be in accordance with Roche standards and local regulations.

Upon arrival of investigational products at the site, site personnel should check them for damage and verify proper identity, quantity, integrity of seals, and temperature conditions, and report any deviations or product complaints to the monitor upon discovery.

4.3.1.1 Ocrelizumab and Ocrelizumab Placebo

Ocrelizumab will be supplied by the Sponsor as a sterile, clear or slightly opalescent, and colorless to pale brown solution supplied as a single-use formulation containing 30 mg/mL ocrelizumab in 20 mM sodium acetate, 106 mM trehalose dihydrate and 0.02% (w/v) polysorbate 20 at pH 5.3. The drug product is supplied at a volume of 10.0 mL in a 15 mL glass vial.

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 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/ocrelizumab placebo vials are stable at 2°C–8°C (refrigerated storage) and must be stored refrigerated until use.

Ocrelizumab/ocrelizumab placebo vials should not be frozen or shaken and should be protected from light during storage.

Ocrelizumab placebo is presented in the identical vial with the same fill volume and formulation components (20 mM sodium acetate at pH 5.3, with 106 mM trehalose dihydrate and 0.02% polysorbate 20), but does not contain ocrelizumab.

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

For more details regarding study drug preparation, storage, and handling, see the Study WN42086 study drug manual.

4.3.1.2 Fingolimod and Fingolimod Placebo

Fingolimod will be supplied by the Sponsor as 0.25 mg or 0.5 mg capsules in bottles/blisters.

The marketed product is modified to ensure blinding of fingolimod and placebo capsules by over-encapsulating original capsules.

The hospital units and/or pharmacy will receive study medication kits for each patient.

To reduce the burden to the participant and their family of having to attend the study site to collect the additional medication and maintain treatment compliance, fingolimod/fingolimod placebo kits may be delivered to the participant at their home address. The sponsor will contract a courier service to provide a temperature-controlled delivery of fingolimod/fingolimod placebo to the participant. The study site will remain responsible for dispensing of the kits via the IxRS. The courier will collect the dispensed medication from the study site and be responsible for completing the delivery. This will

be an optional service available to the participant and their family, where approved according to local regulations.

Fingolimod placebo capsules are presented in identical form and packaging as the active capsules, but do not contain fingolimod.

For information on the formulation of fingolimod, refer to the prescribing information.

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

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1. All study treatments (except premedications) required for completion of this study will be provided by the Sponsor.

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration eCRF. Cases of accidental overdose, and error in drug administration along with any associated adverse events, should be reported as described in Section 5.3.5.13.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

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

Study treatments will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied study treatments must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied study treatments are destroyed, and study treatment destruction must be documented on the appropriate form.

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

Refer to the study drug manual for information on study treatment handling, including preparation and storage, and accountability.

4.3.2.1 Ocrelizumab and Ocrelizumab Placebo

Patients randomized to active fingolimod group will also receive ocrelizumab placebo during the double-blind, double-dummy treatment period.

For patients with a body weight <35 kg: Patients will be administered IV infusions of 300 mg ocrelizumab/ocrelizumab placebo every 24 weeks. The first dose of ocrelizumab/ocrelizumab placebo will be administered as two 150 mg IV infusions given 14 days apart. For the subsequent doses, ocrelizumab/ocrelizumab placebo will be administered as a single dose of 300 mg IV infusion every 24 weeks.

For patients with a body weight ≥35 kg: Patients will be administered IV infusions of 600 mg ocrelizumab/ocrelizumab placebo every 24 weeks. The first dose of ocrelizumab/ocrelizumab placebo will be administered as two 300 mg IV infusions given 14 days apart. For the subsequent doses, ocrelizumab/ocrelizumab placebo will be administered as a single dose of 600 mg IV infusion every 24 weeks.

Patients initially assigned to 300mg dose and who reach a body weight of $\geq$35 kg during the study should be switched to the 600mg dose at their next infusion visit. This subsequent dose will be administered as two infusions of half the dose 14 days apart.

A minimum interval of 22 weeks must be maintained between each full dose.

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).

4.3.2.1.1 Preparation of Infusion Bags with Ocrelizumab/Ocrelizumab Placebo

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

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

Evacuated glass containers must not be used to prepare the infusion solution because these containers require vented administration sets that cause foaming as air bubbles pass through the solution.

The ocrelizumab/ocrelizumab placebo 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/ocrelizumab placebo 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 for up to 8 hours at room temperature. The ocrelizumab/ocrelizumab placebo 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.

Specific instructions are provided separately in the WN42086 study drug manual and must be followed exactly.

4.3.2.1.2 Monitoring Prior to and During Infusions with Ocrelizumab/Ocrelizumab Placebo

All patients should receive premedications before any infusion of ocrelizumab/ocrelizumab placebo (for detailed information see Section 4.3.2.1.5).

Procedures on first administration of study treatment with ocrelizumab/ocrelizumab placebo and fingolimod/fingolimod placebo at the Day 1 visit should be followed as outlined in Section 4.5.3.

12-Lead ECG

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 4.6.12.

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 until 1 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 physician in charge of supervising the infusion in the event of an IRR or if clinically indicated.

Further details are provided in Section 4.6.13.

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

4.3.2.1.3 Dosage and Infusion Procedures with Ocrelizumab/Ocrelizumab Placebo

It should be noted that:

- The dose of ocrelizumab/ocrelizumab placebo 600 mg is only for patients with a body weight ≥35 kg.
- Patients with a body weight < 35 kg will receive ocrelizumab/ocrelizumab placebo 300 mg.

Precautions with Each Infusion

Prior to the start of the infusion, the content of the bag must be at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.

Ocrelizumab/ocrelizumab placebo should be administered as an IV infusion through a dedicated line under the close supervision of the physician with access to appropriate medical support to manage severe reactions such as serious IRRs. The infusions should not be administered as an intravenous push or bolus.

It is recommended to schedule all infusion visits in the morning to allow enough time to perform all assessments as per the schedule of activities (Appendix 1) and to allow the patient to stay at the hospital (or infusion center) with medical supervision and monitoring as required, and for 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. This is important for the first infusion visit (Day 1 of Dose 1) as the occurrence of IRRs is higher with the first dose.

Patients may be hospitalized for a 24-hour observation after completion of the infusion at the discretion of the physician in charge of supervising the infusion.

It should be noted that 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), it will not be considered as a serious adverse event (see Section 5.3.5.12).

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 patients and parents/legal guardians 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.

For more information, refer to the study drug manual.

For patients with a body weight ≥35 kg:

Initial 600 mg Dose (Dose 1) as Two Infusions of Half the Dose 14 Days Apart

The initial 600 mg dose is administered as two separate IV infusions; first as 300 mg (Day 1), followed 2 weeks later by a second 300 mg (Week 2).

Subsequent 600 mg Doses

Subsequent doses of ocrelizumab/ocrelizumab placebo thereafter are administered as a single 600 mg IV infusion every 24 weeks (see Table 2).

Table 2 Dose and Schedule of 600 mg Ocrelizumab/Ocrelizumab Placebo for Patients ≥ 35 kg

Dose		Amount to be Administered	Infusion Instructions
1st Dose (600 mg); administered as 2 separate IV infusions of 300 mg each	Day 1 Infusion	300 mg in 250 mL	• Initiate the infusion 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. • Each infusion should be given over approximately 2.5 hours.
	Day 15 Infusion	300 mg in 250 mL	
2nd Dose (600 mg)	Week 24 Infusion	600 mg in 500 mL	• Initiate the infusion 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. • Each infusion should be given over approximately 3.5 hours.
Subsequent Doses (600 mg)	Every 24 Weeks	600 mg in 500 mL	

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

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

For patients with a body weight < 35kg:

Initial 300 mg Dose (Dose 1) as Two Infusions of Half the Dose 14 Days Apart

The initial 300 mg dose is administered as two separate IV infusions; first as 150 mg (Day 1), followed 2 weeks later by a second 150 mg (Week 2).

Subsequent 300 mg Doses

Subsequent doses of ocrelizumab/ocrelizumab placebo thereafter are administered as a single 300 mg IV infusion every 24 weeks (see Table 3), until the patient reaches at least 35 kg. Once the patient reaches at least 35 kg, the patient will switch to the 600 mg dosing regimen and the first 600 mg dose will be administered as two infusions of half the dose 14 days apart to mitigate the risk and severity of IRRs (see Table 2).

Table 3 Dose and Schedule of 300 mg Ocrelizumab/Ocrelizumab Placebo for Patients < 35 kg

Dose		Amount to be Administered	Infusion Instructions
1st Dose (300 mg); administered as 2 separate IV infusions of 150 mg each	Day 1 Infusion	150 mg in 250 mL	• Initiate the infusion 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. • Each infusion should be given over approximately 2.5 hours.
	Day 15 Infusion	150 mg in 250 mL	
2nd Dose (300 mg)	Week 24 Infusion	300 mg in 250 mL	• Initiate the infusion at a rate of 30 mL/hr.

Subsequent Doses (300 mg)	Every 24 Weeks	300 mg in 250 mL	• Thereafter, the rate can be increased in 30 mL/hr increments every 30 minutes to a maximum of 180 mL/hr. • Each infusion should be given over approximately 2.5 hours.

Infusions Schedule

For the first dose (i.e., Dose 1) of ocrelizumab/ocrelizumab placebo, which is divided as two infusions of half the dose, a minimum interval of 20 weeks should be maintained between Day 15 of Dose 1 and the next infusion of Dose 2 at Week 24.

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

If for logistical reasons a subsequent (i.e., at Weeks 2, 24, 48, or 72) ocrelizumab/ocrelizumab placebo infusion cannot be administered on the scheduled study visit day, the infusion should be given within the time window of the respective dosing visit as indicated in Appendix 1 (see Section 4.3.3).

The treating investigator must verify that all re-treatment criteria, including safety laboratory parameters, are met before allowing the infusion of ocrelizumab/ocrelizumab placebo to proceed. Refer to Section 4.3.3 for relevant information relating to criteria for re-treatment with study treatment.

Patients who cannot receive their infusion within the time window of a scheduled infusion visit should be re-scheduled for a delayed dosing visit.

4.3.2.1.4 Delayed Dosing Visit with Ocrelizumab/Ocrelizumab Placebo

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 treating 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.

If a scheduled dosing visit cannot occur within the scheduled visit time window or if an infusion cannot be administered as planned, a delayed dosing visit should be scheduled as soon as possible.

If the second infusion of Dose 1 is delayed, a minimum of 20 weeks should be kept between this infusion and the next infusion of Dose 2.

For Dose 2 and all subsequent doses, a minimum interval of 22 weeks between the delayed dose and subsequent dose should be maintained.

The next visits will be scheduled with reference to the date of this delayed dosing visit, rather than in reference to the Day 1 visit (see Section 4.5).

Of note, MRI assessments will keep the same schedule, as described in Section 4.6.5.

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.

To ensure that patients meet re-treatment criteria (see Section 4.3.3), an unscheduled site visit (or unscheduled Mobile Nurse (MN) visit) should be scheduled within 2 weeks in advance of that delayed dosing visit.

Note: If a laboratory assessment for retreatment criteria was performed within the last 4 weeks, there is no requirement to repeat these assessments for the delayed dosing visit.

The treating investigator must verify that all re-treatment criteria (see Section 4.3.3), including safety laboratory parameters, are met before allowing the infusion of ocrelizumab/ocrelizumab placebo to proceed.

A patient who had all assessments of a dosing visit performed, but could not receive the infusion, should be rescheduled for the infusion on another day. At the delayed dosing visit, additional tests or assessments, such as routine safety laboratory tests, may be performed as clinically indicated.

4.3.2.1.5 Premedication for Infusion-Related Reactions

To reduce the frequency and severity of IRRs due to ocrelizumab/ocrelizumab placebo, all patients will be premedicated with IV methylprednisolone and an antihistamine (oral or IV) as described below.

Anti-Histamine 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 IRRs compared with pretreatment with methylprednisolone alone. Therefore, all patients will receive mandatory prophylactic treatment with an anti-histaminic drug (e.g., diphenhydramine) approximately 30–60 minutes before each infusion of ocrelizumab/ocrelizumab placebo 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 anti-histaminic for the treatment or prevention of IRRs should be given appropriate warnings concerning drowsiness and potential impairment of ability to drive or operate machinery.

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

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/ocrelizumab placebo 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).

4.3.2.1.6 Managing Infusion-Related Reactions

Treatment of Infusion Related Reactions

IRRs should be treated symptomatically as per clinical practice, e.g., 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 physician in charge of supervising the infusion.

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 the completion of 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).

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/ocrelizumab placebo treatment may need to be discontinued. The guidance for handling IRRs is provided in Section 5.1.6.2.1.

4.3.2.2 Fingolimod and Fingolimod Placebo

Patients randomized to active ocrelizumab group will also receive fingolimod placebo during the double-blind, double-dummy treatment period.

The first dose of fingolimod/fingolimod placebo will be supervised by an independent physician (see Section 4.2.3) not involved in patient care to ensure that blinding is not compromised by the known lowering of the heart rate on fingolimod treatment initiation.

4.3.2.2.1 Important Administration and Safety Instructions for Fingolimod

The safety profile of fingolimod in pediatric patients is similar to that in adults and the "Warnings and Precautions" for adults therefore also apply to pediatric patients.

Note: An ophthalmological evaluation should be performed at screening and as indicated in Section 4.6.14 and Table 1 of Appendix 1. If patients report visual disturbances at any time while on therapy, evaluation of the fundus, including the macula, should be carried out.

Clinically significant liver injury has occurred in patients treated with fingolimod in the post-marketing setting; therefore, therapy with fingolimod/fingolimod placebo should be interrupted in any patient found to have:

- Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$ ULN (of which $\geq 35\%$ is direct bilirubin) or
- Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with clinical jaundice

The following parameters will be unblinded when they meet the levels required for safety monitoring and for reviewing of re-treatment criteria (see Section 4.6.18.2):

- ALT or AST > 3 x ULN including Hy's Law
- GGT > 5 x ULN

Treatment with fingolimod/fingolimod placebo should not be resumed if a plausible alternative etiology for the signs and symptoms cannot be established, because these patients are at risk for severe drug-induced liver injury.

If elevation of liver enzymes (ALT, AST and/or GGT) reaches $> 5 \times$ ULN, therapy with fingolimod/fingolimod placebo should be interrupted and hepatic monitoring should continue. For patient who are asymptomatic, at the investigator's discretion and with the evaluation by a liver expert, when serum liver enzyme levels return to normal (including

if an alternative cause of the hepatic dysfunction is discovered), fingolimod/fingolimod placebo may be restarted based on a careful benefit-risk assessment of the patient (refer to the fingolimod prescribing information).

Investigators will be notified of their patient's abnormal laboratory. The reflex messages from the central laboratory, together with non-blinded laboratory results, should be carefully reviewed by the treating investigator before continuing with study treatment.

Patients who initiate fingolimod/fingolimod placebo, and patients who reinitiate treatment after discontinuation and meet the rules stated in Section 4.3.2.2.4, require first-dose monitoring (Section 4.3.2.2.3). This monitoring is also recommended when the dose is increased in pediatric patients.

When fingolimod is stopped, symptoms of MS can return and become worse compared to before or during treatment. Many people who have worsening of MS symptoms after stopping fingolimod do not return to the level of function that they had before stopping fingolimod. This worsening happens most often within 12 weeks after stopping fingolimod, but can happen later.

Refer to the prescribing information of fingolimod for more details.

4.3.2.2.2 Recommended Dosage of Fingolimod/Fingolimod Placebo

Patients will take fingolimod/fingolimod placebo PO QD with or without food, preferably at the same time every day.

In pediatric patients 10 years of age and older weighing >40 kg, the recommended dosage of fingolimod is 0.5 mg PO QD.

The first dose of fingolimod should be taken at the clinic to allow for monitoring, as described below.

In pediatric patients 10 years of age and older weighing ≤ 40 kg, the recommended dosage of fingolimod is 0.25 mg PO QD.

During the course of the study any patient receiving the lower fingolimod/fingolimod placebo dose of 0.25 mg who reaches the weight of >40 kg (confirmed over two visits, at least 3 months apart), should be switched to the 0.5 mg dose strength.

4.3.2.2.3 First-Dose Monitoring by a Blinded Independent Physician

As outlined in Section 4.2.3, a blinded independent physician will be involved in the first-dose monitoring of the patients. Other staff (e.g., study nurse) involved in monitoring of the patient during the first dose of fingolimod/fingolimod placebo must also be independent of the main study team.

Initiation of fingolimod treatment may result in a decrease in heart rate and may result in atrioventricular conduction delay, for which monitoring in the clinic for at least 6 hours is mandated as per the prescribing information.

Prior to dosing and at the end of the observation period, an ECG should be obtained from all patients.

First 6-Hour Monitoring

It is recommended to administer the first dose of fingolimod/fingolimod placebo in a setting in which resources to appropriately manage symptomatic bradycardia are available. The patients will be monitored for 6 hours after the first dose for signs and symptoms of bradycardia with hourly pulse and blood pressure measurement.

Additional Monitoring after 6-Hour Monitoring

The monitoring should be continued until the abnormality resolves if any of the following is present (even in the absence of symptoms) after 6 hours:

- The heart rate 6 hours post-dose is <45 bpm in adults (patients 18 years of age at dosing), <55 bpm in pediatric patients 12 years of age and older, or <60 bpm in pediatric patients 10 or 11 years of age;
- The heart rate 6 hours post-dose is at the lowest value post-dose suggesting that the maximum PD effect on the heart may not have occurred;
- The ECG 6 hours post-dose shows new onset second degree or higher AV block.

In the event of post-dose symptomatic bradycardia, the appropriate management will be initiated, begin continuous ECG monitoring, and continue monitoring until the symptoms have resolved if no pharmacological treatment is required. If pharmacological treatment is required, continue monitoring overnight and repeat 6-hour monitoring after the second dose.

Overnight Monitoring

Continuous overnight ECG monitoring in a medical facility should be instituted:

- In patients that require pharmacologic intervention for symptomatic bradycardia. In these patients, the first dose monitoring strategy should be repeated after the second dose of fingolimod/fingolimod placebo;
- In patients with some preexisting heart and cerebrovascular conditions;
- In patients with a prolonged QTc interval before dosing or during 6-hour observation, or at additional risk for QT prolongation, or on concurrent therapy with QT prolonging drugs with a known risk of torsades de pointes;
- In patients receiving concurrent therapy with drugs that slow heart rate or AV conduction.

4.3.2.2.4 Monitoring with Reinitiation of Fingolimod/Fingolimod Placebo Therapy following Interruption (Blinded Independent Physician)

For any patient that has been off oral study medication (fingolimod/fingolimod placebo), the following rules for oral treatment reinitiation should be followed:

- Within the first 2 weeks of treatment, the same monitoring procedure as for the first dose must be performed after interruption of 1 day or more
- During Weeks 3 and 4 of treatment, first-dose procedures must be performed after treatment interruption of more than 7 consecutive days.
- When restarting fingolimod/fingolimod placebo after discontinuation for >14 consecutive days after the first month of treatment, first-dose monitoring must be performed, due to the effects on heart rate and AV conduction that may recur on reintroduction of fingolimod/fingolimod placebo treatment.

For more details about the "Warnings and Precautions" with fingolimod, refer to the prescribing information.

As outlined in Section 4.2.3, a blinded independent physician will be involved in the monitoring of the patients.

4.3.2.2.5 Patient Counseling Information

All patients, parents and legal guardians will be advised to read the "Information for the user" or "Medication Guide." Patients, parents and legal guardians should be informed not to discontinue fingolimod/fingolimod placebo without first discussing with the treating investigator. Patients, parents and legal guardians should be advised to contact the treating investigator if they accidently take more fingolimod/fingolimod placebo than prescribed.

4.3.2.3 Assessment of Compliance

Compliance with ocrelizumab/ocrelizumab placebo administration will be assessed by maintaining adequate drug preparation and dispensing records. IxRS transactions for drug allocation may also be used to assess compliance.

Patient compliance of daily administration of fingolimod/fingolimod placebo will be monitored via reconciliation of medications returned to site at each visit, and discussion with the patient and parents/legal guardian at the clinic visits.

The treating investigator and/or study personnel should promote compliance of fingolimod/fingolimod placebo by instructing the patient, and parents /legal guardian to take the study drug exactly as prescribed and by stating that compliance is necessary for the patient's safety and validity of the study. The patient, and parent /legal guardian should be instructed to contact the site if the patient is unable to take the study drug as prescribed for any reason.

4.3.3 Criteria for Re-Treatment with Ocrelizumab/Placebo and Fingolimod/Placebo

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

For all patients, 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.

During the Double-Blind treatment Period, prior to re-treatment with ocrelizumab/ocrelizumab placebo or therapy continuation with fingolimod/fingolimod placebo, the following conditions must be met:

- Absence of life-threatening (Grade 4) infusion-related event that occurred during a previous ocrelizumab/ocrelizumab placebo infusion
- Absence of severe allergic or anaphylactic reaction
- 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 5.1.1.1.2)
- A patient with active TB infection or a Grade 3 infection must suspend study 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 study treatment if it is considered beneficial for him or her. Otherwise, the treating investigator can decide to permanently stop study treatment.
- Absence of any significant or uncontrolled medical condition or treatment-emergent, clinically significant, laboratory abnormality (Section 4.3.2.2.1)
- Absence of severe liver injury as defined by Hy's Law (see Section 5.3.5.8)
- Treatment with fingolimod/fingolimod placebo should not be resumed if a plausible alternative etiology for the signs and symptoms cannot be established, because these patients are at risk for severe drug-induced liver injury (refer to fingolimod prescribing information; see also Section 4.7.1.
- Absence of signs of macular edema (in case of diagnosis of macular edema, the patient should be discontinued from study treatment, see Section 4.7.1)
- No initiation of protocol-prohibited medications (see Section 4.4.3)
- Body weight $\geq$ 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 and parents/legal guardian (if appropriate) as to the risks of continuing with the pregnancy and the possible effects on the fetus.

  For ocrelizumab associated risks refer to "Pregnancy and Breast Feeding" Section 5.1.5; for fingolimod associated risks refer to the prescribing information.

In addition, prior to re-treatment with ocrelizumab/ocrelizumab placebo, the following conditions must be met:

- ANC (or neutrophil count) $\geq 1.5 \times 10^3/\mu L$
- 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

The treating investigator must ensure that he or she has reviewed the laboratory results of the patient prior to therapy continuation. Any repeat laboratory tests must be performed, analyzed, and reviewed before therapy continuation with ocrelizumab/ocrelizumab placebo or fingolimod/fingolimod placebo.

If any of these conditions are not met prior to re-dosing with ocrelizumab/ocrelizumab placebo or prior to therapy continuation with fingolimod/fingolimod placebo, further administration of study treatment will be suspended (paused) until resolved or held indefinitely (see Section 4.7.1).

A patient experiencing a life-threatening (Grade 4) infection will be permanently discontinued from study treatment but will continue in the double-blind period until the primary analysis is performed.

Investigators will be notified of their patient's critical laboratory test result as per Section 4.6.18.2. 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.

Refer to Section 5.3.5.6 for reporting of abnormal laboratory values.

During the Open-Label Extension Period, prior to re-treatment with ocrelizumab, the following conditions must be met:

- Absence of life-threatening (Grade 4) infusion-related event that occurred during a previous ocrelizumab/ocrelizumab placebo infusion
- Absence of severe allergic or anaphylactic reaction
- 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 5.1.1.1.2)
- A patient with active TB infection or a Grade 3 infection must suspend study 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 study treatment if it is considered beneficial for him or her. Otherwise, the treating investigator can decide to permanently stop study treatment.
- Absence of any significant or uncontrolled medical condition or treatment-emergent, clinically significant, laboratory abnormality
- Absence of severe liver injury as defined by Hy's Law (see Section 5.3.5.8)
- No initiation of protocol-prohibited medications (see Section 4.1.2.3)
- Body weight $\geq$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 and parents/legal guardian (if appropriate) as to the risks of continuing with the pregnancy and the possible effects on the fetus.

  For ocrelizumab associated risks refer to "Pregnancy and Breast Feeding" Section 5.1.5; for fingolimod associated risks for patients assigned to Group B during the double-blind period refer to the prescribing information.

- ANC (or neutrophil count) $\geq 1.5 \times 10^3/\mu L$
- CD4 levels **(For patients in Group A – ocrelizumab treatment in the DBP)**:
  - For children and adolescents: percent CD4 $\geq$ 25%
  - For patients $\geq$ 18 years of age, the adult reference applies: CD4 cell count $\geq 250/\mu L$
- CD4 levels **(For patients in Group B – fingolimod treatment in the DBP)**:

  Provided that the CD4 count restored above the LLN (value as per central laboratory) or above the baseline value (Visit 1 or 2 of the DBP), which ever was the lower, the following conditions apply:

  - For children and adolescents: percent CD4 ≥25%
  - For patients ≥18 years of age, the adult reference applies: CD4 cell count ≥250/μL

  If the CD4 count is still lower than LLN or baseline values from the fingolimod treatment, the following condition applies: No signs of alternative causes for low CD4 count other than fingolimod treatment.

- 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

  The laboratory samples to assess eligibility to OLE Dose 1 Day 1 ocrelizumab infusion should be collected within 4 weeks from the OLE Dose 1 Day 1 infusion visit, to ensure that the laboratory samples reflect the current condition of the patients. Similarly, the re-treatment criteria for OLE Dose 1 Day 15 infusion should be assessed based on laboratory samples that are collected within 4 weeks from the OLE Dose 1 Day 15 infusion visit. This is in line with the way visit windows were defined during the double-blind treatment period.

The treating investigator must ensure that he or she has reviewed the laboratory results of the patient prior to therapy continuation. Any repeat laboratory tests must be performed, analyzed, and reviewed before therapy continuation. Patients with abnormal laboratory values from those listed above should not be re-treated until the re-treatment criteria are met and these laboratory values have normalized.

Refer to Section 5.3.5.6 for reporting of abnormal laboratory values.

If any of the above conditions are not met prior to re-dosing with ocrelizumab, further administration of study treatment will be suspended (paused) until resolved or held indefinitely (see Section 4.7.1).

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

4.3.4 Continued Access to Ocrelizumab

Currently, the Sponsor does not have any plans to provide ocrelizumab or any other study treatments 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:

https://assets.roche.com/f/176343/x/1b18e080e0/2025-revision-roche_global_policy_on_continued_access_to_investigational_interventions.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 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 Day 1 visit (including medication taken between screening and Day 1).

Any medications taken for the treatment of MS and any medications taken for the symptoms of MS prior to the Day 1 visit will be recorded at the Day 1 visit.

Additionally, medications administered for any non-MS condition within 30 days prior to the screening visit will be recorded at the Day 1 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 solely based on the occurrence of a relapse, unless the investigator considers him or her to have met the criteria for withdrawal.

4.4.2 Cautionary Therapy

Concomitant use of ketoconazole (or other strong CYP3A inhibitors) in patients treated with fingolimod may lead to an increase in fingolimod plasma concentrations. Patients who initiate ketoconazole (or other strong CYP3A inhibitors) during the study should be informed of this possibility and the investigator should be vigilant as these patients may be at a higher risk of adverse events.

Special consideration should be given towards chronic treatment with medication that has a hepatotoxic potential; the investigator should be vigilant as these patients may be at a higher risk of liver adverse events.

4.4.3 Prohibited Therapy

Therapies for MS noted in the exclusion criteria under Section 4.1.2.3 are not permitted during the treatment periods (i.e., double-blind treatment period and during the OLE period) for as long as patients receive ocrelizumab or fingolimod, with the exception of systemic corticosteroids for the treatment of a relapse.

As per fingolimod prescribing information, during the double-blind period, the following treatments are not allowed concomitantly with the study treatment:

- Class Ia (e.g., quinidine, disopyramide) or Class III (e.g., amiodarone, sotalol) anti-arrhythmics
- Heart-rate-lowering drugs (e.g., beta blockers); heart-rate lowering calcium channel blockers (e.g., verapamil, diltiazem, or ivabradine)
- Digoxin, anticholinesteratic agents, pilocarpine

Use of the treatments to manage potential bradycardia after first dose administration is allowed.

For patients who complete or withdraw from study treatment, an alternative treatment for MS may be initiated as judged clinically appropriate by the treating investigator (see Section 4.2.3).

However, because insufficient data are available to inform risks associated with switching to other products, the following recommendations are given:

- Caution is advised while patients remain B-cell depleted
- The safety risk of administering DMTs for MS after discontinuation of ocrelizumab is unknown. Therefore, 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, due to unknown effects on the immune system (e.g., increased risk, incidence, or severity of infection).

4.4.4 Vaccinations

4.4.4.1 Vaccinations Prior to Initiation of Study Drug For Ocrelizumab

The safety of immunization with live or live-attenuated vaccines following ocrelizumab therapy has not been studied. Therefore, 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 in adults was 72 weeks).

In a randomized open-label study (Study BN29739), patients with RMS who were 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.

Physicians must review the immunization status of children and adolescents being considered for this Phase III 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; MSCCPG 2001; Rubin et al. 2014).

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.

For Fingolimod

As per fingolimod prescribing information, the same recommendation as for ocrelizumab applies that children and adolescents must have received all required childhood vaccinations as per local/national calendar of immunization to be eligible for the study.

If patients are negative for varicella zoster serological testing (see Section 4.1.2.5), the full course of the vaccine for chickenpox will have to be completed before study start, except patients who already received the full course of the vaccine for chickenpox, depending on local regulations.

Known dates of immunizations will be recorded on specific eCRF pages.

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

4.4.4.2 Vaccinations during the Study Period

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/ocrelizumab placebo.

4.5 OVERVIEW OF CLINICAL VISITS DURING THE STUDY

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 Day 1 visit (Visit 2, baseline). However, in case of a delayed dosing, later visits will be scheduled with reference of the date of this delayed dosing visit rather than the Day 1 visit (see Section 4.3.2.1.4).

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

4.5.1 Informed Consent Forms and Screening Log

Prior to any study-specific screening procedures or assessments being performed (including screening evaluations), the current, approved Institutional Review Board (IRB)/EC Informed Consent Form for study participation must be signed by parents or legal guardians. In addition, patient informed assent must be obtained verbally and when possible, in writing, from all pediatric patients old enough to fully comprehend the assent document.

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

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

Each patient screened must be registered in the IxRS by the investigator or the investigator's research staff at screening. Reasons for screen failure must be captured in the IxRS.

A screening examination (medical history and physical examination including Tanner Stage, ophthalmologic evaluation for signs of macular edema, 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 females of childbearing potential, thyroid function tests, hepatitis screening tests, Igs, rapid plasma reagin, CD4 count) will also be performed. A brain MRI scan and an optional hand and wrist X-ray will take place during screening and will serve as baseline assessments.

A patient diagnosis form should be completed by the investigator or designee in order to obtain confirmation of MS diagnosis from the Independent Pediatric MS Review Committee prior to randomization.

The screening period can be extended to a total of 10 weeks should a laboratory blood test need to be repeated for confirmation during the screening interval, or for other

relevant clinical, administrative, or operational reasons (e.g., baseline brain MRI scan to be repeated). Patients must fulfill all the entry criteria for participation in the study (see Section 4.1).

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 patients' medical record that the patient is participating in this clinical study.

4.5.2 Procedures for Enrollment of Eligible Patients

Patient lists will be created using an IxRS. The screening identification will be allocated by IxRS. Sites should log in to the IxRS to enter all subjects into screening and to register a screen failure, where applicable. After the patient's eligibility (i.e., review of inclusion and exclusion criteria) has been confirmed on Day 1 (or immediately prior to Day 1), sites should log in to the IxRS to enroll the patient into the study and receive the study identification and study treatment allocation (blinded) for the patient.

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

No patient may begin treatment prior to assignment of a patient 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 First Study Treatment Administration Visit (Day 1 Visit)

At the Day 1 visit patients will be administered their first dose of fingolimod/fingolimod placebo and the first IV infusion of ocrelizumab/ocrelizumab placebo (Day 1 of Dose 1). Both drugs must be administered on the same day for blinding purposes.

The Day 1 visit should be scheduled in the morning to allow enough time to perform all assessments as per the schedule of activities (Appendix 1, Table 1) and to allow the patient to stay at the hospital (or infusion center) with medical supervision and monitoring as detailed below.

Administration of the first dose of fingolimod/fingolimod placebo and all infusions of ocrelizumab/ocrelizumab placebo should take place in a setting in which appropriate medical support to manage symptomatic bradyarrhythmia and severe IRRs are available, with immediate availability of full resuscitation facilities. The first dose of fingolimod/fingolimod placebo must be taken at the clinic (or infusion center) because initiation of fingolimod treatment results in a decrease in heart rate, for which 6 hours monitoring is mandated (see Section 4.3.2.2.3).

To ensure that blinding is not compromised by the known lowering of the heart rate by fingolimod or the occurrence of an IRR with ocrelizumab at treatment initiation, a **blinded independent physician** not involved in patient care will be responsible for supervising the first dose of fingolimod/fingolimod placebo and the first infusion of ocrelizumab/ocrelizumab placebo. Other staff (e.g., study nurse) involved in monitoring of the patient during the first dose must also be independent of the main study team.

12-Lead ECG and Vital Signs Monitoring by the Blinded Independent Physician

ECGs and vital signs (i.e., pulse rate, systolic and diastolic blood pressure, respiratory rate, and temperature) should be obtained in all patients (Sections 4.6.12 and 4.6.13) as follows:

- ECG and vital signs will be recorded prior to study treatments administration, at least within 45 minutes prior to the methylprednisolone infusion (for further details see Section 4.6.12).
- To combine the first dose monitoring of fingolimod/fingolimod placebo with the monitoring requirements associated with ocrelizumab/ocrelizumab placebo infusion, the first dose of fingolimod/fingolimod placebo must be taken immediately prior to the administration of the premedications for ocrelizumab/ocrelizumab placebo infusions.
- Vital signs should be obtained after the administration of the premedication and prior to ocrelizumab/ocrelizumab placebo IV infusion.
- After intake of the first dose of fingolimod/fingolimod placebo it is mandated to monitor patients for a minimum of 6 hours for signs and symptoms of bradycardia with hourly pulse and blood pressure measurement. This first dose monitoring should be combined with the monitoring requirement during the infusion of ocrelizumab/ocrelizumab placebo as indicated below.
- During the infusion of ocrelizumab/ocrelizumab placebo, vital signs will be assessed every 15 (±5) minutes for the first hour, then every 30 (±10) minutes until 1 hour after the completion of the infusion. Furthermore, recording of 12-lead ECG will be done within 60 minutes after completion of the infusion and at the end of the fingolimod 6-hour observation period.
- Additional vital sign readings and/or 12-lead ECG recordings may be taken at the discretion of the blinded independent physician as clinically indicated.

Patients may be hospitalized for a 24-hour observation at the discretion of the blinded independent physician.

4.5.4 Ocrelizumab/Ocrelizumab Placebo Infusion Visits

Infusions of ocrelizumab/ocrelizumab placebo should be scheduled in the morning to allow all assessments to take place and the patient to stay at the hospital (or infusion center) with medical supervision and monitoring as required and for as long as possible (e.g., until 6 p.m. or 8 p.m. according to the hospital rules). 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 5.2.2). 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.

Physicians should alert patients and parents/legal guardians that IRRs can occur within 24 hours of infusion and that a structured telephone interview (or video call) will be conducted by site personnel 24 (±4) hours after completion of each infusion to check on their clinical status (Section 4.5.8).

4.5.5 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.

Refer also to Section 5.1.1.2.1 for guidance on the diagnosis of PML.

4.5.6 Withdrawal from Treatment Visit

At the moment a patient meets one or more of the withdrawal from treatment criteria (see Section 4.7.1), or if a patient does not want to continue in the study treatment period, this patient is regarded as withdrawn from treatment. These patients must return to the clinic for a treatment withdrawal visit (scheduled or unscheduled visit) to complete all assessments as shown in the schedule of activities (see Table 4 of Appendix 1).

At the withdrawal visit, an MRI scan will be required only if one was not performed in the previous 4 weeks.

Patients who withdraw from study treatment during the double-blind period should be encouraged to remain in the double-blind period of the study until the primary analysis, for additional efficacy and safety assessments as outlined in Table 4 of Appendix 1 and Section 3.1.2.

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

The decision to initiate an alternative treatment for MS after study treatment discontinuation will be at the discretion of the treating investigator. Refer to Section 4.2.3 for more details.

4.5.7 Withdrawal from Study Visit

From the moment a patient discontinues from the treatment and stops being followed for both efficacy and safety, this patient is regarded as withdrawn from study (see Section 4.7.2).

Despite all efforts to keep these patients in the study, patients who withdraw from the study before entering the SFU period or during the SFU period should return to the clinic for a study discontinuation visit to complete all assessments as shown in the schedule of activities (see Appendix 1).

At the withdrawal from study visit, an MRI scan will be required only if one was not performed in the previous 4 weeks.

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

4.5.8 Telephone Interviews (or Video Calls)

Patients (or parents and legal guardians, as appropriate) will be called by the investigator or designee to monitor patient status between visits. Assessments will include, but may not be limited to, new or worsening neurological symptoms, adverse events, concomitant medication review, and any other clinically significant events.

The purpose of the structured interview, by telephone or via video call, 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, change in concomitant medications) that warrant an unscheduled visit. The telephone interview or video call will be conducted by site personnel familiar with the patients at the following points of time:

- Within 24 (± 4) hours after completion of each infusion
- Every 4 weeks between study visits in the double-blind and OLE periods (see Appendix 1)
- In any other situation when the scheduled visit (e.g., at site or with a mobile nurse) cannot take place or when deemed necessary during a mobile nurse visit

During the OLE period, at the discretion of the treating investigators, and with agreement from the patients and parents/legal guardian, the neurologic evaluation performed at the

Week 12 visit between infusion visits can take place via video call to reduce the burden on study participants of commuting to site for this examination (Appendix 1, Table 2).

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

Patients, parents/legal guardians should be reminded of the importance to comply with the daily intake of fingolimod/fingolimod placebo AND not to discontinue fingolimod/fingolimod placebo without first discussing with the treating investigator. They should be advised to contact the treating investigator if they accidently take more fingolimod/fingolimod placebo than prescribed.

The site will record in the eCRF the date of interview/video call or if the site was unable to contact the patient or parents/legal guardian. The documentation of the interview/video call 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).

4.5.9 Mobile Nursing Visits

At applicable sites, certain study assessments, procedures, and blood draws (as indicated in Appendix 1) may be performed by a MN professional trained on the study protocol and study procedures at the patient's home or another suitable location to improve access and convenience for patients participating in the study.

If deemed appropriate, some of the assessments (as indicated in Appendix 1) at a scheduled clinic visit may be completed by the MN at the patient's home to reduce the time required at the site. In this case, the MN visit must be scheduled within the visit time window as specified in Appendix 1, but in advance of the clinic visit to allow the results of these assessments to be available to the site.

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 treating investigator at a participating site determines that MN services are appropriate for a patient, and the parents/legal guardian (and patient as appropriate) gives written informed consent, the MN network will communicate with the parents/legal guardian (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 draws may be performed by an MN professional.

If required, mobile nurse services may be requested by the treating investigator outside of scheduled visits to perform or repeat some assessments/procedures for patient's convenience.

4.6 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient.

Specific clinical outcome assessments are described in Section 4.6.17.

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

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), vaccination status, reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline (screening to Day 1).

In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 30 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Medical history will also include thorough recording of MS history, including prior MS therapies.

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

4.6.2 Assessment of Clinical 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 examining investigator within 7 days of the onset of the relapse, to assess the FS and EDSS independently to allow confirmation as to whether or not the clinical relapse meets the criteria for protocol-defined relapse.

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, as well as on the Adverse Event eCRF. Individual symptoms of a relapse should not be reported as individual AEs but can be described in additional case details field of the AE form.

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 FS scales, or 1 point on two or more of the appropriate FS scales. The change must affect the selected FS (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 the diagnosis of a relapse.

4.6.3 Kurtzke Expanded Disability Status Scale (Examining Investigator or Rater)

The EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10 (death). 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 FS. Each FS is an ordinal clinical rating scale ranging from 0–5 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.

Note: determination of fatigue and sexual dysfunction scores is optional.

EDSS will be administered by the examining investigator (rater), who will assess EDSS scores independently (Section 4.2.2), at the timepoints indicated in the schedule of activities (see Appendix 1). The examining investigator (rater) should not consult prior EDSS/FS scores when performing the current EDSS/FS assessments. Results of the neurologic examination (or anything related to patient health) and EDSS scores will not be shared between the treating and examining investigator.

Additional EDSS assessments for individual patients may be requested between visits (i.e., during an MS relapse, neurological worsening, etc.).

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

EDSS examination should be completed before any other clinical assessments, blood sampling and prior to study drug administration.

During the double-blind treatment period, the EDSS will be completed through use of an electronic device (pre-printed booklets should be used as backup only in case of unavailability of electronic version) provided by the Sponsor. The data will be transmitted to a centralized database maintained by the electronic device vendor and data will be available for access by appropriate study personnel. During OLE, the EDSS will directly be entered in the eCRF.

4.6.4 Neurologic Examination (Treating Investigator)

Neurologic examination should be performed by the treating investigator (see Appendix 1). Results of the neurologic examination (or anything related to patient health) and EDSS scores will not be shared between the treating and examining investigator.

During the OLE period, as indicated in Appendix 1, Table 2, at the discretion of the treating investigator and with agreement from the patient and parents/legal guardian, the neurologic evaluation performed at the Week 12 visit between infusion visits can take place via video call to reduce the burden on study participants of commuting to site for this examination.

In the presence of newly identified or worsening neurologic symptoms at any given time in the study, a neurologic evaluation should be scheduled promptly at the site. In case of events suggestive of relapse, the patient should be referred to the examining investigator within 7 days of the onset of the relapse, to assess the FS and EDSS independently to allow confirmation as to whether or not the clinical relapse meets the criteria for protocol-defined relapse.

If the clinical relapse is confirmed to be worsening neurologic symptoms, it will be reported on the prespecified MS Relapse eCRF, as well as on the Adverse Event eCRF.

Treating 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; please refer to Section 5.1.1.2.1 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).

4.6.5 Brain Magnetic Resonance Imaging

Magnetic resonance imaging is a useful tool for monitoring CNS lesions and other physiopathology in MS. Different MRI-derived parameters have been related to clinical activity, and T1-weighted Gd–enhancing lesions or new or enlarging T2 lesions have been related to relapses.

For all countries except Germany: Contingent on IRB/EC approval, qualifying MRI scans will be performed on healthy volunteers having provided informed consent at each MRI center as part of the scanner certification process with the MRI service provider, if not already available.

Alternatively, if scanning a healthy adult volunteer is not allowed for the dry run, the first patient study scan may be used.

For Germany: Contingent on IRB/EC approval, qualifying MRI scans will be performed without contrast agent on healthy volunteers having provided informed consent at each MRI center as part of the scanner certification and standardization process with the MRI service provider, if not already available.

There will be one healthy volunteer per study site.

Inclusion Criteria Related to MRI Healthy Volunteer

- Male or female between 18 and 55 years old.

Exclusion Criteria Related to MRI Healthy Volunteer

- Pregnant women or women who plan to become pregnant.
- People who weigh more than 158 kg (350 pounds).
- People suffering from claustrophobia.
- People with metallic foreign bodies in the eye, the mouth (some types of teeth braces), cardiac pacemakers, clips in the central nervous system, automatic internal cardiac defibrillators, implanted infusion pumps, implanted insulin pumps, bone growth stimulators, non-removable neurological stimulators, cochlear implants, or shrapnel.

Important for all countries including Germany: All regulatory approvals must be in place before performing the dry run MRI. It is the responsibility of the site to ensure that the volunteer has signed the relevant MRI Site Qualification Informed Consent Form before the dry run MRI is performed.

Brain MRI scans should be obtained in all patients as detailed in the schedule of activities (see Appendix 1).

The quality of each MRI scan will be assessed by the central reading center who may request re-scans if needed. After completion of the quality check, all MRI scans will be analyzed by the central reading vendor.

Scans will be performed by trained and certified blinded MRI technicians. The MRI should include the acquisition of scans without and with IV-administered Gd-contrast enhancement.

The following schedule for obtaining MRIs applies:

<u>During the Double-Blind Period</u>:

- A "baseline" MRI should be performed with and without a Gd-contrast agent; it should be performed as soon as possible after the screening visit to allow the Independent Pediatric MS Review Committee to confirm MS diagnosis
- 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 a frequency of every 24 weeks (window of ±4 weeks of these scheduled visits) during the double-blind period.

<u>During the OLE period</u>:

- For patients in Group B (fingolimod) switching to ocrelizumab, a brain MRI scan *without a Gd-contrast agent* will be obtained at the OLE screening visit, if not performed during the previous 4 weeks.
- *For patients in Group A (ocrelizumab), a brain MRI scan without a Gd-contrast agent will be obtained at the OLE Day 1 visit, if not performed during the previous 4 weeks.*
- For all patients, brain MRI *without a Gd-contrast agent* will be performed at 24 Weeks (±4 weeks) after Dose 1, and yearly thereafter.

Additionally:

- Brain MRI scan will be performed at the end of the SFU period and at the end of the prolonged B-cell monitoring (if applicable).
- A brain MRI scan will be obtained in patients discontinuing from OLE treatment period at a withdrawal from treatment visit and in patients discontinuing from the SFU period at a withdrawal from SFU visit, if not performed during the previous 4 weeks.
- For patients who begin an alternative treatment for MS (in the double-blind period or 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).

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 or parents/legal guardian 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.

The use of anesthesia or sedation to help the pediatric patient remain still during the MRI scan is left at the treating investigator's discretion.

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 efficacy endpoints. The centralized reading center is blinded to the treatment assignment and the reading is performed in the absence of clinical information.

During the double-blind period, the central blinded MRI reading center will inform the treating investigator whenever there is a pre-defined deterioration on the MRIs using the following process:

- For any given patients with at least five new or enlarging T2 lesions on any MRI scans from Week 48 inclusive and in comparison to the most recent prior scan.
- As part of this notification process, the treating investigator will be provided with the baseline total count of T2 lesions and the count of new or enlarging T2 lesions from the MRI having triggered the notification, as well as both related MRI images (including Gadolinium-enhancing T1 lesion count at baseline). However, treatment allocation will remain blinded.

Thereafter, the blinding rules regarding the MRI review will be reinstated and notifications will be sent only in case of a scan showing at least five new or enlarging T2 lesions on any MRI scans in comparison with the most recent prior scan.

During the double-blind period, MRI scan reports containing unexpected findings (e.g., non-MS pathology) will be provided to the treating investigator (see Section 4.2.3 for definition). At the investigational site, only the local radiologist/technician assigned to this study may have access to the MRI scans post-randomization; to protect the blind, the treating investigator should not review the MRI scans obtained after randomization unless a safety concern arises. In the event that the treating investigator does become aware of these MRI results, this should be documented at site and reported as a protocol deviation, indicating the reason.

Note that after the study has been unblinded, it is possible for the treating investigator to have access to MRI scans during the OLE period and SFU period.

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

Further details on scanning acquisition sequences, methods, handling and transmission of the scans, certification of site MRI radiologist/technicians, and the procedures for the blinded 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 for safety by a local blinded radiologist.

4.6.6 Physical Examinations

A complete physical examination will be performed at screening and Day 1 and should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline (screening to Day 1) 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. Limited, symptom-directed physical examinations may be performed by an MN professional as indicated in Appendix 1.

Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.6.7 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 (see Appendix 1).

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. The height of consenting biological mothers and fathers can be measured or self-reported. This information may 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.

4.6.8 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).

Note: Patients initially assigned to 300mg dose and who reach a body weight of ≥ 35 kg during the study should be switched to the 600mg dose at their next infusion visit (Section 4.3.2.1).

During the course of the study any patient receiving the lower fingolimod/fingolimod placebo dose of 0.25 mg who reaches the weight of 40 kg (over two visits, at least 3 months apart), should be switched to the 0.5 mg dose strength. Thus, additional weight measurements will be required for these patients as indicated in Appendix 1.

4.6.9 Tanner Staging

Tanner stages (1–5) (Tanner 1986) will be determined yearly as outlined in Appendix 2 and according to schedules of activities in Appendix 1 until patients reach Tanner Stage 5. At sites where Tanner staging is not performed routinely, data can be obtained from the child's primary pediatrician, if available, or at a designated site arranged by the investigator.

4.6.10 Female Reproductive Status

Patients with changes in childbearing potential (e.g., a patient experiences menarche) or risk of pregnancy (e.g., a female patient becomes heterosexually active) that occur after the start of the study should be advised by the investigator on the risks of becoming pregnant while on treatment and the most appropriate method of contraception should be agreed (see Section 4.1.1.1 and 5.1.5).

Female patients who are premenarchal at the time of screening should be asked about the date of first menarche, as per the schedule of activities in Appendix 1. The date of first menarche should be recorded on the eCRF.

For female patients who are postmenarchal at the time of screening, the date of first menarche should be recorded on the eCRF.

4.6.11 Bone Age Assessment (Optional): Wrist/Hand Radiographs

Bone age should be assessed by obtaining one combined standard posterior-anterior radiograph of the left wrist and hand. The baseline radiograph should be obtained within 4 weeks of Day 1 and then repeated yearly (±4 weeks) during the double-blind period and OLE.

If the bone age is determined to be ≥16 years of age, this indicates that the patient has reached full pubertal status and no further bone X-rays are required. If the bone age at baseline is <16 years of age, then the X-ray should be repeated as per Appendix 1, Table 1.

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/legal guardian, and patient assent (where possible). If a site's IRB/EC does not approve the radiographic assessment, this section will not be applicable.

4.6.12 Electrocardiogram

ECGs should be performed prior to any procedures, such as vital sign measurements and blood draws.

Twelve-lead ECG will be obtained in all patients as outlined in the schedule of activities (see Appendix 1), at screening, prior to dosing and at the end of the observation period for any ocrelizumab/ocrelizumab placebo infusion (see Section 4.3.2.1.2). ECGs will also be obtained as part of the first dose monitoring with fingolimod/placebo, i.e., prior to dosing and at the end of the 6 hours observation period (see Sections 4.3.2.2.3 and 4.5.3).

See Section 4.5.3 for study drug administration and first dose monitoring.

The physician in charge of supervising study drug administration 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 and/or electronic copies should be kept as part of the patient's permanent study file at the site. 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 study treatment. Additional ECGs may be taken at the discretion of the treating investigator if clinically indicated and corresponding ECG outcomes should be reported on the unscheduled eCRF.

For fingolimod, refer to the prescribing information for more details on the monitoring requirements.

4.6.13 Vital Signs

Vital signs (pulse rate, systolic and diastolic blood pressure, respiratory rate, and temperature) should be taken in all patients as outlined in the schedule of activities (see Appendix 1), at screening, prior to dosing, during and after completion of any ocrelizumab/ocrelizumab placebo infusion (see Section 4.3.2.1.2), Vital signs will also be obtained as part of the first dose monitoring for fingolimod/fingolimod placebo (see Sections 4.3.2.2.3 and 4.5.3).

See Section 4.5.3 for study drug administration and first dose monitoring.

Blood pressure measurements should be obtained using a child-appropriate cuff size.

On non-infusion visit, vital signs may be taken at any time during the visit.

Additional vital signs readings may be taken at the discretion of the physician supervising study drug administration if clinically indicated and should be recorded on the unscheduled vital signs eCRF.

New or worsened abnormalities should be recorded as adverse events on the Adverse Event or Infusion-Related Reaction (IRR) eCRF if clinically appropriate.

4.6.14 Ophthalmologic Examination

Fingolimod increases the risk of macular edema. An examination of the fundus (including the macula) should thus be performed by an ophthalmologist or by a qualified professional or by optical coherence tomography (OCT) at screening, at 12 weeks after starting treatment as indicated in Table 1 of Appendix 1, and at any time after a patient reports visual disturbances while on therapy.

The examining ophthalmologist or qualified professional should follow standard procedure for this type of examination and may use, at their clinical discretion, the method(s) they deem best suitable to either provide medical clearance for the patient or perform further workup as needed.

4.6.15 Clinical Outcome Assessments

Patient-reported outcome (PRO) data will be collected through the use of the following instruments: PedsQL Generic Core Scale; PedsQL Multidimensional Fatigue Scale; EQ-5D-5L; and PGIC for fatigue, cognition, and overall MS symptoms.

Observer-reported outcome (ObsRO) data will be collected through the use of the following instruments: CaGI-C for fatigue, cognition, and overall MS symptoms; Caregiver (proxy) PedsQL Generic Core Scale 4.0. If the caregiver declines to complete the ObsROs, this will not affect the participation of the patient in the study. If the parent or caregiver withdraws consent during the course of the study, or is no longer available to complete ObsROs, the parent or caregiver will not be replaced, and the patient's participation in the study will not be affected.

PROs and ObsRO measures will be self-administered (by the patient and caregiver respectively) at specified timepoints throughout the double blind period of the study (see schedule of activities in Appendix 1). The questionnaires, translated and culturally validated into the local language as appropriate, will be completed in their entirety. In the case the translated and culturally validated questionnaires are not readily available, the sponsor will initiate translation and validation of the PROs and ObsRO measures. However, since the timelines for availability are lengthy and unpredictable, and in order not to delay a patient's opportunity to enroll in Study WN42086, the PRO and ObsRO assessments listed in Section 4.6.15.1 and 4.6.15.2 will not be conducted until the translations become available. To ensure instrument validity and that data standards meet health authority requirements, questionnaires will be self-administered before the patient or caregiver receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of ocrelizumab/ocrelizumab placebo, unless otherwise specified.

In the event that the patient is unable to complete PROs on his or her own (e.g., due to problems with eyesight or reading difficulties), appropriate site personnel (except the examining investigator) may read the PRO to the patient; however, staff should not influence or interpret responses in any way and questions and response options should be read out verbatim.

PROs and ObsRO measures will be completed using an electronic device provided by the site staff at the clinic. In case of device failure, a different device can be used that has access to the web. The device will be pre-programmed to ensure the appropriate instruments are administered in a standardized order at each specified timepoint. The data will be transmitted to a centralized database maintained by the electronic device vendor and data will be available for access by appropriate study personnel.

During clinic visits, PROs and ObsROs should be administered as outlined below:

- Patients' health status should not be discussed prior to administration of the instruments

- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers
- Site staff should not interpret or explain questions, but may read questions verbatim upon request
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments

The same caregiver will provide feedback on all informant-based assessments throughout the study from screening onwards. Should the caregiver be unable to attend a site visit in person, the ObsRO measures will then be completed electronically at home by the same caregiver on the same day as the scheduled site visit.

4.6.15.1 Patient Reported Outcomes

Pediatric Quality of Life Inventory Generic Core Scale 4.0

The PedsQL™4.0 Generic Core Scale assessment is a 23-item patient reported outcome encompassing 4 core scale domains: Physical Functioning (8 items); Emotional Functioning (5 items); Social Functioning (5 items); and School Functioning (5 items) (Varni et al. 1999; Varni et al. 2001). Items are scored referring to a 1-month recall on a 5-point Likert-type response scale (0=never a problem; 1=almost never a problem; 2=sometimes a problem; 3=often a problem; and 4=almost always a problem). Once completed, items are reverse scored and linearly transformed to a 0–100 scale (0=100, 1=75, 2=50, 3=25, 4=0), so that higher scores indicate better health-related quality of life. Different versions exist for 8–12 and 13–18 year age ranges.

Pediatric Quality of Life Inventory Multidimensional Fatigue Scale

The PedsQL Multidimensional Fatigue Scale is an 18–item self-reported measure used to assess fatigue across three dimensions consisting of general fatigue, sleep/rest fatigue and cognitive fatigue (Varni et al. 2004; MacAllister et al. 2009). This is rated referring to a 1-month recall on a 5-point Likert scale from never (0) to almost always (4). Once completed, this can be scored by dimension level or by global score where items are reverse scored and linearly transformed to a 0–100 scale (0=100, 1=75, 2=50, 3=25, 4=0). The sum of all the items over the number of items answered is used to calculate the total score, where a higher score corresponds to less fatigue.

EQ-5D-5L

The EQ-5D-5L, is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013). There are two components to the EQ-5D-5L: a five-item health state profile that assesses

mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analogue scale that measures health state. The EQ-5D-5L is designed to capture the patient's current health status. Published weighting systems allow for creation of a single composite score of the patient's health status. The EQ-5D-5L will be used in this study for informing pharmacoeconomic evaluations.

Patient Global Impression of Change for Fatigue, Cognition and Overall Multiple Sclerosis Symptoms

The PGIC is a six-item questionnaire used to assess the patient's impression about changes in their fatigue, cognition and overall MS symptoms compared to the beginning of the study. Change in each of the symptoms is first rated on a 5-point scale, ranging from much improved (1) to much worse (5), followed by a binary (yes/no) rating of whether this change is important to the patient.

4.6.15.2 Observer-Reported Outcomes

Caregiver (Proxy) PedsQL Generic Core Scale 4.0

The caregiver (proxy) PedsQL Generic Core Scale 4.0 is identical to the patient reported PedsQL Generic Core Scale (described in Section 4.6.15.1), but self-completed by the caregiver, from their perspective. Refer to the patient reported PedsQL Generic Core Scale for details on number of items, response options and scoring.

Caregiver Global Impression of Change for Fatigue, Cognition and Overall Multiple Sclerosis Symptoms

This CaGI-C for fatigue, cognition and overall MS symptoms is conceptually identical to the six items in the PGIC (described under the PRO section above), but requires the caregiver to report any changes they have observed in the patient, from their perspective.

4.6.16 Performance Measures

Symbol Digit Modalities Test

The 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. Using a reference key, the examinee has 90 seconds to pair specific numbers with given geometric figures. Responses will be oral, and administration time is approximately 5 minutes.

SDMT will be administered by the examining investigator or a qualified designee at the timepoints indicated in the schedule of activities (see Appendix 1).

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

The SDMT will be administered orally and the responses transcribed by the examiner on paper forms provided by the Sponsor. During the double-blind treatment period, the

score will then be transcribed through the use of an electronic device. The data will be transmitted to a centralized database maintained by the electronic device vendor and data will be available for access by appropriate study personnel. During OLE, the score will directly be entered in the eCRF. Instruments must not be copied from the protocol.

4.6.17 Patient and Caregiver (Optional) Interviews

In a selected sub-set of countries, patient and caregivers will be given the option to participate in a 30–60 minute telephone/video interview conducted in the weeks following the patient's Week 48 and 96 site visit in the double-blind treatment period (if applicable), conducted by an experienced qualitative vendor. The patient will also be asked to create a collage or draw a picture before the first interview. This task is intended to help the interview discussion, is optional, and the patient can spend as much or as little time on it as he/she wants. If the task is not completed, the patient can still participate in the interviews. The rationale for the interviews is to enable the patient and caregiver to provide details of 1) changes in cognition and fatigue experienced by patients due to treatment, 2) changes in any other symptom and general HRQL changes experiences by patients, and 3) the relative importance of the symptom and HRQL changes experiences by patients.

All patients and caregivers in the selected countries will be approached to take part in the optional interviews at Week 48 of their double-blind treatment period until approximately 30 patients and 30 caregivers have been recruited. The same individuals will be given the option to participate in a telephone/video interview at Week 96 of the double-blind treatment period, if applicable. Interviews will be recorded (voice only), transcribed verbatim and themes emerging from these transcripts will be interpreted in relation to changes other than clinical outcome assessments collected in the study. Consent for this portion of the study will be included in the assent or Informed Consent Forms for patients and caregivers.

4.6.18 Laboratory, Biomarker, and Other Biological 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.

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.

The maximum total volume of blood collected, at any given visit, ranges from approximately 9 to 30 mL (the maximum is expected at screening [Visit 1] and at baseline [Visit 2]).

The collection is aligned with the different existing recommendations (e.g., European Medicines Agency, National Institutes of Health, or WHO, stating that the total blood volume should not exceed 3% of the total blood volume during a period of 4 weeks and should not exceed 1% at any single time.

Any deviation from the recommended blood volume collection should be justified (e.g., repeat of laboratory test).

4.6.18.1 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 (postmenarchal prior to study entry or during the study).

  When monthly urine pregnancy tests are required as per local recommendations, patients will be asked to perform the tests at home.

On infusion visits, the urine samples for the urinalysis and pregnancy test should be performed prior to the methylprednisolone infusion and study treatment should be 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 administration of study treatment.

Because of the potential of unblinding, only the laboratory tests mentioned above should be performed using a local laboratory. All other laboratory parameters should be analyzed by the central laboratory as mentioned in Section 4.6.18.2.

At the time of the transition to the OLE period, for patient in Group B (fingolimod), as per Section 3.1.3 and 4.1.3, local laboratory tests are allowed to allow fast laboratory parameter review to check eligibility, as per investigator discretion. However, central lab tests should still be performed in parallel.

4.6.18.2 Central Laboratory Assessments

On infusions visits, all samples must be taken prior to the methylprednisolone infusion; refer to the schedule of activities for the corresponding timepoints (see Appendix 1).

Note: During the double-blind period, some laboratory parameters that could reveal patient's allocation to study treatment, such as flow cytometry cell counts, WBC count, lymphocyte counts (including CD4 lymphocytes), Ig levels, and liver function tests, will

be blinded. To ensure patients' safety in the study and to allow for assessments of the re-treatment criteria, a central laboratory will provide study investigators and Medical Monitors with reflex messages triggered by critical blinded laboratory results.

As such, the following parameters are being unblinded when they meet the levels required for safety monitoring and for reviewing of re-treatment criteria:

- ALT or AST > 3 x ULN including Hy's Law
- GGT > 5 x ULN
- CD4 levels (for ocrelizumab-treated patients):
  - For children and adolescents: percent CD4 < 25%
  - For patients ≥ 18 years of age, the adult reference applies: CD4 cell count < 250/µL
- 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
- Total Lymphocyte Count – toxicity Grade 4 as per NCI CTCAE v5.0
- Total WBC – toxicity Grade 3 and Grade 4 as per NCI CTCAE v5.0

Investigators notified of their 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 4.3.3). The reflex messages from a central laboratory/Sponsor medical monitor, together with non-blinded laboratory results, should be carefully reviewed before continuing with study treatment.

The reflex messages will be in effect until the completion of the primary analysis. Further details will be provided in Laboratory Manual.

Repeated tests are allowed at any time during the study at the investigator's discretion and should be sent to the central laboratory for analysis.

The following laboratory samples will be collected as per the Schedules of Activities (see Appendix 1):

- Hematology: WBC count (absolute and differential), RBC count, RBC morphology, hemoglobin, hematocrit, quantitative platelet count, and ANC count
- Blood chemistry: AST, ALT, GGT, ALP, amylase, lipase, total protein, albumin, cholesterol, total bilirubin (direct and indirect will be performed if total bilirubin is greater than the ULN), urate, potassium, sodium, chloride, calcium, phosphate, LDH, creatine phosphokinase, creatinine, BUN 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 (flow cytometry): Analysis will include the determination of the B-cell number (CD19+), high-sensitivity assay B-cell counts (MRB1.1), Bcell subsets (e.g., CD19, CD27, IgD, CD38 markers to assess naive, memory, plasmablasts, and/or other populations), Tcell counts (CD3+, CD4+, CD8+) and natural killer cells (CD56+).
- Quantitative Ig levels: Including total Ig, IgG, IgM, and IgA isotypes
- Antibody titers: Measurement of antibody titers to common antigens (mumps, rubella, varicella zoster, *Streptococcus 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.

4.6.18.3 Central 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 reagin (RPR; with fluorescent treponemal antibody absorption test for confirmation if RPR is positive)
- MOG and AQP4 antibody testing
- HIV serology test (except where national or local regulations do not approve this testing)
- Tuberculosis serology test (except where national or local regulations do not approve this testing)
- CD4 determination

See also Section 4.1.2.5 for more information.

4.6.18.4 Hepatitis Screening and Renal or 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 study treatment and will either remain in the double-blind study period without study treatment or enter the SFU period (see Sections 3.1.2 and 3.1.4).

Liver function (i.e., ALT, AST, GGT, alkaline phosphatase, and total bilirubin) should be reviewed throughout the study. ALT, AST and GGT will be blinded on the central laboratory reports. Reflex messages for critical blinded laboratory results will be sent to study investigators and Medical Monitors as detailed in Section 4.6.18.2. Patients developing evidence of liver dysfunction should be assessed for viral hepatitis or drug-induced liver injury, if necessary, referred to a hepatologist or other appropriately qualified expert. Study treatment should be withheld until the diagnosis of viral hepatitis or drug-induced liver injury has been excluded. Patients developing hepatitis B or C or drug-induced liver injury should be withdrawn from the study treatment and should remain in the double-bling period or enter the SFU period as described in Sections 3.1.2 and 3.1.4.

Renal function should be reviewed throughout the study. In case of elevated serum creatinine, estimated glomerular filtration rate should be monitored using the bedside Schwartz equation (or another appropriate formula as per local guidelines), to estimate patient renal function, as per standard clinical practice.

Should a 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.

4.6.18.5 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 5.1.1.2.1). Plasma and urine samples will be collected as per the schedule of activities (see Appendix 1). As there have been no cases of unconfounded 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.

4.6.18.6 Pharmacokinetic/Pharmacodynamic Assessments

Pharmacokinetics

PK samples will be collected on the infusion days at 5–30 minutes before the methylprednisolone infusion and 30 (±10) minutes after the completion of the ocrelizumab/ocrelizumab placebo infusion, and at any time on non-infusion visits as indicated in the schedule of activities (Appendix 1).

Note: For the blood sampling post-infusion, the PK sample must be collected from the arm opposite the arm receiving the IV infusion of ocrelizumab/ocrelizumab placebo.

Pharmacodynamics

CD19 B-cell count in blood (included under the immunologic assessments performed by the central lab) will be performed according to the schedule of activities (see Appendix 1).

CD19 B-cell count will be kept blinded until the completion of the primary analysis (see Section 4.6.18.2).

4.6.19 Blood Samples for Biomarker Research

Blood samples will be sent to the central laboratory and/or to the Sponsor or designated processing site, and 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).

A serum sample will be collected at the timepoints specified in Appendix 1 and analysis will include, but may not be limited to NfL. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient or parents/legal guardian gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.6.20), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Serum samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

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

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

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators, patients or parents/legal guardians 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.

4.6.20 Optional Samples for Research Biosample Repository

4.6.20.1 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 ≥50 kg who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

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

4.6.20.2 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 4.6.20) will not be applicable at that site.

4.6.20.3 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, immune cells, diseases, or drug safety:

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

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).

4.6.20.4 Confidentiality

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

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

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

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

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

4.6.20.5 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 parents/legal guardian the objectives, methods, and potential hazards of participation in the RBR. Patients and parents/legal guardian will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's and/or parents/legal guardian (as appropriate) agreement to provide optional RBR samples. Patients and parents/legal guardian who decline to participate will not provide a separate signature.

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

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

4.6.20.6 Withdrawal from the Research Biosample Repository

Patients or parents/legal guardian who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient or parents/legal guardian 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's or parents/legal guardian wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient or parents/legal guardian 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 patient number to the following email address:

global.rcr-withdrawal@roche.com

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

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

4.7 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.7.1 Study Treatment Discontinuation

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

- Any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator 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
- Severe liver injury as defined by Hy's Law (See Section 5.3.5.8). If a plausible alternative etiology for the signs and symptoms cannot be established, patients are at risk for severe drug-induced liver injury (refer to fingolimod prescribing information)
- Diagnosis of macular edema
- 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 study treatment should be encouraged to remain in the study for additional efficacy and safety assessments as outlined in Section 3.1.2 and Section 3.1.3. These patients will need to return to the clinic for a treatment withdrawal visit (scheduled or unscheduled visit; see Appendix 1 for additional details).

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

The decision to initiate an alternative treatment for MS after study treatment discontinuation will be at the discretion of the treating investigator. Refer to Section 3.1.5 for more details.

4.7.2 Patient Discontinuation from the Study

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

Patients or parents/legal guardian have the right to voluntarily withdraw (their child) from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

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

- Patient withdrawal of consent or assent, as applicable
- Parent/legal guardian withdrawal of consent
- Study termination or site closure
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. Patients who withdraw from the study will not be replaced.

Patients discontinuing from the study will need to return to the clinic for a study withdrawal visit (scheduled or unscheduled visit; see Appendix 1 and schedule of activities for additional details).

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

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 the medical records. 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 or parents/legal guardian decide to withdraw (their child), all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible.

4.7.3 Study Discontinuation

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

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

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

4.7.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Ocrelizumab is not approved in pediatric indication, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with ocrelizumab in completed and ongoing studies in adult population, and experience from an ongoing pediatric Phase II study. Fingolimod is approved in pediatric patients with highly active RRMS as single disease-modifying therapy. The safety profile in pediatric patients is similar to that in adults; therefore, the warnings and precautions for adults also apply to pediatric patients.

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/ocrelizumab placebo infusions and/or oral daily fingolimod/fingolimod placebo tablets is required unless an adjustment is necessary for safety reasons. During study visits when the ocrelizumab/ocrelizumab placebo infusion and/or fingolimod/fingolimod placebo tablets 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 fingolimod, and recommendations for vigilance with signs and symptoms of particular safety events are summarized in the following sections.

Please refer to the current version of the Ocrelizumab Investigator's Brochure and fingolimod local prescribing information for a complete summary of safety information.

5.1.1 Risks Associated with Ocrelizumab

5.1.1.1 Identified Risks and Adverse Drug Reactions

5.1.1.1.1 Infusion-Related Reactions

All CD20 depleting agents administered via the IV route, including ocrelizumab have been associated with acute IRRs. Following the approved administration regimen (which includes the use of premedication prior to treatment with ocrelizumab in order to reduce frequency and severity of IRRs), symptoms of IRRs may occur during any ocrelizumab infusion, but have been more frequently reported during the first infusion. Physicians should alert patients and parents/legal guardian 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 symptoms of IRR. They will be informed about the possibility of delayed post–infusion symptoms and instructed to contact their study physician if they develop such symptoms.

Additional caution will be taken 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 refer to Section 4.3.2.1.5.

5.1.1.1.2 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 interferon β-1a

group (2.9%); in PPMS, the proportion of patients with serious infections, was similar in both groups: 6.7% in the placebo group compared with 6.2% in the ocrelizumab group.

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 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 one reported in a patient with rheumatoid arthritis treated with ocrelizumab. Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with ocrelizumab as per local guidelines. Patients with active HBV should not be treated with ocrelizumab. Patients with positive serology should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent Hepatitis B reactivation.

Delay ocrelizumab administration in patients with an active infection until the infection is resolved. For PML, see Section 5.1.1.2.1.

5.1.1.1.3 Impaired Response to Vaccination

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

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

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

Due to the potential depletion of B-cells in neonates and infants of mothers, who have been exposed to ocrelizumab during pregnancy, it is recommended that vaccination with

live or live-attenuated vaccines should be delayed until B-cells have recovered; therefore, measuring CD19-positive B cell level, in neonates and infants, prior to vaccination is recommended.

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

5.1.1.1.4 Decrease in Immunoglobulins

Treatment with ocrelizumab resulted in a decrease in total Ig over the controlled period of the studies, mainly driven by reduction in IgM. The proportion of patients with decrease in Igs below LLN increased over time and with successive dosing. Based on additional patient exposure, in cases of continuous decrease over time, a higher risk of serious infection cannot be ruled out (see Section 5.1.1.1.5).

Patients with IgG and IgM below the exclusionary levels per Section 4.1.2 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/ocrelizumab placebo treatment and require specific medical care or management, repeat dosing may be suspended until resolved or held indefinitely as per the judgment of the treating investigator.

5.1.1.1.5 Serious Infections Related to Decrease in Immunoglobulins

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

5.1.1.1.6 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 time-point of assessment) as an expected pharmacologic effect. This was sustained throughout the treatment period. The longest follow-up time after the last ocrelizumab infusion from Phase II Study WA21493 in 51 patients of 600 mg ocrelizumab group indicates that the median time to repletion (returned to baseline/LLN, whichever occurred first) of B-cells was 72 weeks (range 27−175 weeks). Patients with prolonged B-cell depletion should be monitored until their B-cells have repleted.

5.1.1.1.7 *Liver Injury*

Liver injury is an identified risk associated with ocrelizumab treatment. Clinically significant liver injury, without findings of viral hepatitis, has been observed rarely in

the postmarketing setting in participants treated with ocrelizumab. Signs of liver injury, including markedly elevated serum hepatic enzymes with elevated total bilirubin, have occurred from days to months after administration of the first dose. Refer to the Ocrelizumab Investigator's Brochure for more details.

5.1.1.2 Potential Risks

5.1.1.2.1 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 (to be 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.

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. Presence of such neurological findings will be recorded in the Adverse Event eCRF. If a diagnosis for the deficits is identified, the symptoms should be replaced by the diagnosis in the Adverse Event eCRF.

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 at the regular site study visits as indicated in Appendix 1. Patients will be required to undergo a

neurologic examination for calculation of an EDSS score every 12 weeks during the double-blind period and every 24 weeks in the OLE and SFU period. This requires that FS score also be determined. The examination to calculate the FS score includes cognitive, visual, and motor assessments; the neurologic systems most often affected by PML.

In addition to the neurologic evaluation performed regularly at site, there will be regular study visits (site or MN visits, as applicable) in between; furthermore, patients or parents/legal guardian (as appropriate) 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. Patients and parents/legal guardians 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 Appendix 5 for guidance for diagnosis of PML. Also refer to the ocrelizumab Investigator's Brochure for more details.

5.1.1.2.2 Hypersensitivity Reactions

Hypersensitivity may be difficult to distinguish from IRRs in terms of symptoms. A hypersensitivity reaction may present during any infusion, although typically would not present during the first infusion. For subsequent infusions, more severe symptoms than previously experienced, or new severe symptoms, should prompt consideration of a potential hypersensitivity reaction. If a hypersensitivity reaction is suspected during infusion, the infusion must be stopped immediately and permanently. Patients with known IgE-mediated hypersensitivity to ocrelizumab must not be treated.

5.1.1.2.3 Malignancies Including Breast Cancer

An increased risk of malignancy with ocrelizumab may exist. In controlled trials in MS, malignancies, including breast cancer, occurred more frequently in ocrelizumab-treated patients. Breast cancer occurred in 6 of 781 females treated with ocrelizumab and 0 of 668 females treated with interferon β 1a or placebo.

Patients should follow standard breast cancer screening guidelines. Refer to the ocrelizumab Investigator's Brochure for more details.

5.1.1.2.4 Neutropenia

In 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 were mild to moderate in severity, approximately 1% of the patients had Grade 3 or 4 neutropenia; and no temporal association with infections was identified. Based on additional patient exposure, an association between neutropenia and serious infections with ocrelizumab treatment was not observed.

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. Refer to Section 4.3.3 for information on criteria for re-treatment with ocrelizumab/ocrelizumab placebo.

Refer to the ocrelizumab Investigator's Brochure for more details.

5.1.1.2.5 *Non-Infectious Colitis*

Non-infectious colitis is a non-specific term referring to the inflammation of the mucosal lining of the colon. The clinical presentation of colitis typically includes symptoms such as watery diarrhea, abdominal pain, tenesmus, fever, and blood in the stool. The risk encompasses a variety of colitis sub-types, which can have variable severity (non-infectious colitis, inflammatory colitis, immune-mediated colitis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, and microscopic colitis). The clinical course of colitis cases in ocrelizumab-treated participants appears similar to that in the general and MS population, with most cases resolved while ocrelizumab was still present in the body and B cells were still depleted.

Based on a thorough review of all available data, a causal relationship between ocrelizumab and non-infectious colitis has not been established. The incidence rates of colitis in participants treated with ocrelizumab are low and comparable to those in the general or MS populations.

Monitoring participants for typical symptoms followed by diagnostic workups can lead to early diagnosis and treatment, potentially preventing severe outcomes.

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

5.1.2 Risks Associated with Fingolimod

The safety profile in pediatric patients receiving 0.25 or 0.5 mg daily is similar to that in adults and the risks identified for adults therefore also apply to pediatric patients. A summary of main risks associated with fingolimod is presented below.

For more details on risks associated with fingolimod as well as risk mitigation measures, refer to current fingolimod local prescribing information.

Bradyarrhythmia

Initiation of fingolimod treatment results in a transient decrease in heart rate and may also be associated with atrioventricular conduction delays. Conduction abnormalities were typically transient and asymptomatic. They usually did not require treatment and resolved within the first 24 hours on treatment. Should post-dose bradyarrhythmia-related symptoms occur, appropriate clinical management should be initiated and monitoring should be continued until the symptoms have resolved.

QT Interval

In the MS studies, clinically relevant effects on prolongation of the QTc-interval have not been observed but patients at risk for QT prolongation were not included in clinical studies.

Immunosuppressive Effects

Fingolimod has an immunosuppressive effect that predisposes patients to an infection risk, including opportunistic infections that can be fatal, and increases the risk of developing lymphomas and other malignancies, particularly those of the skin.

Infections

The immune system effects of fingolimod may increase the risk of infections, including opportunistic infections. Thus, the initiation of treatment with fingolimod should be delayed in patients with severe active infection until resolution.

Patients need to be assessed for their immunity to varicella (chickenpox) prior to fingolimod treatment. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with fingolimod. Initiation of treatment with fingolimod should be postponed for 1 month to allow full effect of vaccination to occur.

Progressive Multifocal Leukoencephalopathy

PML is a rare, serious, and potentially fatal opportunistic infection caused by JCV. It has been reported in patients undergoing fingolimod treatment, particularly after two or more years of exposure. Risk factors for PML include prolonged fingolimod use, prior treatment with immunosuppressants or immunomodulators, and severe lymphopenia ($<0.5 \times 10^9$/L). PML occurs only in the presence of JCV infection, and a negative anti-JCV antibody test does not rule out future infection.

If PML is suspected, immediate MRI should be performed, and fingolimod treatment must be suspended until PML is excluded. If confirmed, the treatment must be permanently discontinued.

Immune Reconstitution Inflammatory Syndrome

Discontinuation of fingolimod in patients with PML may lead to immune reconstitution inflammatory syndrome (IRIS), a condition marked by rapid neurological decline, often with serious complications or death. IRIS typically develops weeks to

months after fingolimod treatment cessation and requires monitoring and prompt management of inflammation.

Macular Edema

Macular edema with or without visual symptoms has been reported in 0.5% of patients treated with fingolimod 0.5 mg, occurring predominantly in the first 3–4 months of therapy. An ophthalmological evaluation is recommended at 3–4 months after treatment initiation. Multiple sclerosis patients with diabetes mellitus or a history of uveitis are at increased risk of developing macular edema and should undergo an ophthalmological evaluation prior to initiating therapy and have follow-up evaluations while receiving therapy. Fingolimod should be discontinued if a patient develops macular edema.

Liver Function

Increased hepatic enzymes, in particular ALT but also GGT and AST have been reported in multiple sclerosis patients treated with fingolimod. In clinical studies, transaminase elevations occurred at any time during treatment although the majority occurred within the first 12 months. Serum transaminase levels returned to normal within approximately 2 months after discontinuation of fingolimod. Mild isolated bilirubin increases have been noted in pediatric patients on fingolimod. Due to the immunosuppressive properties of fingolimod, initiation of treatment should be delayed in patients with active viral hepatitis until resolution.

Malignancies

Basal cell carcinoma and other cutaneous neoplasms, including malignant melanoma, squamous cell carcinoma, Kaposi's sarcoma, and Merkel cell carcinoma, have been reported in patients receiving fingolimod. Vigilance for skin lesions is warranted and a medical evaluation of the skin is recommended at initiation, and then every 6 to 12 months taking into consideration clinical judgment.

There have been cases of lymphoma in clinical studies and the post-marketing setting. The cases reported were heterogeneous in nature, mainly non-Hodgkin's lymphoma, including B-cell and T-cell lymphomas. If lymphoma is suspected, fingolimod should be discontinued.

Nervous System Disorders

Depression and anxiety are known to occur with increased frequency in the multiple sclerosis population. Depression and anxiety as well as seizures have also been reported in pediatric patients treated with fingolimod.

Return of disease activity (rebound) after fingolimod discontinuation

In the post-marketing setting, severe exacerbation of disease has been observed rarely in some patients stopping fingolimod. This has generally been observed within 12 weeks after stopping fingolimod, but has also been reported up to 24 weeks after fingolimod discontinuation. Caution therefore indicated when stopping fingolimod

therapy. If discontinuation of fingolimod is deemed necessary, the possibility of recurrence of exceptionally high disease activity should be considered and patients should be monitored for relevant signs and symptoms and appropriate treatment initiated as required.

Immune System Effects Following fingolimod discontinuation

Fingolimod remains in the blood and has pharmacodynamic effects, including decreased lymphocyte counts, for up to 2 months following the last dose of fingolimod. Lymphocyte counts generally return to the normal range within 1–2 months of stopping. Because of the continuing pharmacodynamic effects of fingolimod, initiating other drugs during this period warrants the same considerations needed for concomitant administration (e.g., risk of additive immunosuppressant effects).

Fetal risk

Women of childbearing potential should use effective contraception during fingolimod treatment and for 2 months after stopping fingolimod.

5.1.3 Risks Associated with Corticosteroids

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

5.1.4 Risks Associated with Antihistamines

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

5.1.5 Pregnancy and Breastfeeding

Female patients of childbearing potential (postmenarchal) should take all appropriate precautions to avoid becoming pregnant during this study.

As such, female patients of childbearing potential must agree either to remain abstinent or to use two methods of contraception, including at least one method with a failure rate of $<1\%$ per year, during the treatment periods and for the following time periods:

- At least 24 weeks after receiving their final dose of ocrelizumab/ocrelizumab placebo during the double-blind period and for 2 months after their last dose of fingolimod/fingolimod placebo, whichever is later (for patients who withdraw from treatment during the double-blind period).
- At the end of the double-blind period, for at least 24 weeks after receiving their final dose of ocrelizumab for patients treated in Group A; and for 2 months after their final dose of fingolimod for patients treated in Group B (see Section 4.1.1.1).

Once the treatment allocated during the double-blind period has been revealed to the investigators, he/she should advise the patients on the timeframe for taking the contraception.

Adherence to local requirement, if more stringent, is required.

Regular pregnancy tests will be performed during the study as described in Appendix 1.

Monthly urine pregnancy tests may be required as per local recommendations.

A female patient/parent/legal guardian must be instructed to immediately inform the investigator if she/the daughter becomes pregnant during the treatment periods and within 24 weeks after her final dose of ocrelizumab/ocrelizumab placebo or 2 months after final dose of fingolimod/fingolimod/placebo.

Given that there are insufficient, well-controlled data from studies testing the use of ocrelizumab and/or fingolimod in pregnant or breastfeeding women, all infusions of ocrelizumab/ocrelizumab placebo and oral therapy with fingolimod/fingolimod placebo 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 further treatment (oral daily treatment with fingolimod/fingolimod placebo and/or infusions with ocrelizumab/ocrelizumab placebo) 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/ocrelizumab placebo and/or fingolimod/fingolimod placebo treatment following pregnancy and breastfeeding will be decided as a result of a thorough benefit-risk discussion between the patient and parents/legal guardian, investigator (as appropriate; see Section 4.3.3) and the Roche Medical Monitor. For reporting requirements for pregnancies in female patients, see Section 5.4.3.

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 and parents/legal

guardian (as appropriate) 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. Authorization will be sought in order for the Sponsor to collect information on the health and wellbeing of the infant of a female patient.

Animal studies with fingolimod have shown reproductive toxicity including fetal loss and organ defects, notably persistent truncus arteriosus and ventricular septal defect. Furthermore, the receptor affected by fingolimod (sphingosine 1-phosphate receptor) is known to be involved in vascular formation during embryogenesis.

The rate of congenital malformations observed in babies exposed to fingolimod during pregnancy is about 2 times the rate observed in the general population (in whom the rate of congenital malformations is about 2–3%). The most frequently reported malformations included cardiac, renal, and musculoskeletal malformations. Further details on the fingolimod teratogenic risk in a case of pregnancy are available in the local prescribing information.

For pregnancies occurring in female patients during the treatment periods or within 24 weeks after their last dose of ocrelizumab/ocrelizumab placebo, pregnancy outcome and the health status of the child will be followed until the child is one 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-positive B-cell levels in neonates and infants prior to vaccination is recommended.

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

5.1.6 Management of Patients Who Experience Adverse Events

5.1.6.1 Treatment Interruption

Study drug treatment may be temporarily suspended in patients who experience relevant adverse events considered to be related to study drug and prevent the patient from re-treatment with the study drug (see Section 4.3.3 for details on re-treatment criteria).

For female patients who become pregnant during the study, study drug treatment must be withheld for the duration of the pregnancy and breastfeeding. Study drug may be

restarted following the delivery/end of breastfeeding, after discussing the risks and benefits of continuing the treatment (see Section 5.4.3).

5.1.6.2 Management Guidelines

5.1.6.2.1 Infusion-Related Reactions

Slowing of the infusion rate or interruption of the infusion may be necessary in the event of an infusion reaction. In rare cases, ocrelizumab treatment may need to be discontinued. Handling of IRRs will depend on the intensity of symptoms (see also Table 4 for grading of intensity of IRRs). The following guidance should be followed as a minimum. More stringent procedures may be followed at the discretion of the physician.

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

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

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

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

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/ocrelizumab placebo 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 the event of a suspected anaphylactic reaction during study treatment infusion, please refer to Appendix 3.

5.1.6.2.2 *Liver Injury*

Liver function tests should be performed before initiation of treatment with ocrelizumab, and participants should be monitored for signs and symptoms of any hepatic injury during treatment. Serum aminotransferases, alkaline phosphatase, and bilirubin levels should be measured in participants who report symptoms that may indicate liver injury, including new or worsening fatigue, anorexia, nausea, vomiting, right upper abdominal discomfort, dark urine, or jaundice. If liver injury is confirmed, discontinue ocrelizumab. If an alternative etiology is identified, treatment with ocrelizumab can be resumed only when the event has been fully resolved.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.10 and 5.3.5.11 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, Xray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)
- This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.12)
- 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 terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

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

- 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 or parents/legal guardian (as appropriate) contact. All adverse events whether reported by the patient, parents/legal guardian or noted by study personnel, 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 5.4.2 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 48 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 v 5.0 will be used for assessing adverse event severity. Table 4 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 4 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

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

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 5) below:

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

Table 5 Causal Attribution Guidance

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Clinical Relapses

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

5.3.5.3 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than

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

5.3.5.4 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 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

5.3.5.6 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 4.3.3; criteria for re-treatment with ocrelizumab/ocrelizumab placebo and fingolimod/fingolimod placebo) 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 5.3.5.4 for details on recording persistent adverse events).

If a clinically significant vital sign abnormality is observed during the infusion of ocrelizumab/ocrelizumab placebo, the event should be reported on a dedicated Adverse Event eCRF, prespecified Infusion-Related Reaction. Associated signs and symptoms, including severity, should be recorded on this dedicated Infusion-Related Reaction eCRF (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 eCRF.

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 (see Section 5.3.5.6) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.9 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 5.4.2). This includes death attributed to progression of MS.

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

If the death is attributed solely to progression of MS "multiple sclerosis progression" should be recorded on the Adverse Event eCRF.

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

5.3.5.10 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. These data will be captured as exploratory assessment data only. Clinical relapses should be captured on the MS Relapse eCRF (see Section 5.2.1), as well as on the Adverse Event eCRF. 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/ocrelizumab placebo, unless this is more than 24 hours
- Hospitalization for supervision purposes following completion of ocrelizumab/ocrelizumab placebo 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 Cases of Accidental 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 5.4.2).

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

The highest dose of ocrelizumab 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 ocrelizumab overdose; interrupt the infusion immediately and observe the patient for IRRs.

Single fingolimod doses up to 80 times the recommended dose (0.5 mg) were well tolerated in healthy adult subjects. At 40 mg, 5 of 6 subjects reported mild chest tightness or discomfort, which was clinically consistent with small airway reactivity.

Upon treatment initiation, fingolimod can induce bradycardia within one hour of the first dose, and is steepest within 6 hours. Usually, bradycardia persists beyond 6 hours and progressively attenuates over subsequent days of treatment. Isolated reports of slow atrioventricular conduction and transient, spontaneously resolving complete AV block have been reported. If an overdose constitutes first exposure to fingolimod, it is important to monitor patients with a continuous (real time) ECG and hourly measurement of heart rate and blood pressure, at least during the first 6 hours.

Additionally, monitoring should be extended at least overnight and until the findings have resolved if the heart rate after 6 hours is <45 bpm in adults, <55 bpm in patients aged ≥ 12 years, or <60 bpm in patients aged ≥ 10 to < 12 years, or if the ECG after 6 hours shows second degree or higher AV block or a QTc interval ≥ 500 msec. If third degree AV block occurs at any time, extended monitoring, including overnight monitoring, should be performed.

5.3.5.14 Patient-Reported Outcome Data

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

5.3.6 Special Situations: Accidental Overdose And/or Medication Error

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

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug (e.g., wrong drug, expired drug, accidental overdose, underdose, wrong dosing schedule, incorrect route of administration)

After initiation of study drug, special situations associated with blinded ocrelizumab/matching placebo and any associated adverse events will be reported until the end of the SFU period, which is at least 48 weeks after the last infusion but may be extended in patients whose B-cells take longer to replete.

Special situations and any associated adverse events should be reported within 30 days after the investigator becomes aware of the situation. However, if an associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, both the event and the special situation should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), as described in Section 5.4.2.

Special situations are not in themselves AEs but may result in AEs. For blinded ocrelizumab, AEs associated with special situations should be recorded as described below for each situation:

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

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

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

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

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

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

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

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

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

5.4.1 Emergency Medical Contacts and Medical Monitor

Investigators will be provided with contact information for the Medical Monitor. An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track

all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until during the study through the end of the SFU period, which is at least 48 weeks after the last infusion but may be extended in patients whose B cells take longer to replete (B-cell monitoring period).

Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

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

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

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential (and parents/legal guardian, as applicable) will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the treatment periods of the study or within 6 months after the last dose of study drug. The investigator should report the pregnancy on the paper 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. The investigator must discontinue study drug and counsel the patient and parents/legal guardian (as appropriate), discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy (see Section 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 with additional information on the patient and the course and outcome of the pregnancy as it becomes available.

For pregnancies occurring in female patients during treatment with ocrelizumab/ocrelizumab placebo or within 6 months after their last dose of ocrelizumab/ocrelizumab placebo, attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status during the first 12 months after birth (see Section 5.1.5).

5.4.3.2 Abortions

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

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

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

5.4.3.3 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient or parents/legal guardian 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, 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, with follow-up information on the infant collected according to procedures outlined in Section 5.4.3.

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 48 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 *as described in the eCRF Completion Guidelines.*

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 Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously

communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

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 authorities (which includes the use of applicable systems, such as EudraVigilance), IRBs, ECs, and investigators.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the document(s) listed below:

Drug	Document
Ocrelizumab	Investigator's Brochure
Fingolimod	EU SmPC

SmPC = Summary of Product Characteristics.

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

Full details of all statistical issues and planned statistical analyses will be specified in a separate SAP, which will be finalized prior to the database lock and unblinding.

6.1 DETERMINATION OF SAMPLE SIZE

The sample size for this study is estimated based on data from ocrelizumab Phase III studies in adults with RMS (WA21092 OPERA I and WA21093 OPERA II) and from a fingolimod Phase III study in pediatric patients with MS (PARADIGMS).

In a non-inferiority trial, a larger non-inferiority margin allows for a reduced sample size. Given the low incidence of pediatric MS and as a rare disease, this would increase the feasibility of this study.

The protocol-defined ARR in patients treated with fingolimod is 0.12. Assuming patients treated with ocrelizumab have the same ARR of 0.12 and a dispersion parameter of 1, a sample size of 171 patients in total (1:1 randomization allocation) is required for a non-inferiority margin of 3 at a power of 80% and a one-sided type I error rate of 2.5%, given a recruitment period of around 30 months and a drop-out rate of 3% per year.

An adaptation in sample size or follow-up duration may be considered in the event of changes to the sample size assumptions on the basis of blinded data review or factors external to the study.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study discontinuation will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results. Intercurrent events will be listed and summarized. Study drug administration, including the number of doses received, will be listed and summarized.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

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

Except where stated, assessments performed at the Day 1 visit will be used for summarizing baseline characteristics.

6.4 EFFICACY ANALYSES

The analysis population for the efficacy analyses will consist of all randomized patients, with patients grouped according to their assigned treatment.

6.4.1 Primary Efficacy Endpoint

The primary efficacy objective is to demonstrate non-inferiority of ocrelizumab versus fingolimod in protocol-defined ARR, as measured through the rate ratio in counts during the double-blind treatment period, in the hypothetical situation that patients do not withdraw from the study treatment; only data collected prior to treatment withdrawal will be included in the primary analysis.

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

The treatment effect and ARR on each treatment arm will be estimated based on a negative binomial regression model with randomized treatment as the main effect and adjusted for the stratification factors (region [United States vs. ROW], pre-pubertal status (yes vs. no), and presence of T1 Gd lesions at baseline [yes vs. no]). The response variable is the number of protocol-defined relapses during the double-blind period for each patient. The log-transformed exposure for each patient will be included in the model as an offset variable in order to adjust for varying duration of follow-up. For patients who discontinue the study treatment early, only data collected before the early treatment discontinuation will be included in this analysis (with the exception of subsequent data used to confirm protocol defined relapse); no imputation of missing data will be performed.

The primary estimand follows a hypothetical strategy based on the following attributes:

a) Treatment: ocrelizumab administered by IV infusion every 24 weeks versus fingolimod taken PO QD.

b) Population: patients with RRMS aged between ≥ 10 and < 18 years. The analysis population will consist of all randomized patients, with patients grouped according to their assigned treatment.

c) Variable: the number of protocol-defined relapses during the double-blind treatment period from when patients having initiated study treatment

d) Intercurrent events will be handled as follows:

- Premature discontinuation from treatment: only data collected before this intercurrent event will be included in the analysis, with the exception of subsequent data used to confirm protocol-defined relapse; no imputation will be performed.

e) Summary measure: rate ratio of protocol-defined ARR

Hypothesis Test

The null hypothesis for the primary analysis will be tested at the $\alpha = 0.025$ level (one−sided test) with a non-inferiority margin of 3:

- H0 (null hypothesis): Protocol-defined ARR is higher in patients treated with ocrelizumab compared to patients treated with fingolimod, i.e., ocrelizumab is inferior to fingolimod in protocol-defined ARR.
- H1 (alternative hypothesis): Protocol-defined ARR is not higher in patients treated with ocrelizumab compared to patients treated with fingolimod.

The test of the hypothesis will be based on a negative binomial regression model with randomized treatment as the main effect and adjusted for the stratification factors.

Sensitivity Analysis for the Primary Estimand

To assess the robustness of the estimated treatment effect to the proposed missing data handling strategy, a tipping point analysis will be performed. Missing data from each treatment arm will be imputed based on the "missing at random" assumption, and then a penalty will be added to the imputed data in the ocrelizumab arm that reduces the treatment effect. The impact of different penalties will be assessed.

Supplementary Estimand to Estimate the Treatment Effect Regardless of Adherence to the Randomized Treatment

The supplementary estimand will use a treatment policy strategy for the intercurrent event of treatment discontinuation to estimate the treatment effect of ocrelizumab versus fingolimod regardless of adherence to the randomized treatment. All data collected during the double-blind period will be included in the analysis. For premature study discontinuation, multiple imputation of missing data based on trajectories from patients within the same treatment arm who withdraw from treatment but remain in the study will be performed.

6.4.2 Secondary Efficacy Endpoints

If the primary estimand is statistically significant, all secondary estimands will be tested in a fixed sequence at a 0.05 significance level (or 0.025 for one-sided test). The sequence of hierarchical testing for all secondary endpoints will be specified in the SAP.

The main secondary efficacy objective for this study is to demonstrate non-inferiority of ocrelizumab compared with fingolimod on the basis of the number of new or enlarging T2 lesions during the double-blind period. The test of the non-inferiority hypothesis and the estimation of the treatment effect in the number of new or enlarging T2 lesions will be based on a negative binomial regression model with randomized treatment as the main effect and adjusted for the stratification factors. The response variable is the number of new or enlarging T2 lesions for each patient, calculated as the sum of the individual number of new or enlarging T2 lesions from baseline during the double-blind treatment period; data from the withdrawal visit assessments will be included in this analysis; data from the unscheduled visit assessments will not be included in this analysis. The log-transformed number of brain MRI scans received by each patient will be included in the model as an offset variable in order to adjust for varying duration of follow-up as well as intermediate missing assessments. Intermediate missing assessments at scheduled visits will not be imputed. For patients who discontinue the study treatment early, only data collected before the early treatment discontinuation will be included in this analysis; no imputation of missing data will be performed.

Other secondary efficacy objectives include testing superiority hypotheses for the following measures:

- Number of T1 Gd lesions at Week 12
- Number of new or enlarging T2 lesions per MRI scan during the double-blind period

- Protocol-defined ARR during the double-blind period

The estimands for the secondary endpoints follow the same hypothetical strategy for the intercurrent event of treatment discontinuation as for the primary estimand. All comparisons will be made in the hypothetical situation that patients do not withdraw from the study treatment; only data collected prior to treatment withdrawal will be included in the secondary analyses.

The same supplementary estimand applied to the primary endpoint will also be applied to the secondary endpoints where a treatment policy strategy for the intercurrent event of treatment discontinuation will be followed.

6.4.3 Exploratory Efficacy Endpoints

The exploratory efficacy objective is to evaluate the efficacy of ocrelizumab compared with fingolimod as reflected by the endpoints listed in Section 2.1.3.

The analyses of exploratory efficacy endpoints will be described in the SAP.

6.4.4 Subgroup analyses

The primary and key secondary efficacy endpoints will be analyzed by the following subgroups if sufficient numbers of patients in subgroups are observed:

- Stratification factor: region (United States vs. ROW)
- Stratification factor: pre-pubertal status (yes vs. no)
- Stratification factor: presence of T1 Gd lesions at baseline (yes vs. no)
- Demography: baseline weight ($\geq$ 35 kg vs. $<$ 35 kg)
- Time of enrollment: enrollment time (early vs late)
- Wash out period of prior corticosteroids use: >30 days vs ≤ 30 days

Estimates of treatment effect and associated 95% CIs will be presented in forest plots.

6.5 SAFETY ANALYSES

The safety objective for this study is to evaluate the safety profile of ocrelizumab compared with fingolimod on the basis of the endpoints listed in Section 2.2.

The analysis population for all of the safety endpoint analyses will consist of all randomized patients (approximately 171 patients) who receive at least one dose (partial or complete) of study drug (ocrelizumab or fingolimod), with patients grouped according to their actual treatment received. Safety data will be summarized by treatment arm regardless of premature study treatment discontinuation but until switch to another DMT (including commercial ocrelizumab or commercial fingolimod) during the double-blind period. The exposure (time at risk) for each safety endpoint is defined as the time from the date of the first exposure to the study treatment to the date of double-blind period completion, study withdrawal or switch to another DMT (including commercial

ocrelizumab or commercial fingolimod), whichever occurs earlier. In addition, all safety data until the end of the study will be reported.

Safety data will be listed and summarized descriptively. 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 and diastolic blood pressure, pulse rate, respiratory rate, body temperature) and incidence of vital sign and ECG abnormalities

The incidence count for each AE 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 treatment group. In addition, the rate per 100 patient-years by treatment group (along with the 95% CI using the exact method based on the Poisson distribution) will be calculated for all AEs and SAEs.

6.5.1 Analyses of Exposure, Adverse Event, Laboratory, and Vital Sign Data

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

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

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to

summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

6.6 PHARMACOKINETIC ANALYSES

Nonlinear mixed-effects modeling will be used to analyze the sparse concentration-time data of ocrelizumab via the population PK approach. Patients who have measurable concentrations of ocrelizumab will be included in the PK analysis unless major protocol deviations or unavailability of information (e.g., exact blood sampling time) occurred which may interfere with PK evaluation. The PK data of this study may be pooled with data from other studies. The PK analysis may be reported separately from the main study Clinical Study Report (CSR).

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining postbaseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported via descriptive statistics if there is sufficient data.

6.8 BIOMARKER ANALYSES

Biomarkers will be assessed at baseline and subsequent timepoints following administration of ocrelizumab. PD biomarkers will be presented as absolute value over time and/or percent change relative to baseline over time. Biomarker levels at baseline or over time may be compared with efficacy or safety measurements to assess prognostic or predictive properties. Descriptive or summary statistics will be used to describe biomarker assessments.

6.9 OPTIONAL INTERIM ANALYSIS

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one interim analysis. This is to avoid unnecessary long exposure to some patients if the recruitment is too slow. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed.

If an interim analysis is conducted, the Sponsor will remain blinded. The interim analysis will be conducted by an external statistical group and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter.

The decision to conduct the optional interim analysis, along with the rationale, timing, thresholds for declaring positive efficacy or futility, and statistical details for the analysis, will be documented in the SAP. The SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis. The iDMC Charter will be updated to document potential recommendations the iDMC can make to the Sponsor as a result of the analysis (e.g., end the double-blind period early for positive efficacy or futility), and the iDMC Charter will also be made available to relevant health authorities.

If there is a potential for the study to end the double-blind period for positive efficacy as a result of the interim analysis, the type I error rate will be controlled to ensure statistical validity is maintained. Specifically, the Lan-DeMets α-spending function that approximates the Pocock boundary will be applied to determine the critical value for stopping for positive efficacy at the interim analysis (DeMets and Lan 1994). Additional criteria for recommending to end the double-blind period for positive efficacy may be added to the iDMC Charter. If the study continues beyond the interim analysis, the critical value at the final analysis would be adjusted accordingly to maintain the protocol-specified overall type I error rate, per standard Lan-DeMets methodology.

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, MRI, electronic clinical outcome assessment, and other electronic data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data. eCRFs and correction documentation will be maintained in the

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

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 ELECTRONIC PATIENT-, OBSERVER-, AND CLINICIAN-REPORTED OUTCOME DATA

A secure web portal will be used to capture PRO and ObsRO data. The web portal may be accessed via an electronic device provided by the same vendor at the site. If the caregiver is unable to attend an in-person site visit, the ObsRO measures should be completed at home using any device with internet access by the same caregiver on the same day as the scheduled site visit. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with FDA regulations for electronic records (21 CFR Part 11). The data will be stored in a centralized database maintained by the electronic device vendor.

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

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

7.4 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.5 USE OF COMPUTERIZED SYSTEMS

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

7.6 RETENTION OF RECORDS

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

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

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

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. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the Clinical Trials Regulation (536/2014) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

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

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient and parents/legal guardian the objectives, methods, and potential risks associated with each optional procedure. Patients and parents/legal guardian (as appropriate) 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 and/or parents/legal guardian (as appropriate) agreement to participate in optional procedures.

Patients and/or parents/legal guardian 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 and/or parents/legal guardian to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

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

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

For sites in the United States, each Consent Form may also include patient and parents/legal guardian (as appropriate) 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 and parents/legal guardian (as appropriate) 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 parents/legal guardian, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse 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 and/or parents/legal guardian, 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 9.6).

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

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters

(e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

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

Approximately 150 sites globally will participate to enroll approximately 171 patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An iDMC will be employed to monitor and evaluate patient safety throughout the study, until the primary analysis is performed. Monitoring details will be described in the iDMC Charter.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and 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 CSR. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

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

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

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

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

9.7 PROTOCOL AMENDMENTS

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

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

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Appendix 1
Schedule of Activities

Table 1 Double-Blind Period

	Screening [a]	Baseline	Double-Blind Period																		Delayed Dosing Visit [d]	Opt Inf Visit for Split Dose [d]	Unscheduled Site / MN [e]	Withdrawal from Treatment [f]	End of Study
Site or Optional MN Visits [b]	1	2	3	4	5(MN)	6	7	8(MN)	9	10	11(MN)	12	13	14(MN)	15/Additional Treatment Cycles										
Week	–8 to–1	1	2	12	22 [c]	24	36	46 [c]	48	60	70 [c]	72	84	94 [c]	96	96 +12 wks	(MN) 96 +22 wks[c]	D1 (N)	D1 +12 wks	(MN) D1 +22 wks [c]					
Study Day (±days)	–56 to –1	1[g] (+1)	15 (±3)	85 (±10)	155 (±7)	169 (±7)	253 (±10)	323 (±7)	337 (±7)	421 (±10)	491 (±7)	505 (±7)	589 (±10)	659 (±7)	673 (±7)	757 (±10)	827 (±7)	n (±7)	n+84 (±10)	n+154 (±7)					
Informed consent/assent [h]	x																								
Telephone interview (or video call) (±7 days) [i]		x	x	At Weeks 4, 8, 16, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88, and 92 and every 4 weeks (±7 days)																	x	x	(x)		
Demographic data	x																								
Medical history and baseline conditions	x	x																							
Review of the eligibility criteria	x	x																							
PROs and ObsROs [j]	x	x				x			x			x			x			x			(x)			(x)	x
Caregiver/Patient interviews (optional) [j]									x						x										
Physical examination [k]	x (MN)	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x	(x)	x	x
Weight [l]	x	x		(x)		x	(x)		x	(x)		x	(x)		x	(x)		x	(x)		(x)		(x)	(x)	x
Height [m]	x					x			x			x			x			x			(x)			(x)	x
Tanner staging [n]	x	(x)		Yearly [n]																	(x)			(x)	x
Date of menarche [o]		(x)	(x)	(x)(MN)	(x)	(x)	(x)(MN)	(x)	(x)	(x)(MN)	(x)	(x)	(x)(MN)	(x)	(x)	(x)(MN)	(x)	(x)	(x)(MN)	(x)	(x)			(x)	x

Appendix 1: Schedule of Activities

Table 1 Double-Blind Period (cont.)

	Screening [a]	Baseline	Double-Blind Period																			Delayed Dosing Visit [d]	Opt Inf Visit for Split Dose [d]	Unscheduled Site / MN [e]	Withdrawal from Treatment [f]	End of Study
Site or Optional MN Visits [b]	1	2	3	4	5(MN)	6	7	8(MN)	9	10	11(MN)	12	13	14(MN)	15/Additional Treatment Cycles											
Week	–8 to–1	1	2	12	22 [c]	24	36	46 [c]	48	60	70 [c]	72	84	94 [c]	96	96 +12 wks	(MN) 96 +22 wks [c]	D1 (N)	D1 +12 wks	(MN) D1 +22 wks [c]							
Study Day (±days)	–56 to –1	1[g] (+1)	15 (±3)	85 (±10)	155 (±7)	169 (±7)	253 (±10)	323 (±7)	337 (±7)	421 (±10)	491 (±7)	505 (±7)	589 (±10)	659 (±7)	673 (±7)	757 (±10)	827 (±7)	n (±7)	n+84 (±10)	n+154 (±7)							
Wrist/Hand X-ray [p]	x [p]	Yearly [p]																				(x)			(x) [q]	x [q]
Brain MRI scan [r,s]	x [s]			x [s]		x			x			x			x			x				(x)		(x)	(x)	x
Ophthalmologic evaluation [t]	x			x		(x)			(x)			(x)			(x)			(x)				(x)		(x)		
Neurologic examination [u]	x	x		x		x	x		x	x		x	x		x	x		x	x			(x)		(x)	(x)	x
EDSS[u]	x	x		x		x	x		x	x		x	x		x	x		x	x			(x)		(x)	(x)	x
SDMT	x	x				x			x			x			x			x				(x)			(x)	x
Concomitant medication		x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x		x	x		(x)	x	
Adverse events	Only SAEs	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x		x	x		(x)	x	
Clinical relapses			x	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x		x	x		(x)	x	
Thyroid function tests [v]	x(MN)				x			x			x			x			x			x		(x)		(x)	(x)	
Hepatitis screening [w]	x(MN)																									
Hepatitis B virus DNA [w]	x(MN)	(x)		(X(MN))	(x)		(X(MN))	(x)		(X(MN))	(x)		(X(MN))	(x)		(X(MN))	(x)		(X(MN))	(x)		(x)			(x)	(x)	
Rapid plasma reagin	x(MN)																									
AQP-4 antibody testing	x(MN)																									

Appendix 1: Schedule of Activities

Table 1 Double-Blind Period (cont.)

	Screening [a]	Baseline	Double-Blind Period																			Delayed Dosing Visit [d]	Opt Inf Visit for Split Dose [d]	Unscheduled Site / MN [e]	Withdrawal from Treatment [f]	End of Study
Site or Optional MN Visits [b]	1	2	3	4	5(MN)	6	7	8(MN)	9	10	11(MN)	12	13	14(MN)	15/Additional Treatment Cycles											
Week	–8 to–1	1	2	12	22 [c]	24	36	46 [c]	48	60	70 [c]	72	84	94 [c]	96	96 +12 wks	(MN) 96 +22 wks [c]	D1 (N)	D1 +12 wks	(MN) D1 +22 wks [c]						
Study Day (±days)	–56 to –1	1[g] (+1)	15 (±3)	85 (±10)	155 (±7)	169 (±7)	253 (±10)	323 (±7)	337 (±7)	421 (±10)	491 (±7)	505 (±7)	589 (±10)	659 (±7)	673 (±7)	757 (±10)	827 (±7)	n (±7)	n+84 (±10)	n+154 (±7)						
MOG antibody testing	x(MN)																									
HIV testing [x]	x(MN)																									
Tuberculosis testing [x]	x(MN)																									
Varicella testing [y]	x(MN)																									
CD4 percentage	x(MN)																							(x)		
Total Ig, IgA, IgG, and IgM	x(MN)	x		x(MN)	x		x(MN)	x		x(MN)	x		x(MN)	x		x(MN)	x		x(MN)	x				(x)	(x)	x
Immunologic assessments (including CD4%) [z]		x	x	x(MN)	x		x(MN)	x		x(MN)	x		x(MN)	x		x(MN)	x		x(MN)	x				(x)	(x)	x
Routine safety laboratory [aa]	x(MN)	x	x	x(MN)	x	(x)	x(MN)	x	(x)	x(MN)	x	(x)	x(MN)	x	(x)	x(MN)	x	(x)	x(MN)	x	(x)			(x)	(x)	x
Urinalysis [aa]	x(MN)	x	x	x(MN)	x	(x)	x(MN)	x	(x)	x(MN)	x	(x)	x(MN)	x	(x)	x(MN)	x	(x)	x(MN)	x	(x)			(x)	(x)	x
Pregnancy test [bb]	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x		(x)	(x)	x
Antibody titers [cc]		x		x(MN)	x			x			x			x			x			x			(x)	(x)	x
Plasma/urine banking for JCV [dd]		x			x			x			x			x			x			x				(x)	x
Biomarker serum sample [ee]		x		x(MN)	x			x			x			x			x			x				(x)	x
RBR DNA sample (optional) [ff]		x													x						(x)			x	x

Appendix 1: Schedule of Activities

Table 1 Double-Blind Period (cont.)

	Screening [a]	Baseline	Double-Blind Period																		Delayed Dosing Visit [d]	Opt Inf Visit for Split Dose [d]	Unscheduled Site / MN [e]	Withdrawal from Treatment [f]	End of Study
Site or Optional MN Visits [b]	1	2	3	4	5(MN)	6	7	8(MN)	9	10	11(MN)	12	13	14(MN)	15/Additional Treatment Cycles										
Week	–8 to–1	1	2	12	22 [c]	24	36	46 [c]	48	60	70 [c]	72	84	94 [c]	96	96 +12 wks	(MN) 96 +22 wks [c]	D1 (N)	D1 +12 wks	(MN) D1 +22 wks [c]					
Study Day (±days)	–56 to –1	1[g] (+1)	15 (±3)	85 (±10)	155 (±7)	169 (±7)	253 (±10)	323 (±7)	337 (±7)	421 (±10)	491 (±7)	505 (±7)	589 (±10)	659 (±7)	673 (±7)	757 (±10)	827 (±7)	n (±7)	n+84 (±10)	n+154 (±7)					
Review of re-treatment criteria [c]			x			x			x			x			x			x			x	x	(x)		
Twelve-lead ECG (predose and postdose) [gg]	x	x	x			x			x			x			x			x			x	x		x	x
Vital signs [hh]	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	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			x			x			x				
Premedications [kk]		x	x			x			x			x			x			x			x	x			
Administration of IV ocrelizumab/placebo [c, g, ll]		x	x			x			x			x			x			x			x	x			
Dispense fingolimod/placebo and compliance check		x	x	x		x	x		x	x		x	x		x	x		x	x		(x)			x	x
First dose monitoring for fingolimod/placebo [mm]		x	Additional monitoring as required (refer to prescribing information)																						

Table 1 Double-Blind Period (cont.)

ADA=anti-drug antibody; AQP-4=; β-hCG=beta-human chorionic growth hormone; eCRF=electronic Case Report Form; CD=cluster of differentiation; D=day; EC=Ethics Committee; ECG=electrocardiogram; EDSS=Expanded Disability Status Scale; FS=Functional System; Gd=gadolinium; HBcAb=hepatitis B core antibody; HBV=hepatitis B virus; HBsAg=hepatitis B surface antigen; HepCAb=hepatitis C antibody; Inf=infusion; IRB=Institutional Review Board; IRR=infusion-related reaction; IxRS=interactive voice or web-based response system; JCV=JC–virus; MN=mobile nursing; MOG=myelin oligodendrocyte glycoprotein; MRI=magnetic resonance imaging; MS=multiple sclerosis; OCT=optical coherence tomography; Opt=optional; PA=posteroanterior; PCR=polymerase chain reaction; PedsQL=Pediatric Quality of Life Inventory; PK=pharmacokinetic; PRO=patient-reported outcome; ObsRO=observer reported-outcome; Opt=optional; RBR=Research Biosample Repository; SAE=serious adverse event; SDMT=Symbol Digit Modalities Test; SFU= safety follow-up; 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/ocrelizumab placebo infusion.

(MN) indicates that this visit may be performed as a mobile nursing visit OR that some assessments may be done (or repeated) remotely by a MN.

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. During screening if any laboratory repeats are required the MN professional can be contacted for the blood collection and shipment to the central laboratory.

[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. 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. Optional MN visits may also be used in situation where some assessments have to be done or repeated remotely (e.g., blood collection and shipment to the central laboratory). Some of the assessments (as indicated) at a scheduled clinic visit may be completed by the MN at the patient's home to reduce the time required at the site. In this case, the MN visit must be scheduled within the visit time window as specified, but in advance of the clinic visit to allow the results of these assessments to be available to the site

[c] **Prior to re-treatment with ocrelizumab/**ocrelizumab **placebo**, 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/ocrelizumab placebo. 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/ocrelizumab placebo. 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

Table 1 Double-Blind Period (cont.)

be required to collect blood samples (except if the last laboratory analyses were performed within 4 weeks) and patient's information to enable the treating investigator to assess whether a patient meets criteria for re-treatment with ocrelizumab/ocrelizumab placebo (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.

[e] 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 by the blinded examining investigator (or rater) within 7 days of the onset of the relapse. Other tests/assessments may be done as appropriate.

[f] Withdrawal from treatment visit takes place when a patient discontinues prematurely from study treatments during the double-blind period. Patients withdrawing from study treatments will be encouraged to remain in the double-blind period and will follow the schedule of activities until completion of the primary analyses and communication from the Sponsor (Sections 3.1.2 and 3.1.5). If the patient does not want to continue in the study, that visit will be a withdrawal from study visit and all assessments (including those in parenthesis) will be performed.

[g] Vital signs and ECGs are to be performed on the dosing day, with all blood tests (including PK) and the review of adverse events and concomitant medications

[h] 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).

[i] **A telephone interview (or video call)** will be conducted by site personnel within 24 (± 4) hours after completion of each infusion and every 4 weeks (± 7 days) between any visit (MN or site visit) and throughout the entire double-blind period. The purpose of the structured interview is to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit (i.e., new or worsening neurologic symptoms, signs of infection, any unusual signs or symptoms since the patient left the clinic after the infusion, change in concomitant medications). Moreover, in any situation when the scheduled visit (at site or with a mobile nurse) cannot take place or whenever it's deemed necessary a telephone interview or video call can take place.

[j] PROs and ObsROs include patient and caregiver reported PedsQL Generic Core Scale, patient reported fatigue as measured by the PedsQL Multidimensional Fatigue Scale, EQ-5D-5L, caregiver and patient reported Global Impression of Change on fatigue, cognition and overall MS symptoms. Should the caregiver be unable to attend a site visit in person, the ObsRO measures will then be completed electronically at home by the same caregiver on the same day as the scheduled site visit. The patient and caregiver global impression of change questions are the only PRO/ObsRO not collected at screening and Day 1 and are administered from Week 24 onwards. Optional patient and caregiver interviews will be conducted in selected countries within four weeks following the pediatric MS participant's Weeks 48 and 96 visits in the double-blind period. The semi-structured interviews will be completed by telephone/video with a qualitative vendor and will enable the patient and the caregiver to provide details of any changes in regards to MS symptoms and any associated impact throughout the study to date. Consent for this portion of the study will be included in the Assent Form or Informed Consent Form.

[k] At screening and Day 1, 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 adverse event

Table 1 Double-Blind Period (cont.)

accordingly. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

[l] 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. Patients initially assigned to 300mg dose and who reach a body weight of ≥ 35 kg during the study should be switched to the 600mg dose at their next infusion visit. During the course of the study any patient receiving the lower fingolimod/fingolimod placebo dose of 0.25 mg who reaches the weight of 40 kg (over two visits, at least 3 months apart), should be switched to the 0.5 mg dose strength. Additional weight measurements will be required every 12 weeks for confirmation of the weight change as indicated in this table.

[m] Height should be measured in a standing position. 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 may 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.

[n] Tanner staging assessment: Patients will have their Tanner stages documented or assessed yearly until they reach Stage 5. Tanner staging will be documented on the eCRF at screening and yearly thereafter, as applicable.

[o] Date of menarche: Female patients who are premenarchal at the time of screening should be asked about the date of first menarche. The date of first menarche should be recorded on the eCRF. For female patients who are postmenarchal at the time of screening, the date of first menarche should be recorded on the eCRF.

[p] 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 Day 1 (baseline X-ray) and repeated yearly (± 4 weeks). If the bone age is determined to be ≥ 16 years of age, no further bone X-rays are required .

[q] If a prior X-ray was obtained within the last 6 months before the WD from treatment visit, the X-ray should not be repeated.

[r] **"Baseline" MRI scan should be performed after the screening visit**. Subsequent MRI scans will be performed without a Gd-contrast agent during the double-blind period (window of ± 4 weeks of these scheduled visits). Also, MRI scans will be obtained in patients withdrawing from treatment (at a withdrawal from treatment visit), if not performed during the last 4 weeks. For patients who begin an alternative treatment for MS in the double-blind 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).

[s] MRI scans at screening and Week 12 will be performed before and after administration of Gd-contrast agent.

[t] An examination of the fundus, including the macula, should be performed by an ophthalmologist or by a qualified professional or by optical coherence tomography at screening and again at Week 12 after starting treatment, and at any time after a patient reports visual disturbances while on therapy. Please refer to the prescribing information for fingolimod for more information. This examination cannot be performed by the optional MN.

Table 1 Double-Blind Period (cont.)

[u] Neurologic examination (treating investigator) and EDSS (examining investigator or rater): At the visits indicated, the treating investigator will perform a neurologic evaluation of the patient (see Sections 4.6.4 and 5.1.1.2.1). The examining investigator role during the study is to assess independently FS and EDSS at the visits indicated and during an unscheduled visit. The examining investigator and treating investigator should not switch role during the double-blind period and the same rater should assess the EDSS in the same patient (see Sections 4.2.3 and 4.6.2). Results of the neurologic examination (or anything related to patient health) and EDSS scores will not be shared between the treating and examining investigator.

[v] Sensitive thyroid-stimulating hormone will be tested at screening and during the treatment period as indicated. Thyroid autoantibodies will be assayed only at screening.

[w] Hepatitis B Virus 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 as per the schedule of activities.

[x] As allowed by local or national regulations.

[y] In case of negative serological testing for varicella zoster, vaccination must be considered for study eligibility (see Section 4.1.1.1).

[z] Immunologic assessments: Analysis will include the determination of the B-cell number (CD19+), high-sensitivity assay B-cell counts (MRB1.1), B-cell subsets (e.g., CD19, CD27, IgD, CD38 markers to assess naive, memory, plasmablasts, and/or other populations), T-cell counts (CD3+, CD4+, CD8+) and natural killer cells (CD56+) (see Section 4.6.18.2). On infusion visits, blood samples should be collected prior to the methylprednisolone administration.

[aa] 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 locally. If abnormal and applicable a microscopic examination will be performed on site (local laboratory). For more information related to safety laboratory assessments see Section 4.6.18.

[bb] Serum β-hCG must be performed at screening in female patients of childbearing potential (postmenarchal). 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. Monthly urine pregnancy tests may be required as per local recommendations.

[cc] Antibody titers: Measurement of antibody titers against common antigens (mumps, rubella, varicella zoster, and *Streptococcus pneumoniae*) will be performed.

[dd] Plasma and urine samples for JCV will be collected at specified timepoints and analyzed in batches, if decided by the Sponsor.

[ee] Blood to be drawn for serum prior to dosing at the indicated timepoints.

[ff] RBR DNA blood samples to be collected in patients ≥50 kg for research purposes if patient and/or parents/legal guardian agrees to separate optional RBR consent. These RBR DNA samples should be collected at the Day 1 visit and at visit 15 or treatment withdrawal, whichever comes first.

Table 1 Double-Blind Period (cont.)

[gg] ECG (predose and postdose): At screening, ECG should be performed prior to any procedures such as vital signs and blood draws. On infusion visits with ocrelizumab/ocrelizumab placebo, 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/ocrelizumab placebo infusion. **Please refer to Section 4.5.3 for monitoring instructions on the first administration of study treatments** (NB: recording of 12-lead ECG should be done within 60 minutes after completion of the ocrelizumab/ocrelizumab placebo infusion and at the end of the fingolimod 6–hour observation period). Additional ECGs may be taken at the discretion of the physician, as required during an unscheduled visit (Section 4.6.12).

[hh] Vital signs (i.e., pulse rate, systolic and diastolic blood pressure, respiration rate, and temperature). On infusion visits with ocrelizumab/ocrelizumab placebo, 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/ocrelizumab placebo infusion, then every 15 (± 5) minutes for the first hour, then every 30 minutes (±10 minutes) until 1 hour after the end of the infusion. **Please refer to Section 4.5.3 for monitoring instructions on the first administration of study treatments** (NB: monitor patients for a minimum of 6 hours for signs and symptoms of bradycardia with hourly pulse and blood pressure measurements). 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 physician (Section 4.6.13).

[ii] PK samples (predose and postdose): On infusion visits with ocrelizumab/ocrelizumab placebo, 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/ocrelizumab placebo. For the blood sampling post-infusion, the PK sample must be collected from the arm opposite the arm receiving the IV infusion of ocrelizumab/ocrelizumab placebo. At other timepoints (non-infusion visits), samples will be collected at any time during the visit.

[jj] ADA: On infusion visits with ocrelizumab/ocrelizumab placebo (except on Day 15), a serum sample is collected 5–30 minutes prior to the methylprednisolone administration.

[kk] **All patients will receive prophylactic treatment with an antihistamine and methylprednisolone prior to any infusion of ocrelizumab/**ocrelizumab **placebo**. 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/ocrelizumab placebo. IV or oral antihistamine (e.g., diphenhydramine) will be administered 30–60 minutes prior to ocrelizumab/ocrelizumab placebo. The addition of an analgesic/antipyretic, such as acetaminophen/paracetamol, may also be considered.

[ll] **Administration of IV ocrelizumab/**ocrelizumab **placebo**: Refer to Section 4.3.2 for guidance on the infusion procedures and monitoring. The first dose of ocrelizumab/ocrelizumab placebo must be administered as two infusions of half the dose 14 days apart. Subsequent doses will be administered as single infusions. Prior to subsequent infusion of ocrelizumab/ocrelizumab placebo, 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 (or video) interview will be conducted by site personnel within 24 (±4) hours after completion of each infusion (Footnote g). Guidance on First Study Treatment Administration Visit is provided in Section 4.5.3.

Table 1 Double-Blind Period (cont.)

[mm] **First dose monitoring with fingolimod/**fingolimod **placebo**: The first dose of fingolimod/fingolimod placebo must be taken at the clinic, because initiation of fingolimod treatment may result in a decrease in heart rate and may result in atrioventricular conduction delay, for which monitoring in the clinic for at least 6 hours is mandated (Section 4.3.2.2.3). Refer to Section 4.5.3 for guidance on First Study Treatments Administration Visit. Note that an independent physician not involved in patient care will supervise the first dose of fingolimod/fingolimod placebo to ensure that blinding is not compromised by the known lowering of the heart rate on fingolimod treatment initiation.

Appendix 1: Schedule of Activities

Table 2 Ocrelizumab Open-Label Extension Period

Site or Optional MN visits [b]	Open-Label Extension Period [a]											Delayed Dosing Visit [f]	Opt Inf Visit for Split Dose [f]	Unscheduled Site / MN [g]	Withdrawal from Treatment Visit [h]	End of Study [i]
		Dose 1				Dose 2			Dose N [a]							
	Screening [c]	Day 1 [d]	Day 15 [d]	Week 12 [e]	Week 22 [b] (MN)	Day 1	Week 12 [e]	Week 22 [b] (MN)	Day 1	Week 12 [e]	Week 22 [b] (MN)					
Week (windows in days)		0	2 (±3)	12 (±10)	22 (±7)	24 (±7)	36 (±10)	46 (±7)	N (±7)	N+12 week (±10)	N+22 week (±7)					
Telephone interview (or video call) (±7 days) [e]		x	At Weeks 4, 8, 16, 20, 28, 32, 40, 44, 52, and every 4 weeks (±7 days)									x	x	(x)		
Review of eligibility criteria	x	x														
SDMT		x				x			x			(x)			x	x
Physical examination [j]	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x	(x)	x	x
Weight [k]		x				x			x			(x)		(x)	x	x
Height [l]		x				x			x			(x)			(x)	x
Tanner staging [m]		Yearly										(x)				
Date of menarche [n]		(x)		(x)(MN)	(x)	(x)	(x)(MN)	(x)	(x)	(x)(MN)	(x)	(x)			(x)	
Wrist/Hand X-ray [o]		Yearly										(x)				
Brain MRI scan [q]	x [r]	Week 24 after Dose 1 and yearly thereafter										(x)		(x)	x	x
Neurologic examination [s]		x		x [s]		x	x [s]		x	x [s]		(x)		(x)	x	x
EDSS assessment [t]		x				x			x			(x)		(x)	x	x

Appendix 1: Schedule of Activities

Table 2 Ocrelizumab Open-Label Extension Period (cont.)

Site or Optional MN visits [b]	Open-Label Extension Period [a]															
		Dose 1				Dose 2			Dose N [a]							
	Screening [c]	Day 1 [d]	Day 15 [d]	Week 12 [e]	Week 22 [b] (MN)	Day 1	Week 12 [e]	Week 22 [b] (MN)	Day 1	Week 12 [e]	Week 22 [b] (MN)	Delayed Dosing Visit [f]	Opt Inf Visit for Split Dose [f]	Unscheduled Site / MN [g]	Withdrawal from Treatment Visit [h]	End of Study [i]
Week (windows in days)		0	2 (±3)	12 (±10)	22 (±7)	24 (±7)	36 (±10)	46 (±7)	N (±7)	N+12 week (±10)	N+22 week (±7)					
Concomitant medication		x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x	(x)	x	x
Adverse events	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x	(x)	x	x
Clinical relapses	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x	(x)	x	x
Thyroid function tests [u]		x			x			x			x	(x)		(x)	x	x
Hepatitis B Virus DNA [v]		(x)		(x(MN))	(x)		(x(MN))	(x)		(x(MN))	(x)			(x)	(x)	(x)
Total Ig, IgA, IgG, and IgM	x(MN)			x(MN)	x		x(MN)	x		x(MN)	x	(x)		(x)	x	x
Immunologic assessments (including CD4%) [w]	x(MN)			x(MN)	x		x(MN)	x		x(MN)	x	(x)		(x)	x	x
Routine safety laboratory [x]	x(MN)	(x)	(x)	x(MN)	x		x(MN)	x		x(MN)	x	(x)		(x)	x	x
Urinalysis [x]	x(MN)	(x)		x(MN)	x		x(MN)	x		x(MN)	x	(x)		(x)	x	x
Pregnancy test [y]	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x	(x)	x	x
Antibody titers [z]		x			x			x			x	(x)		(x)	x	x
Plasma/Urine banking for JCV [aa]		x														

Table 2 Ocrelizumab Open-Label Extension Period (cont.)

Site or Optional MN visits [b]	Open-Label Extension Period [a]														
		Dose 1				Dose 2			Dose N [a]			Delayed Dosing Visit [f]	Opt Inf Visit for Split Dose [f]	Unscheduled Site / MN [g]	Withdrawal from Treatment Visit [h]	End of Study [i]
	Screening [c]	Day 1 [d]	Day 15 [d]	Week 12 [e]	Week 22 [b] (MN)	Day 1	Week 12 [e]	Week 22 [b] (MN)	Day 1	Week 12 [e]	Week 22 [b] (MN)					
Week (windows in days)		**0**	**2 (±3)**	**12 (±10)**	**22 (±7)**	**24 (±7)**	**36 (±10)**	**46 (±7)**	**N (±7)**	**N+12 week (±10)**	**N+22 week (±7)**					
Biomarker serum samples [bb]		x			x			x			x				x	x
Review of re-treatment criteria [cc]	x	x	x			x			x			x	x	(x)		
Twelve-lead ECG (predose and postdose) [dd]		x	x			x			x			x	x		x	x
Vital signs [ee]	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x(MN)	x	x	x	(x)	x	x
ADA [ff]		x				x			x			x			x	x
Ocrelizumab Premedications [gg]		x	x [d]			x			x			x	x			
Administration of IV ocrelizumab [e, cc, hh]		x	x [d]			x			x			x	x			

Table 2 Ocrelizumab Open-Label Extension Period (cont.)

ADA = anti-drug antibody; β-hCG = beta-human chorionic growth hormone; eCRF = electronic Case Report Form; CD = cluster of differentiation; EC = Ethics Committee; EDSS = Expanded Disability Status Scale; Gd = gadolinium HBcAb = hepatitis B core antibody; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; Inf = infusion; IRB = Institutional Review Board; IRR = infusion-related reaction; JCV = JC–virus; MN = mobile nursing; MRI = magnetic resonance imaging; MS = multiple sclerosis; OLE = open-label extension; Opt = optional; PA = posteroanterior; PCR = polymerase chain reaction; PK = pharmacokinetic; SDMT = Symbol Digit Modalities Test; 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 OR that some assessments may be done (or repeated) remotely by a MN.

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] **Open-Label Extension Period**: The OLE period will start for all patients after the primary analysis and communication from the Sponsor, and if the benefit-risk of the use of ocrelizumab in children and adolescents is established. The OLE period will last for at least 144 weeks for all patients, 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 (see Section 3.1.3).

[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. 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. Optional MN visits may also be used in situation where some assessments have to be done or repeated remotely (e.g., blood collection and shipment to the central laboratory). Some of the assessments (as indicated) at a scheduled clinic visit may be completed by the MN at the patient's home to reduce the time required at the site. In this case, the MN visit must be scheduled within the visit time window as specified, but in advance of the clinic visit to allow the results of these assessments to be available to the site.

[c] For patients from Group A: the screening visit for OLE will occur 2 weeks +/- 7 days prior to the next scheduled dosing visit. For patients from Group B: the treating investigator will determine the best timing to transition patients to OLE based on a careful benefit-risk assessment, but the Day 1 visit in OLE should not occur less than 5 days after the last dose of fingolimod in the double-blind treatment period (Section 3.1.3).

[d] **First Dose of Ocrelizumab in OLE:** For patients with a body weights of less than 35 kg at the OLE screening visit: Patients assigned to fingolimod during the double-blind period will receive their first dose as a split dose of ocrelizumab, i.e., 150 mg IV administered on Days 1

Table 2 Ocrelizumab Open-Label Extension Period (cont.)

and 15. Patients initially assigned to ocrelizumab in the double-blind period will continue with a single infusion of ocrelizumab 300 mg on Day 1 and hence are not expected to complete the Week 2 visit. Patients will then continue with a single infusion of ocrelizumab 300 mg on a 24-week basis until they reach 35 kg, at which point they should switch to the 600 mg ocrelizumab dosing regimen. For patients with a body weight of 35 kg or higher at the OLE screening visit: Patients assigned to fingolimod during the double-blind period will receive their first dose as a split dose of ocrelizumab, i.e., 300 mg IV administered on Days 1 and 15. Patients initially assigned to ocrelizumab in the double-blind period will continue with a single infusion of ocrelizumab 600 mg on Day 1 and hence are not expected to complete the Week 2 visit. All patients should meet the eligibility and treatment criteria with ocrelizumab, as described in Section 3.1.3.

[e] **A telephone interview (or video call)** will be conducted by site personnel within 24 (±4) hours after completion of each infusion and every 4 weeks (±7 days) between any visit (MN or site visit). The purpose of the structured interview is to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit (i.e., new or worsening neurologic symptoms, signs of infection, any unusual signs or symptoms since the patient left the clinic after the infusion, change in concomitant medications). Moreover, in any situation when the scheduled visit (at site or with a mobile nurse) cannot take place, a telephone interview can take place. Note: At the discretion of the treating investigators, parents/legal guardian and patients the neurologic evaluation performed at Week 12 between infusion visits can take place via video call to reduce the burden on study participants of commuting to site for this examination; in this case the Week 12 visit between infusion visits may be combined with a MN and video call.

[f] **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 (except if the last laboratory assessments were performed within the last 4 weeks) and patient's information to enable the treating investigator to assess whether a patient meets criteria for re-treatment with ocrelizumab (see Footnote e). 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.

[g] **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.

[h] **Withdrawal from treatment visit** only takes place if patient discontinues treatment prematurely from the OLE period; patient will be encouraged to enter the 48-week safety-follow up period (see Table 3 in Appendix 1 and Section 3.1.4).

[i] Applicable for any patients who withdraw consent during OLE.

Table 2 Ocrelizumab Open-Label Extension Period (cont.)

[j] A limited, symptom-directed physical examination should be performed. Any abnormality identified should be entered as an adverse event. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

[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.

[l] Height should be measured in a standing position. 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.

[m] Patients will have their Tanner stages documented or assessed yearly until they reach Stage 5.

[n] Date of menarche: Female patients who are premenarchal at the time of screening should be asked about the date of first menarche. The date of first menarche should be recorded on the eCRF.

[o] 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 and repeated yearly (±4 weeks). If the bone age is determined to be ≥16 years of age, no further bone X-rays are required.

[p] If a prior X-ray was obtained within the last 6 months before the WD visit, the X-ray should not be repeated.

[q] Brain MRI scans will be performed without a Gd-contrast agent 24 weeks after Dose 1 and yearly thereafter (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 treatment visit), if not performed during the last 4 weeks.

[r] For patients in Group B (fingolimod) switching to ocrelizumab: A brain MRI scan *without a Gd-contrast agent* will be obtained at the OLE screening visit, if not performed during the previous 4 weeks. *For patients in Group A (ocrelizumab): a brain MRI scan without a Gd-contrast agent will be obtained at the OLE Day 1 visit, if not performed during the previous 4 weeks.*

[s] Neurologic examination: At the discretion of the treating investigators, parents/legal guardian and patients the neurologic evaluation performed at Week 12 between infusion visits can take place via video call instead of a site visit to reduce the burden on study participants of commuting to site for this examination. In the presence of newly identified or worsening neurologic symptoms, a neurologic evaluation should be scheduled promptly at the site and patient referred for an EDSS assessment if required.

[t] EDSS assessment: Additional EDSS assessments for individual patients may be requested between visits (i.e., during an MS relapse, neurological worsening, etc.). See Section 4.6.2.

[u] Sensitive thyroid-stimulating hormone will be tested during the treatment period as indicated.

Table 2 Ocrelizumab Open-Label Extension Period (cont.)

[v] Hepatitis B virus DNA monitoring: For those patients enrolled with negative HBsAg and positive total HBcAb, HBV DNA (PCR) must be repeated as per the schedule of activities.

[w] Immunologic assessments: Analysis will include the determination of the B-cell number (CD19+), high-sensitivity assay B-cell counts (MRB1.1), B-cell subsets (e.g., CD19, CD27, IgD, CD38 markers to assess naive, memory, plasmablasts, and/or other populations), T-cell counts (CD3+, CD4+, CD8+) and natural killer cells (CD56+) (see Section 4.6.18.2). On infusion visits, blood samples should be collected prior to the methylprednisolone administration. *The laboratory samples to assess eligibility to OLE Dose 1 Day 1 ocrelizumab infusion should be collected within 4 weeks from the OLE Dose 1 Day 1 infusion visit, to ensure that the laboratory samples reflect the current condition of the patients. Similarly, the re-treatment criteria for OLE Dose 1 Day 15 infusion should be assessed based on laboratory samples that are collected within 4 weeks from the OLE Dose 1 Day 15 infusion visit.*

[x] 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 locally. If abnormal and applicable a microscopic examination will be performed on site (local laboratory). For more information related to safety laboratory assessments (see Section 4.6.18). *The laboratory samples to assess eligibility to OLE Dose 1 Day 1 ocrelizumab infusion should be collected within 4 weeks from the OLE Dose 1 Day 1 infusion visit, to ensure that the laboratory samples reflect the current condition of the patients. Similarly, the re-treatment criteria for OLE Dose 1 Day 15 infusion should be assessed based on laboratory samples that are collected within 4 weeks from the OLE Dose 1 Day 15 infusion visit.*

[y] 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.

[z] Antibody titers: Measurement of antibody titers against common antigens (mumps, rubella, varicella zoster, and *Streptococcus pneumoniae*) will be performed.

[aa] Plasma and urine samples for JCV will be collected at specified timepoints and analyzed in batches, if decided by the Sponsor.

[bb] Blood to be drawn for serum prior to dosing at the indicated timepoints.

[cc] **Prior to (Re)-Treatment with Ocrelizumab**, 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 2 Ocrelizumab Open-Label Extension Period (cont.)

[dd] ECG (predose and postdose): On infusion visits with ocrelizumab, 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. Additional ECGs may be taken at the discretion of the treating investigator, as required during an unscheduled visit.

[ee] Vital signs (i.e., pulse rate, systolic and diastolic blood pressure, respiration rate, and temperature). On infusion visits with ocrelizumab, 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 minutes (±5 minutes) for the first hour, then every 30 minutes (±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.

[ff] ADA: On infusion visits with ocrelizumab (except on Day 15), a serum sample is collected 5–30 minutes prior to the methylprednisolone administration.

[gg] **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.

[hh] **Administration of IV ocrelizumab**: It is recommended to schedule the infusion of ocrelizumab 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. Prior to subsequent infusion of ocrelizumab, the treating investigator must review the clinical and laboratory re-treatment criteria (Footnote e). 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 hours (±4 hours) after completion of each infusion (Footnote e).

Table 3 Safety Follow-Up (Including Prolonged B-Cell Monitoring if Required)

	Safety Follow-Up [a] (At Least 48 Weeks from the Date of Last Infusion of Ocrelizumab)				**Prolonged B-Cell Monitoring [b]**	**End of Study or WD from SFU**
Site Visits (weeks from the date of last infusion of ocrelizumab) (± 7 days) [a]		24		48	Visits every 24 weeks (±7 days)	
Site or opt MN visits (weeks from the date of last infusion of ocrelizumab) (± 7 days) [a]	12		36			
Urine pregnancy test [c]	x (MN)	x (MN)				
Routine safety laboratory [d]	x (MN)	x (MN)	x (MN)	x (MN)	x	x
Urinalysis [d]	x (MN)	x (MN)	x (MN)	x (MN)	x	x
Immunologic assessments [e]	x (MN)	x (MN)	x (MN)	x (MN)	x	x
Total Ig, IgA, IgG, IgM	x (MN)		x (MN)			
ADA		x		x	x	
Antibody titers [f]	x (MN)		x (MN)		x	x
Hepatitis B Virus DNA [g]	(x (MN))	(x (MN))	(x (MN))	(x (MN))	(x)	(x)
Vital signs	x (MN)	x (MN)	x (MN)	x (MN)	x	x
Neurological examination and EDSS		x		x	x	x
Physical examination [h]	x (MN)	x (MN)	x (MN)	x (MN)	x	x
SDMT		x		x	x	x
Clinical relapses	x (MN)	x (MN)	x (MN)	x (MN)	x	x

Table 3 Safety Follow-Up (Including Prolonged B-Cell Monitoring if Required) (cont.)

	Safety Follow-Up [a] (At Least 48 Weeks from the Date of Last Infusion of Ocrelizumab)				**Prolonged B-Cell Monitoring [b]**	**End of Study or WD from SFU**
Site Visits (weeks from the date of last infusion of ocrelizumab) (± 7 days) [a]		24		48	Visits every 24 weeks (±7 days)	
Site or opt MN visits (weeks from the date of last infusion of ocrelizumab) (± 7 days) [a]	12		36			
Adverse events	x (MN)	x (MN)	x (MN)	x (MN)	x	x
Concomitant medication	x (MN)	x (MN)	x (MN)	x (MN)	x	x
Brain MRI [i]						x

ADA = anti-drug antibody; β-hCG = beta-human chorionic growth hormone; EC = Ethics Committee; eCRF = electronic case report form; EDSS = Expanded Disability Status Scale; Gd = gadolinium; HBcAb = hepatitis B core antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; IRB = Institutional Review Board; MRI = magnetic imagining resonance; MS = multiple sclerosis; PA = posteroanterior; PK = pharmacokinetic; SDMT = Symbol Digit Modalities Test; SFU = safety follow-up; WD = withdrawal.

Note: Marks in parentheses are optional and may be done as appropriate (e.g., if needs to be repeated).

(MN) indicates that this visit may be performed as a mobile nursing visit OR that some assessments may be done (or repeated) remotely by an MN.

Table 3 Safety Follow-Up (Including Prolonged B-Cell Monitoring if Required) (cont.)

[a] **SFU** will be carried out for at least 48 weeks starting from the date of last infusion of ocrelizumab and SFU visits will be performed at 12-week intervals. SFU applies to study patients who have completed the treatment period with ocrelizumab and to patients who withdraw early from ocrelizumab treatment (i.e., blinded or OLE period). Patients who have discontinued study treatment prematurely during the double-blind period will remain in the double-blind period until the primary analysis; those who were treated with ocrelizumab and who have not yet reached 48-week follow-up after their last infusion by the time the double-blind period is ended, will enter SFU and will be followed for the remainder of the required 48-week SFU. At applicable sites, site visits will alternate with mobile nursing visits. If B cells have returned to normal levels at the end of this SFU period (i.e., Week 48), then the last scheduled SFU visit will become the end-of-study 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 48 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. Refer to Section 3.1.5 (Use of Alternative MS Treatment After Study Treatment Discontinuation) for details.

[b] Patients whose B cells have not returned to normal levels after 48 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-study visit, and the patient will have completed the study. During the prolonged B-cell monitoring period, patients who begin 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. Refer to Section 3.1.5 (Use of Alternative MS Treatment After Study Treatment Discontinuation) for details.

[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 (post-menarchal) must agree to remain completely abstinent or to use reliable means of contraception for at least 24 weeks after the last dose of ocrelizumab (or as per local requirement if more stringent). 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 locally. If abnormal and applicable a microscopic examination will be performed on site (local laboratory). For more information related to safety laboratory assessments see Section 4.6.18.

[e] Immunologic assessments: Analysis will include the determination of the B-cell number (CD19+), high-sensitivity assay B-cell counts (MRB1.1), B-cell subsets (e.g., CD19, CD27, IgD, CD38 markers to assess naive, memory, plasmablasts, and/or other populations), T-cell counts (CD3+, CD4+, CD8+) and natural killer cells (CD56+) (see Section 4.6.18.2).

[f] Antibody titers: Measurement of antibody titers against common antigens (mumps, rubella, varicella zoster, and *Streptococcus pneumoniae*) will be performed.

[g] Hepatitis B Virus to be monitored only in patients with screening results of HBsAg negative, HBcAb positive, and HBV DNA negative, inclusive.

Table 3 Safety Follow-Up (Including Prolonged B-Cell Monitoring if Required) (cont.)

[h] A limited, symptom-directed physical examination should be performed. Any abnormality identified should be entered as an adverse event. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

[i] Brain MRI scans will be performed without a Gd-contrast agent with a window of ±4 weeks of the end of study 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. 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).

Table 4 Patients who Withdraw from Study Treatment during the Double-Blind Period

	Double-Blind Period							Unscheduled Site / MN [a]
Site Visits	**3**	**4**	**6**	**9**	**12**	**15**	**Additional 24 weeks cycles**	
Week	**2**	**12**	**24**	**48**	**72**	**96**	**D1 (N)**	
Study Day (±days)	**15 (±3)**	**85 (±10)**	**169 (±7)**	**337 (±7)**	**505 (±7)**	**673 (±7)**	**n (±7)**	
Telephone interview (or video call) (±7 days) [b]	x	Every 4 weeks (□ 7 days)						(x)
PROs and ObsROs [c]			x	x	x	x		
Physical examination [d]	x	x(MN)	x(MN)	x(MN)	x(MN)	x(MN)	x(MN)	(x)(MN)
Weight [e]		(x)	x	x	x	x	x	
Height [f]			x	x	x	x	x	
Tanner staging [g]		(Yearly)						
Date of menarche [h]	(x)	(x)(MN)	x(MN)	x(MN)	x(MN)	x(MN)	x(MN)	
Brain MRI scan [i,j]		x	x	x	x	x	x	(x)
Ophthalmologic evaluation [k]		At investigator discretion						(x)
Neurologic examination [l]		x	x	x	x	x	x	(x)
EDSS[l]		x	x	x	x	x	x	(x)
SDMT			x	x	x	x	x	
Concomitant medication	x	x(MN)	x(MN)	x(MN)	x(MN)	x(MN)	x(MN)	(x)(MN)

Table 4 Patients who Withdraw from Study Treatment during the Double-Blind Period (cont.)

Adverse events	x	x(MN)	x(MN)	x(MN)	x(MN)	x(MN)	x(MN)	(x)(MN)
Clinical relapses	x	x(MN)	x(MN)	x(MN)	x(MN)	x(MN)	x(MN)	(x)(MN)
Thyroid function tests [m]			x	x	x	x	x	(x)
Hepatitis B virus DNA [n]		(x(MN))	(x(MN))	(x(MN))	(x(MN))	(x(MN))	(x(MN))	(x(MN))
Total Ig, IgA, IgG, and IgM		x(MN)	x(MN)	x(MN)	x(MN)	x(MN)	x(MN)	(x)(MN)
Immunologic assessments (including CD4%) [o]	x	x(MN)	x(MN)	x(MN)	x(MN)	x(MN)	x(MN)	(x)(MN)
Routine safety laboratory [p]	x	x(MN)	x(MN)	x(MN)	x(MN)	x(MN)	x(MN)	(x)(MN)
Urinalysis [p]	x	x(MN)	x(MN)	x(MN)	x(MN)	x(MN)	x(MN)	(x)(MN)
Pregnancy test [q]	x	x(MN)	x(MN)	x(MN)	x(MN)	x(MN)	x(MN)	(x)(MN)
Antibody titers [r]		x(MN)	x(MN)	x(MN)	x(MN)	x(MN)	x(MN)	
Twelve-lead ECG[s]	x		x	x	x	x	x	(x)
Vital signs [t]	x	x(MN)	x(MN)	x(MN)	x(MN)	x(MN)	x(MN)	(x)(MN)
PK samples (predose and postdose) [u]			x	x	x	x	x	
ADA			x	x	x	x	x	

CD=cluster of differentiation; D=day; ECG=electrocardiogram; EDSS=Expanded Disability Status Scale; FS=Functional System; Gd=gadolinium; HBcAb=hepatitis B core antibody; HBV=hepatitis B virus; HBsAg=hepatitis B surface antigen; HepCAb=hepatitis C antibody; MN=mobile nursing; MRI=magnetic resonance imaging; PK=pharmacokinetic; PRO=patient-reported outcome; ObsRO=observer reported-outcome; SAE=serious adverse event; SDMT=Symbol Digit Modalities Test.

Notes:

Marks in parentheses are optional and may be done as appropriate

(MN) indicates that some assessments may be done (or repeated) remotely by a MN.

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 4 Patients who Withdraw from Study Treatment during the Double-Blind Period (cont.)

[a] Unscheduled site or MN 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 by the blinded examining investigator (or rater) within 7 days of the onset of the relapse. Other tests/assessments may be done as appropriate.

[b] **A telephone interview (or video call)** will be conducted by site personnel every 4 weeks (± 7 days) between any visit and throughout the entire double-blind period. The purpose of the structured interview is to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit (i.e., new or worsening neurologic symptoms, signs of infection, any unusual signs or symptoms since the patient left the clinic after the last visit, change in concomitant medications). Moreover, in any situation when the scheduled visit (at site or with a mobile nurse) cannot take place or whenever it's deemed necessary a telephone interview or video call can take place.

[c] These include patient and caregiver reported PedsQL Generic Core Scale, patient reported fatigue as measured by the PedsQL Multidimensional Fatigue Scale, EQ-5D-5L, caregiver and patient reported Global Impression of Change on fatigue, cognition and overall MS symptoms. Should the caregiver be unable to attend a site visit in person, the ObsRO measures will then be completed electronically at home by the same caregiver on the same day as the scheduled site visit.

[d] A limited, symptom-directed physical examination should be performed. Any abnormality identified should be entered as adverse event accordingly. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

[e] 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.

[f] Height should be measured in a standing position. 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.

[g] Tanner staging assessment: Patients will have their Tanner stages documented or assessed yearly until they reach Stage 5. Tanner staging will be documented on the eCRF at screening and yearly thereafter, as applicable.

[h] Date of menarche: Female patients who are premenarchal at the time of screening should be asked about the date of first menarche. The date of first menarche should be recorded on the eCRF. For female patients who are postmenarchal at the time of screening, the date of first menarche should be recorded on the eCRF.

[i] MRI scans will be obtained in patients withdrawing from treatment, at a withdrawal from treatment visit (if not performed during the last 4 weeks) and every 24 weeks as per the visit schedule. For patients who begin an alternative treatment for MS during the double-blind 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 the prior 8 weeks) and will continue on the 24 weeks schedule.

[j] MRI scans at screening and Week 12 will be performed before and after administration of Gd-contrast agent.

[k] An examination of the fundus, including the macula may be performed by an ophthalmologist, at investigator discretion. Please refer to the prescribing information for fingolimod for more information.

Table 4 Patients who Withdraw from Study Treatment during the Double-Blind Period (cont.)

[l] Neurologic examination (treating investigator) and EDSS (examining investigator or rater): At the visits indicated, the treating investigator will perform a neurologic evaluation of the patient (see Sections 4.6.4 and 5.1.1.2.1). The examining investigator role during the study is to assess independently FS and EDSS at the visits indicated and during an unscheduled visit. The examining investigator and treating investigator should not switch role during the double-blind period and the same rater should assess the EDSS in the same patient (see Sections 4.2.3 and 4.6.2).

[m] Sensitive thyroid-stimulating hormone will be tested at screening and during the double-blind period as indicated.

[n] Hepatitis B Virus monitoring: For those patients enrolled with negative HBsAg and positive total HBcAb, HBV DNA (PCR) must be repeated as per the schedule of activities.

[o] Immunologic assessments: Analysis will include the determination of the B-cell number (CD19+), high-sensitivity assay B-cell counts (MRB1.1), B-cell subsets (e.g., CD19, CD27, IgD, CD38 markers to assess naive, memory, plasmablasts, and/or other populations), T-cell counts (CD3+, CD4+, CD8+) and natural killer cells (CD56+) (see Section 4.6.18.2).

[p] 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 locally. If abnormal and applicable a microscopic examination will be performed on site (local laboratory). For more information related to safety laboratory assessments see Section 4.6.18.

[q] 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 (post-menarchal) must agree to remain completely abstinent or to use reliable means of contraception for at least 24 weeks after the last dose of ocrelizumab or 2 months after the last dose of fingolimod, whichever is the later date (or as per local requirement if more stringent). Confirmation by a serum pregnancy test will be performed for positive urine pregnancy test.

[r] Antibody titers: Measurement of antibody titers against common antigens (mumps, rubella, varicella zoster, and *Streptococcus pneumoniae*) will be performed.

[s] ECG: should be performed prior to vital sign measurements and blood draws.

[t] Vital signs (i.e., pulse rate, systolic and diastolic blood pressure, respiration rate, and temperature).

[u] PK samples: samples will be collected up to the next scheduled 24 weeks visit, after the withdrawal of treatment visit.

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
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 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 (±4) hours after completion of each infusion of ocrelizumab/ocrelizumab placebo, and every 4 weeks between the study visits during the double-blind period and open-label extension. 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.

For the interview conducted 24 hours after each infusion, please ask questions 3 to 6. For the interview conducted every 4 weeks between study visits, please ask questions 1, 2, 4–6, and 8 (question 8 only to be asked during the double-blind period).

When monthly urine pregnancy tests are required as per local recommendations, please ask question 7.

Read aloud and record patient's or parents/legal guardian (as appropriate) 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 If yes, specify_____	☐ Yes	☐ No

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 (feeling lightheaded, dizzy, and fainting)	☐ 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 _____

7. (When monthly urine pregnancy tests are required as per local recommendations) Since your last visit or telephone interview, have you performed a pregnancy test?
☐ Yes ☐ No
If yes, specify the result: ☐ Negative ☐ Positive

8. Since your last visit or telephone interview, did you miss any capsule of fingolimod/fingolimod placebo? If yes, please inform us about the precise treatment interruption start and end dates to determine if monitoring at reinitiation of fingolimod/fingolimod placebo is required.
☐ Yes ☐ No
If yes, specify dates: _____

If the patient or parents/legal guardian (as appropriate) answered YES to any question, contact the Investigator and review the 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 or parents/legal guardian (as appropriate) during the interview:

Appendix 4: Telephone 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/ocrelizumab placebo**.** For medications that should not be used concomitantly to fingolimod/fingolimod placebo, see Section 4.4.3 in the main protocol.

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®)

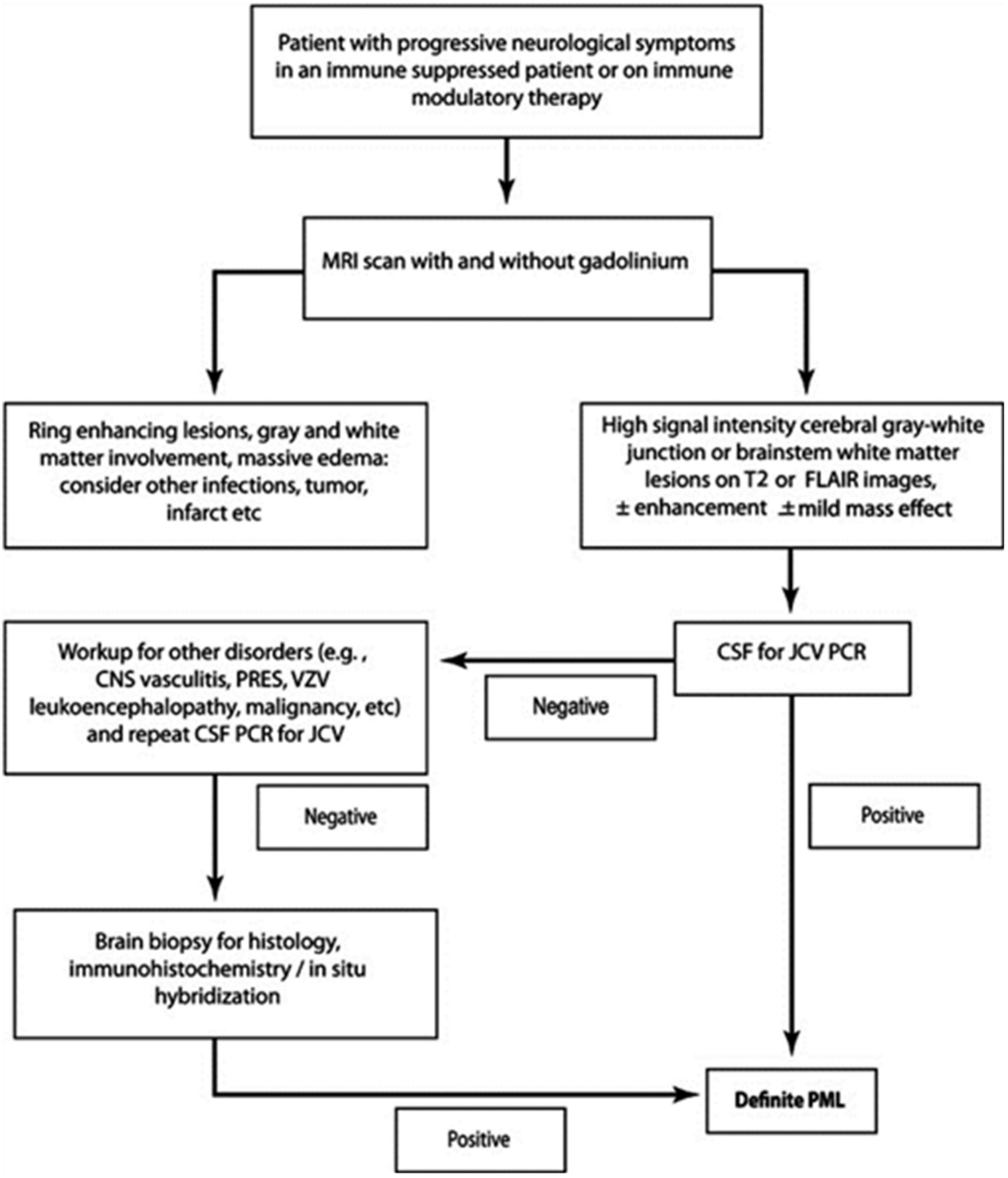
- Rituximab (Rituxan/MabThera®) Trastuzumab (Herceptin®)

This list does not include all drugs that can suppress the immune system.
Patients or parents/legal guardian (as appropriate) 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)



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, please 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 • Normally stabilizes • Resolves spontaneously or with treatment	• Over weeks • Progressive
Clinical presentation	• Optic neuritis • Incomplete myelopathy or partial myelitis	• Cortical signs and symptoms • 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	Enhancement is possible, particularly in natalizumab-associated PML (Maas et al. 2016); 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.

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Appendix 6
Investigational, Auxiliary, and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Table 1 Investigational Medicinal Product and Auxiliary Medicinal Product Designations for European Economic Area

Product Name	IMP/AxMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Ocrevus (ocrelizumab IV)/ RO4964913	IMP (test product)	Authorized	Yes
Gilenya (fingolimod)	IMP (test product [a])	Authorized	Yes
Methylprednisolone	AxMP (other [b])	Authorized	Yes
Antihistamine [c]	AxMP (other)	Authorized	Yes
Antipyretic [d]	AxMP (other)	Authorized	Yes

AxMP = auxiliary medicinal product; EEA = European Economic Area; IMP = investigational medicinal product, IRR = infusion-related reaction.

[a] Fingolimod is considered as both test and comparator.

[b] Methylprednisolone administered as premedication

[c] Antihistamines include diphenhydramine.

[d] Antipyretics include acetaminophen and/or paracetamol.

Table 2 Investigational and Non-Investigational Medicinal Product Designations for United Kingdom

Product Name	IMP/NIMP Designation	Marketing Authorization Status in U.K.	Used within Marketing Authorization
Ocrevus (ocrelizumab IV)/ RO4964913	IMP (test product)	Authorized	Yes
Gilenya (fingolimod)	IMP (test product [a])	Authorized	Yes
Methylprednisolone	NIMP (other [b])	Authorized	Yes
Antihistamine [c]	NIMP (other)	Authorized	Yes
Antipyretic [d]	NIMP (other)	Authorized	Yes

IMP = investigational medicinal product; IRR = infusion-related reaction; NIMP= non-investigational medicinal product.

[a] Fingolimod is considered as both test and comparator.

[b] Methylprednisolone administered as premedication

[c] Antihistamines include diphenhydramine.

[d] Antipyretics include acetaminophen and/or paracetamol.

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