THE EU RISK MANAGEMENT PLAN FOR OCREVUS®/ OCRELIZUMAB

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Rationale for submitting an updated EU RMP

The ocrelizumab EU risk management plan (RMP) version 10.0 has been prepared to reflect the change in the lactation related recommendations in the EU Summary of Product Characteristics (SmPC) Section 4.6 and to extend the milestone for the submission date of the Study WA40404 (O'HAND) and Study BA39732 (MELODIC) final clinical study reports.

Summary of significant changes in this RMP:

- Part II, SIV.3: Inclusion of the current data on Ocrevus® use in lactating women.
- The milestones for the submission date for the final clinical study report of Study WA40404 (O'HAND) has been updated to "June 2028" from "June 2024" and of Study BA39732 (MELODIC) has been updated to "June 2030" from "March 2030" in the following sections/Annex:
  - Part III.2 Additional Pharmacovigilance Activities.
  - Part III.3 Summary Table of additional pharmacovigilance activities.
  - Annex 2 "Tabulated Summary of Planned, Ongoing and Completed Pharmacovigilance Studies".
- Part V.1 and Part V.3: the routine risk minimization activities to address the risk of safety in pregnancy and lactation, are updated to reflect the change to the breast-feeding recommendation proposed in the SmPC Section 4.6 Fertility, pregnancy and lactation.
- Annex 7 has been updated to remove the list of the referenced material.
- Annex 8 has been updated to summarize the changes done to the RMP.

In addition, this RMP also reflects the updates proposed via the EU RMP 9.1 in the parallel ongoing procedure EMEA/H/C/004043/0039 (see Annex 8 for the 'summary of significant changes' reflecting changes to both the version 9.1 and 10.0).

Minor editorial and formatting updates were made throughout, as needed.

Other RMP versions under evaluation:

RMP Version Number: 9.1[1]

Submitted in: February 2024

Procedure Number: EMEA/H/C/004043/X/0039

Details of Currently[2] Approved RMP versions:

RMP Version Number: 8.1

Procedure Number: EMEA/H/C/004043/II/0034/G

Date of approval (opinion date): 16 March 2023

See page 1 for signature and date

Dr. Yusuf Tanrikulu (Deputy EU QPPV) | Date

See page 1 for signature and date

Dr. PPD | Date

[1] The pending changes for EU RMP 9.1 for the parallel ongoing procedure EMEA/H/C/004043/0039 are also included within this EU RMP version 10.0 update, as Committee for Medicinal Products for Human Use (CHMP) Opinion for the EU RMP version 9.1 (procedure EMEA/H/C/004043/X/0039) is expected prior to the CHMP Opinion for the current procedure. All updates introduced to the ocrelizumab EU RMP within the EMEA/H/C/004043/X/0039 procedure have been tracked and highlighted in yellow in the RMP working document.

[2] At the Data Lock Point of the EU RMP version 10.0.

PART I: PRODUCT(S) OVERVIEW

Table 1 Product(s) Overview

Active Substance(s) (INN or common name)	Ocrelizumab
Pharmacotherapeutic group(s) (ATC Code)	L04AA36
Marketing Authorization Holder (or Applicant)	Roche Registration GmbH.
Medicinal products to which this RMP refers	One
Invented name(s) in the European Economic Area (EEA)	Ocrevus®
Marketing authorization procedure	Centrally Authorized Product
Brief description of the product including:	Chemical Class: Recombinant humanized monoclonal antibody
	Summary of mode of action: Ocrelizumab selectively targets cluster of differentiation antigen 20 (CD20)-expressing B cells. CD20 is a cell surface antigen found on pre-B cells, mature and memory B cells but not expressed on lymphoid stem cells and plasma cells. The precise mechanisms through which ocrelizumab exerts its therapeutic clinical effects in multiple sclerosis (MS) are not fully elucidated but is presumed to involve immunomodulation through the reduction in the number and function of CD20-expressing B cells. Following cell surface binding, ocrelizumab selectively depletes CD20-expressing B cells through antibody-dependent cellular phagocytosis, antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and apoptosis. The capacity of B-cell reconstitution and preexisting humoral immunity are preserved. In addition, innate immunity and total T-cell numbers are not affected.

	Important information about its composition: Ocrelizumab is a humanised monoclonal antibody produced in Chinese Hamster Ovary cells by recombinant DNA technology. *Excipients:* Ocrelizumab IV Sodium Acetate Trihydrate, Glacial Acetic Acid, Trehalose Dihydrate, Polysorbate 20 Water for Injection. Ocrelizumab SC Recombinant human hyaluronidase, Sodium Acetate Trihydrate, Glacial Acetic Acid, Trehalose Dihydrate, Polysorbate 20, L-Methionine Water for Injection.
Hyperlink to the Product Information	EU PI
Indication	Current: Ocrelizumab is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features. Ocrelizumab is indicated for the treatment of adults with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity. Proposed: No changes proposed.

Dosage in the EEA	Current: Ocrelizumab IV Ocrelizumab is administered by IV infusion as a 600 mg dose every 6 months. *Initial Dose:* The initial 600 mg dose is administered as two separate IV infusions; first as a 300 mg infusion, followed 2 weeks later by a second 300 mg infusion. *Subsequent Doses:* Subsequent doses of ocrelizumab thereafter are administered as a single 600 mg IV infusion every 6 months. The first subsequent dose of 600 mg should be administered 6 months after the first infusion of the initial dose. A minimum interval of 5 months should be maintained between each dose of ocrelizumab. If patients did not experience a serious infusion-related reaction (IRR) with any previous ocrelizumab infusion, a shorter (2-hour) infusion can be administered for their subsequent doses. Ocrelizumab SC The recommended dose of ocrelizumab SC is 920 mg administered every 6 months. No division of the initial dose into separate administrations is required. A minimum interval of 5 months should be maintained between each dose of ocrelizumab. The 920 mg dose (23 mL) should be administered as a subcutaneous injection in the abdomen in approximately 10 minutes. Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Ocrelizumab IV Concentrate for solution for IV infusion. Each vial contains 300 mg of ocrelizumab in 10.0 mL at a concentration of 30 mg/mL. The final drug concentration after dilution is approximately 1.2 mg/mL. Ocrelizumab SC Solution for SC injection. Each vial contains 920 mg of ocrelizumab in 23 mL at a concentration of 40 mg/mL. Proposed: Not applicable
Is or will the product be subject to additional monitoring in the EU?	No

ATC = Anatomical Therapeutic Chemical, CD20 = cluster of differentiation antigen 20; EU = European Union; EEA = European Economic Area, IV = intravenous; IRR = infusion related reactions, MS = multiple sclerosis; PPMS = primary progressive multiple sclerosis; RMS = relapsing forms of multiple sclerosis; SC = subcutaneous.

GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
23-PPV	23-valent pneumococcal polysaccharide vaccine
ADAs	anti-drug antibodies
Ab	antibody
AE	adverse event
Ag	antigen
ALT	alanine transaminase
ARTIS	Antirheumatic Therapies in Sweden
AS	Access Solutions
AST	aspartate transaminase
BSRBR	British Society of Rheumatology Biologics Registers
CCOD	clinical cut-off date
CD	cluster of differentiation antigen
CI	confidence interval
CNS	central nervous system
COVID-19	coronavirus disease 2019
CRCL	creatinine clearance
CSF	cerebrospinal fluid
CV	cardiovascular
DDI	drug-drug interaction
DLP	data lock point
DMARD	disease-modifying anti-rheumatic drug
DMT	disease-modifying therapies
DNA	deoxyribonucleic acid
DSR	Drug Safety Report
EBV	Epstein-Barr virus
ECG	electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
EU5	Germany, France, Italy, Spain, and United Kingdom
FDA	U.S. Food and Drug Administration
GPA	granulomatosis polyangiitis
GVP	Good Pharmacovigilance Practices
HB	Hepatitis B
HBcAb	Hepatitis B core antibody

Abbreviation	Definition
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HIV	Human Immunodeficiency Virus
IBD	International Birth Date
IFN	Interferon
Ig	Immunoglobulin
IR	injection reaction
IRR	Infusion-Related Reaction
IV	Intravenous
KLH	Keyhole Limpet Hemocyanin
LLN	Lower Limit Of Normal
LN	Lupus Nephritis
mAb	monoclonal antibody
MAH	marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
MPA	Microscopic Polyangiitis
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NHL	non-Hodgkin's Lymphoma
NIS	Nationwide Inpatient Sample
NK	Natural Killer
NMSC	Nonmelanoma Skin Cancer
OLE	Open Label Extension
PASS	Post-Authorization Safety Study
PBRER	Periodic Benefit Risk Evaluation Report
PD	Pharmacodynamics
PK	Pharmacokinetics
PML	Progressive Multifocal Leukoencephalopathy
PNDs	Postnatal Developments
PostMS	Pregnancy Outcomes Post MS diagnosis
PPMS	Primary Progressive Multiple Sclerosis
PR+	Progesterone Receptor Positive
PRAC	Pharmacovigilance Risk Assessment Committee
PreMS	pregnancy outcomes before MS diagnosis
PSUR	Periodic Safety Update Reports
PV	Pharmacovigilance
PY	Patient Years

Abbreviation	Definition
QOL	Quality of Life
RA	Rheumatoid Arthritis
RMP	Risk Management Plan
RMS	Relapsing Forms Of Multiple Sclerosis
RoW	Rest Of The World
RR	Relative Risk
RRMS	Relapsing-Remitting Multiple Sclerosis
RWD	Real World Data
SAE	Serious Adverse Event
SC	Subcutaneous
SEER	Surveillance, Epidemiology and End Results
SFU	Safety Follow-Up
SHA	Symphony Health
Sis	Serious Infections
SLE	Systemic Lupus Erythematosus
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SPMS	Secondary Progressive Multiple Sclerosis
TDAR	T-Cell-Dependent Antibody Response
TT	Tetanus Toxoid
U.S.	United States
UTI	Urinary Tract Infection
WHO	World Health Organization

PART II: SAFETY SPECIFICATION

PART II: MODULE SI— EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 Multiple Sclerosis

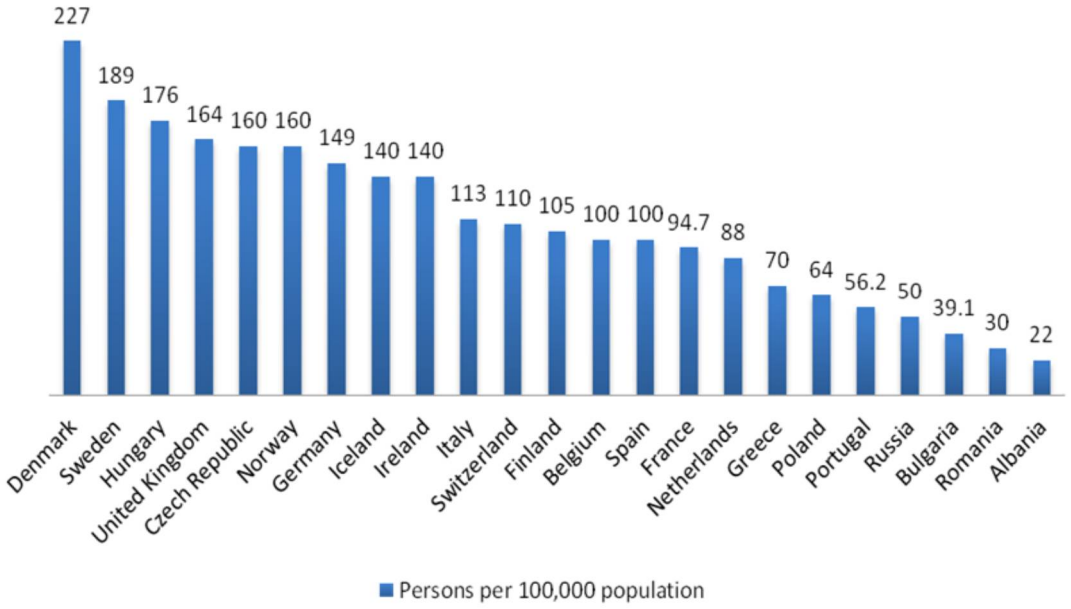
- Incidence and Prevalence

While multiple sclerosis (MS) is present in all regions of the world, its prevalence varies by distance from the equator, where greater prevalence occurs in higher northern and southern latitudes. The prevalence of MS is highest in North America and Europe (140 and 108 persons per 100,000 population, respectively[3]) and lowest in sub-Saharan Africa and East Asia (2.1 and 2.2 persons per 100,000 population, respectively) (Ascherio and Munger 2007a; MSIF 2013a).

In Europe, the prevalence of MS in Scandinavia (227, 189, and 160 persons/100,000 population in Denmark, Sweden, and Norway, respectively), the British isles (164 and 140 persons/100,000 population in the United Kingdom and Ireland, respectively), and several Central European countries including Hungary, Czech Republic, and Germany (176, 160, and 140 persons/100,000 population, respectively) is significantly higher than in Southern Europe (56.2, 39.1, 30, and 22 persons/100,000 population in Portugal, Bulgaria, Romania, and Albania, respectively); refer to Figure 1 . Incidence of MS in Europe is reported with similar disparity, with Bosnia and Herzegovina, Latvia, and Czech Republic reporting incidence of over 10/100,000 population/year while the incidence in Russia and Romania is less than 2/100,000 population/year; refer to Figure 2 (MSIF 2013a).

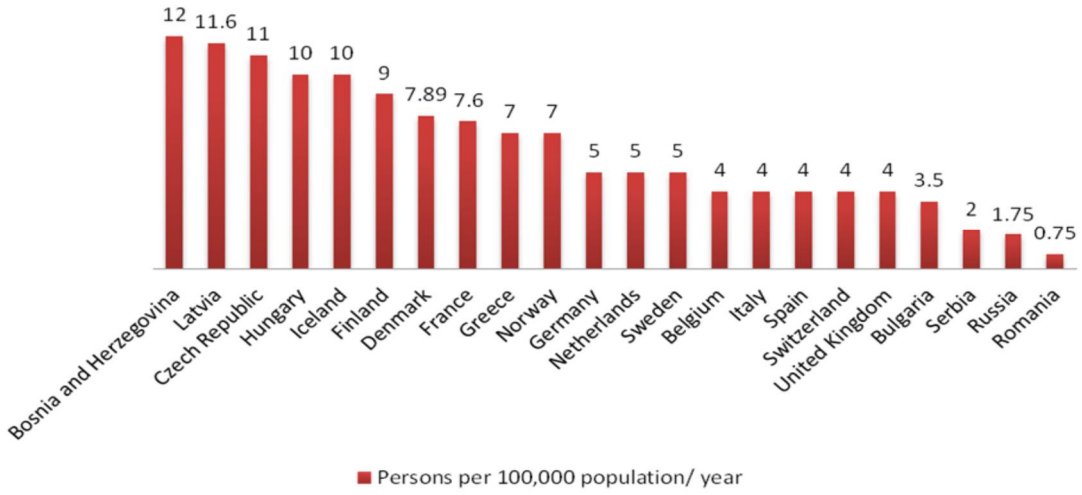
[3] Data specific to relapsing multiple sclerosis and primary progressive multiple sclerosis are not available. However, since approximately 85% of MS patients have relapsing multiple sclerosis, the prevalence of relapsing multiple sclerosis in North America and Europe can be estimated at 119 and 92 persons per 100,000 populations, respectively. The prevalence of progressive forms of MS in North America and Europe can be estimated at 21 and 16 persons per 100,000 populations, respectively.

Figure 1 Prevalence of Multiple Sclerosis in Europe by Country



Note: Data may sometimes be based on unpublished studies or studies completed between 2008 and 2013. Source: MSIF 2013a

Figure 2 Incidence of Multiple Sclerosis in Europe by Country

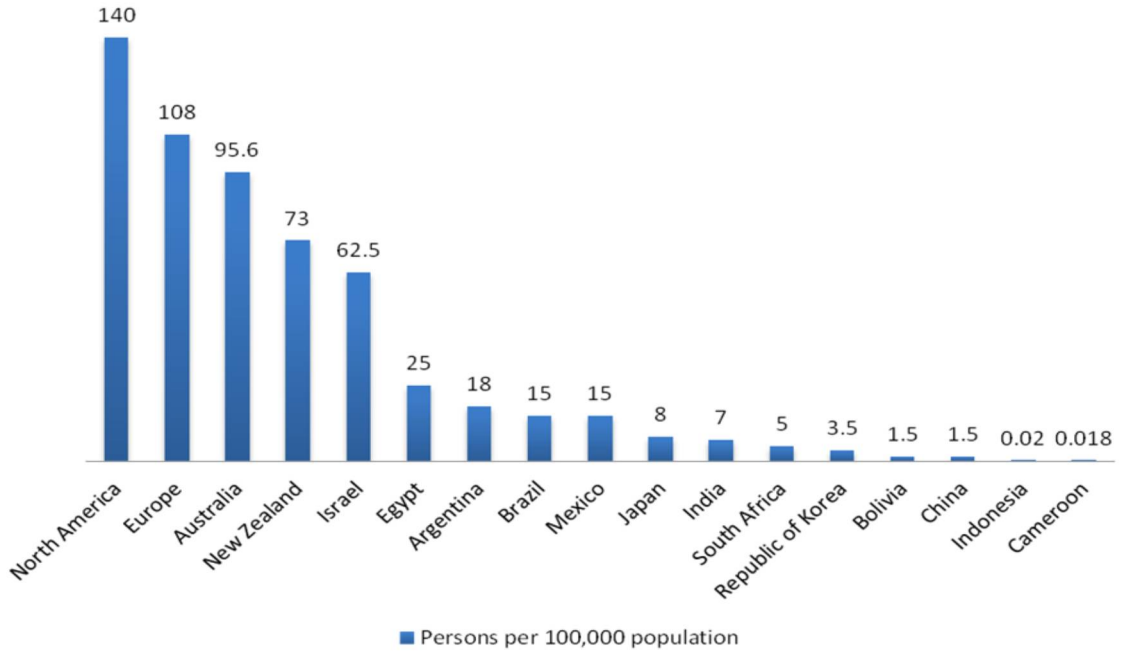


Note: Data may sometimes be based on unpublished studies or studies completed between 2008 and 2013. Source: MSIF 2013a.

The highest prevalence of MS outside of Europe and North America is reported in Australia and New Zealand (95.6 and 73 persons per 100,000 population, respectively). The incidence of MS in these countries is approximately 4 persons per 100,000 population/year (MSIF 2013a).

MS is rare in Asia. Its prevalence in China and Japan is just 1.5 and 8 persons per 100,000 populations, respectively (MSIF 2013a). Figure 3 shows the prevalence of MS in selected countries outside of North America and Europe, with the prevalence in North America and Europe included as a reference.

Figure 3 Prevalence of Multiple Sclerosis in Selected Countries Outside of North America and Europe



Note: Data may sometimes be based on unpublished studies or studies completed between 2008 and 2013. Prevalence in North America and Europe is included as a reference. Source: MSIF 2013a.

- Demographics:

Sex: Overall, females are affected by MS approximately twice to thrice as often as males (the female to male ratio is 2.06 in Australia, 2.33 in France and Germany, 2.64 in the United States, 2.66 in Canada, 3 in Spain, New Zealand, China and Japan, and 3.17 in the United Kingdom) except in individuals with the primary progressive form of the disease, where there is no sex prevalence difference (Cottrell et al. 1999; Tremlett et al. 2005; Tullman et al. 2013; MSIF 2013a).

Age: The average age of disease onset differs by MS subtype. In patients with relapsing multiple sclerosis (RMS) it is approximately 30 years, while in patients with primary

progressive multiple sclerosis (PPMS) it is approximately 40 years (Cottrell et al. 1999; Tremlett et al. 2005; Goodin 2014).

Pediatric patients: Diagnosing MS in children is more challenging than in adults due to the frequency of other childhood disorders with similar symptoms and characteristics (National Multiple Sclerosis Society 2016d). Approximately 2% to 5% MS patients are diagnosed before 18 years of age, with up to 99% of pediatric MS patients diagnosed with relapsing-remitting multiple sclerosis (RRMS) (Inaloo and Haghbin 2013; MSIF 2013a).

The prevalence of pediatric MS pooled across 34 countries that supplied data for Atlas of MS 2013 was 0.63 per 100,000 population. However, the prevalence significantly varied between the reporting countries. In Europe, France reported the highest prevalence (7/100,000 population), and Iceland the lowest (0.3/100,000 population). In North America, the prevalence in Canada was 0.56/100,000 population, and in the United States 0.39/100,000 population. Since the majority of countries provided the data based on the number of patients attending specialist clinics, the actual prevalence of MS in pediatric patients may be higher (MSIF 2013a).

The incidence of pediatric MS has been varyingly reported as between 0.02 and 0.64/100,000 population/year. In Europe, Russia reported the lowest incidence (0.1/100,000 population/year) and Slovenia the highest (0.5/100,000 population/year).

Occurrence of initial symptoms before 10 years of age is exceptional (Ruggieri et al. 2004). The incidence of MS in the pediatric population increases with age, with a considerably higher incidence in adolescence (from 1.10/100,000 population/year in 11-13 year-olds to 2.64/100,000 population/year in 14-15 year-olds in a cohort in Germany; and from no cases in 0-14 year-olds to 0.43/100,000 population/year in 15-19 year-olds in a cohort in the United Kingdom) (Alonso et al. 2007; Reinhardt et al. 2014).

Elderly patients: Occurrence of initial symptoms of MS after 60 years of age is rare (Tullman 2013). Prevalence and incidence of MS in the elderly population decrease with age, although the estimates vary depending on the geographical area and the source of data (e.g., from 855.9 persons/100,000 population aged 55-64 years, to 520.9 persons/100,000 population aged 65-74 years, to 294.7 persons/100,000 population aged ≥75 years in a cohort in Saskatoon, Canada; or from 319.9 persons/100,000 population aged 55-64 years, to 200.0 persons/100,000 population aged 65-74 years, to 111.3 persons/100,000 population aged ≥75 years in a cohort in South Wales) (Hader et al. 2007; Hirst et al. 2009).

Race and Ethnicity: Different racial and ethnic groups may have different susceptibility. A genetic factor in development of MS may explain the uneven distribution of the disease globally, which is rare in Chinese, Japanese, African black people, New Zealand Maori

people, or indigenous people of the Americas, and highly prevalent amongst Sardinians, Parsis, and Palestinians (Rosati 2001).

Data from three areas in the United States showed the highest prevalence in non-Hispanic white people (56.0-99.4/100,000 population/year), followed by non-Hispanic black people (22.1-90.9/100,000 population/year), and Hispanic people (11.2-56.0/100,000 population/year) (Noonan et al. 2010). The higher prevalence of MS in African Americans compared with black Africans may be due to genetic admixture of a resistant African population with a susceptible Caucasian population or environmental factors operative within the United States (for risk factors, see below) (Cree et al. 2004).

- The main existing treatment options:

In addition to treatments for the symptoms of MS and treatment of relapses (such as corticosteroids), there are currently more than a dozen (European Union [EU], United States) disease-modifying therapies (DMTs) such as interferon (IFN) beta-1a, IFN beta-1b, glatiramer acetate, mitoxantrone, natalizumab, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, peginterferon beta-1a, siponimod, ozanimod, and cladribine approved for use in patients with RRMS and/or other forms of RMS.

Prior to the approval of ocrelizumab, in the absence of any approved treatment for PPMS, a variety of unapproved agents including mycophenolate mofetil, cyclophosphamide, mitoxantrone, or rituximab, in addition to other therapies approved for the treatment of RMS, were used in clinical practice despite the lack of Level 1 evidence. This exposes patients to risks without defined benefits. High-dose immunosuppressive therapy followed by autologous hematopoietic stem cell transplant, which aims to suppress active disease and prevent further disability by removing disease-causing cells and resetting the immune system, is being used as an experimental therapy for some patients with refractory forms of MS.

Table 2 Other Currently Approved Disease-Modifying Therapies (By Earliest Approval Date in either United States or European Union)

Brand name(s)	International Non-proprietary Name	Route of Administration	Dose and Frequency of Administration	Year Approved in U.S.[a]	Year Approved in EU[b,c]
Betaseron® (U.S.), Betaferon® (EU)	IFN beta-1b	SC	250 μg every 2 days	1993	1995
Avonex®	IFN beta-1a	IM	30 μg once weekly	1996	1997
Copaxone®	Glatiramer acetate	SC	20 mg once daily or 40 mg three times a week	1996	2001

Brand name(s)	International Non-proprietary Name	Route of Administration	Dose and Frequency of Administration	Year Approved in U.S.[a]	Year Approved in EU[b,c]
Rebif®	IFN beta-1a	SC	22 μg or 44 μg three times a week	1998	1998
Novantrone®	Mitoxantrone[d]	IV infusion	12 mg/m^2 every 3 months. Lifetime cumulative dose limit of approximately 8-12 doses over 2-3 years (140 mg/m^2)	2000	2016
Tysabri®	Natalizumab	IV infusion	300 mg every 4 weeks	2006	2006
Extavia®	IFN beta-1b	SC	250 μg every 2 days	2009	2008
Gilenya®	Fingolimod	Oral	0.5 mg once daily	2010	2011
Aubagio®	Teriflunomide	Oral	7 mg or 14 mg once daily	2012	2013
Tecfidera®	Dimethyl fumarate	Oral	240 mg twice a day (120 mg in the initial week)	2013	2014
Lemtrada®	Alemtuzumab	IV infusion	12 mg daily on 5 consecutive days, followed by 12 mg daily on 3 consecutive days one year later	2014	2013
Plegridy®	Peginterferon beta-1a	SC	125 μg every 2 weeks	2014	2014
Glatopa™	Glatiramer acetate	SC	20 mg once daily	2015	Not approved
Glatiramer acetate	Glatiramer acetate	SC	40 mg/mL	2017	2017

Brand name(s)	International Non-proprietary Name	Route of Administration	Dose and Frequency of Administration	Year Approved in U.S.[a]	Year Approved in EU[b,c]
Mavenclad®	Cladribine	Oral	3.5 mg per kg body weight over two years, administered as one treatment course of 1.75 mg per kg per year. Each treatment course consists of two treatment weeks. Following the administration of two treatment courses, additional courses are not to be administered.	2017	2017
Zeposia®	Ozanimod	Oral	Days 1 – 4: 0.23 mg once daily Days 5 – 7: 0.46 mg once daily Day 8 and thereafter: 0.92 mg once daily	2020	2020
Mayzent®	Siponimod	Oral	Days 1 and 2: 0.25 mg once daily Day 3: doses of 0.5 mg once daily Day 4: 0.75 mg once daily Day 5:1.25 mg once daily to reach the patient's prescribed maintenance dose of siponimod starting on Day 6	2019	2020

Brand name(s)	International Non-proprietary Name	Route of Administration	Dose and Frequency of Administration	Year Approved in U.S.[a]	Year Approved in EU[b,c]
Kesimpta®	Ofatumumab	SC	Initial dosing of 20 mg by SC injection at weeks 0, 1, and 2, followed by subsequent dosing of 20 mg by SC injection once monthly starting at week 4.	2020	2021
Vumerity®	Diroximel fumarate	Oral (PO)	Initial dose: 231 mg twice daily; after 7 days, increase to the maintenance dose of 462 mg twice daily. If maintenance dose is not tolerated, consider temporary dose reduction to 231 mg twice daily; resume recommended maintenance dose of 462 mg twice daily within 4 weeks. Consider discontinuation in patients who cannot tolerate return to the maintenance dose.	2019	2021

Brand name(s)	International Non-proprietary Name	Route of Administration	Dose and Frequency of Administration	Year Approved in U.S.[a]	Year Approved in EU[b,c]
Briumvi™	Ublituximab	IV	Day 1 infusion of 150 mg administered in 4 hours, at Day 15 infusion of 450 mg administered in 1 hour, followed by 450 mg infusions every 24 weeks administered in 1 hour.	2022	2023

EU = European Union IFN = interferon; IM = intramuscular; IV = intravenous; PO = per oral; U.S.= United States, SC = subcutaneous.

a Source: National Multiple Sclerosis Society 2022.

b Source (excluding glatiramer acetate and mitoxantrone): European Medicines Agency 2022.

c Source for glatiramer acetate: Teva 2001.

d In the EU, mitoxantrone is approved for the treatment of MS in France and Germany only, as Elsep, and Ralonova, respectively.

Table 3 Medications Used to Treat Common Symptoms of Multiple Sclerosis

Symptom of Multiple Sclerosis	**Medications used to treat the symptom**
Acute optic neuritis	High dose corticosteroids
Bladder dysfunction and infection	
Urine storage	Antimuscarinic agents, imipramine, desmopressin
Emptying dysfunction	Antimuscarinic agents, antispasticity agents, alpha blockers
Combined dysfunction	Neurotoxins, botulinum toxin A, cannabinoids
Bladder infection	Sulfamethoxazole, ciprofloxacin, nitrofurantoin, methenamine, phenazopyridine
Bowel dysfunction	
Constipation	Laxatives
Incontinence	Loperamide (in chronic diarrhea with incontinence)
Pain	
Central neuropathic pain (e.g., trigeminal neuralgia)	High-dose steroid + carbamazepine or other anticonvulsant, oxcarbazepine, baclofen, misoprostol, tricyclic antidepressants, gabapentin, pregabalin, lamotrigine, carbamazepine, cannabinoid medicines
General pain	Related to suspected symptom cause; similar approach as with non-MS patients

Symptom of Multiple Sclerosis	Medications used to treat the symptom
Sexual problems	
Erectile dysfunction	Phosphodiesterase-5 inhibitors, intracavernosal alprostadil, intracavernosal papaverine + phentolamine + prostaglandin E1
Vaginal dryness	Topical lubricants, hormone replacement treatment, sildenafil
Low libido	Androgen therapy
Sleep disorders	
Excessive daytime sleepiness	Modafinil
Other symptoms of MS	
Restless legs syndrome	Dopaminergic agonists
Spasticity	Baclofen, tizanidine, intrathecal baclofen (for Expanded Disability Status Scale [EDSS] > 7), dantrolene, benzodiazepines, gabapentin, botulinum toxin, cannabinoid medicines, tolperisone, clonidine, cryproheptadine, dalfampridine, levetiracetam, piracetam
Tremor and ataxia	Isoniazid, carbamazepine, topiramate, anticonvulsants, benzodiazepines, lacosamide, beta blockers, beta blocker in combination with antiepileptic agent, primidone, oxitriptan
Walking (gait) difficulties	Dalfampridine
Pseudobulbar affect	Dextromethorphan + quinidine
Seizures	Standard antiepileptic treatment
Cognitive impairment	Donepezil, rivastigmine, amphetamines
Depression	Serotonin-specific reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, tricyclics, moclobemide
Dizziness and vertigo	Vestibular blocking agents, high-dose corticosteroids (in vertigo caused by demyelinating plaques)
Dysarthria	Therapies treating tremor (in rare cases)
Dysphagia	Anticholinesterases
Fatigue	Dalfampridine or other potassium channel blocker, amantadine (in fatigue without sleepiness), modafinil (in fatigue with sleepiness), serotonin-specific reuptake inhibitors, acetyl L-carnitine
Oculomotor disorders	Memantine, gabapentin (also in combination; in pendular nystagmus), baclofen, amifampridine (in upbeat/downbeat nystagmus), high dose corticosteroids (only in initial treatment)

Sources: Amato et al. 2013; Ben-Zacharia 2011; de Sa et al. 2011; European Multiple Sclerosis Platform (EMSP) 2008; Feinstein et al. 2015; Frohman et al. 2011; Jensen et al. 2013; Leussink et al. 2012; National Multiple Sclerosis Society 2016c; Siegert and Abernethy 2005; Solaro et al. 2013; Tubaro et al. 2012

- Risk factors for the disease:

Multiple risk factors are associated with development of MS, including environmental, infectious, and genetic factors.

Multiple sclerosis is rare in tropical and subtropical regions of all continents. Within temperate climate regions, prevalence and incidence increase with latitude on both sides of the equator (Ascherio and Munger 2007a). Latitude is directly associated with duration and intensity of sunlight and there is inverse correlation between prevalence of MS and sunlight exposure. Exposure to sunlight is an important source of vitamin D, and the higher MS incidence at higher latitudes could be attributed to vitamin D deficiency. Munger et al. (2004) found that supplementing vitamin D was associated with a 40% lower risk of developing MS (Munger et al. 2004; Ascherio and Munger 2007b).

Among infectious agents, only Epstein-Barr virus (EBV) has consistently emerged as a risk factor for MS, although an important or critical role of other agents cannot be excluded. People infected with EBV in childhood are 10 times more likely to develop MS compared to uninfected individuals. The risk increases to 20-fold in individuals who developed mononucleosis (Ascherio and Munger 2007a). For those infected with EBV in adolescence and adulthood, the risk is 20-fold higher compared to uninfected individuals (Ascherio 2013; Levin et al.2010) suggest that one's risk for MS increases sharply following EBV infection. In addition, the risk of MS increased 32-fold after infection with EBV but was not increased after infection with other viruses, including the similarly transmitted cytomegalovirus. Serum levels of neurofilament light chain, a biomarker of neuroaxonal degeneration, increased only after EBV seroconversion. These findings cannot be explained by any known risk factor for MS and suggest EBV as the leading cause of MS (Bjornevik et al. 2022).

The risk of developing MS for a first-degree relative of a MS patient is 30-50 times higher compared to the risk observed in the general population (Sadovnick et al. 1988). Studies from Great Britain and Canada showed that monozygotic twins had a 25%-25.9% concordance for MS, as compared to a 2.3%-5.4% concordance for dizygotic twins, and 1.9%-2.9% concordance for non-twin siblings (Ebers et al. 1986; Mumford et al. 1994; Willer et al. 2003).

Several studies found an association between smoking and an increased MS susceptibility (Ascherio and Munger 2007b; Wingerchuk 2012). Wingerchuk 2012 found the relative risk to be approximately 1.5. Earlier start of smoking and heavier cigarette consumption is associated with an increased risk of PPMS development compared with the relapsing-remitting onset (Wingerchuk 2012). Smoking is also associated with an increased risk of disability progression and conversion from RRMS to secondary progressive multiple sclerosis (SPMS) (Wingerchuk 2012; Marrie and Horwitz 2010).

Patients with some autoimmune disorders (e.g., type 1 diabetes mellitus [Nielsen et al. 2006] or inflammatory bowel disease [Gupta et al. 2005]) have an increased risk of

developing MS. Nielsen et al. (2006) found the risk in patients with type 1 diabetes mellitus to be 3-fold higher (Nielsen et al. 2006). The shared risk for these diseases may be due to shared genetic susceptibility and/or environmental exposures such as smoking (Marrie et al. 2011; Marrie et al. 2015d).

- Natural history of the indicated condition in the untreated population:

Mortality and morbidity:

- Multiple sclerosis is a serious, disabling disease and the leading cause of non-traumatic acquired disability in young adults (Tullman 2013). The disease course culminates in deterioration of the physical and cognitive functions of patients, which significantly affects quality of life (QOL) and independence. Patients suffer from a range of MS-associated symptoms including motor weakness, spasticity, gait and coordination imbalance, sensory dysfunction, vision loss, sexual dysfunction, fatigue, depression, chronic pain, sleep disorders, and cognitive impairment (Damal et al. 2013).

Subclinical inflammatory activity and neurodegenerative changes occur early and persist throughout the course of RMS. Emerging evidence suggests that brain volume loss along with cognitive and behavioral changes may be evident by the time the first clinical evidence of MS has appeared (Rocca et al. 2003; Rojas et al. 2015; Labiano-Fontcuberta et al. 2015a; Labiano-Fontcuberta et al. 2015b; Sinay et al. 2015; Azevedo et al. 2015). Following a first clinical attack, nearly all RMS patients develop further disease progression; however, they also continue to exhibit subclinical disease activity in the form of focal inflammatory lesions in clinically silent areas of the brain, and regional and whole brain atrophy (De Stefano et al. 2003; Miller et al. 2005; Compston and Coles 2008; De Stefano et al. 2010; Khan et al. 2014). Left untreated or under-treated, over time both clinically apparent and subclinical disease activity result in central nervous system (CNS) tissue damage, disability accrual and diminishing QOL.

Although the accumulation of severe disability in either clinical variant of MS is not strictly the immediate cause of death, advanced MS carries a risk of systemic complications that can prove fatal. Data from large cohort registries show that 47.1% to 75% of patients die from causes directly related to MS, while the remaining deaths are attributable to the common causes of death found in the general population (Scalfari et al. 2013). In United States, urinary tract infections (UTIs) are an underlying or contributing cause of death in nearly 10% of reported MS deaths, and the odds of UTI reported on the death certificate in MS deaths are more than 10 times higher than in the matched controls. The odds of “pneumonia/influenza”, and pressure ulcers being reported on the death certificate are also higher in MS deaths than matched controls (Redelings et al. 2006).

Comparisons of all-cause mortality with the general population in Europe and North America show that there is a two to three times greater risk of mortality associated with MS (Kingwell et al. 2012a), and life expectancy is reduced by 7 to 14 years compared to

the general population. Similar median and mean ages at death are reported for both RMS and PPMS (MS disease course does not significantly affect time to death from birth) (Scalfari et al. 2013). According to the World Health Organization (WHO), the age-standardized MS mortality rate in Europe ranges from 0.2 to 1.5/100,000 population/year and is 0.9/100,000 population/year in North America. WHO reports that the mortality rate in Europe and North America is higher in females than males (World Health Organization 2012). However, data on the relationship between sex and mortality are contradictory, with studies variably reporting a longer survival in females, males, or no statistical difference between the sexes (Scalfari et al. 2013).

Discussion of the possible stages of disease progression to be treated:

In approximately 85% of patients, MS begins as a relapsing, episodic disorder with gradual complete or incomplete recovery (RRMS).

PPMS is a less common form of MS, accounting for approximately 15% of all cases. It is characterized by a progressive course from disease onset, with infrequent superimposed discrete clinical attacks or relapses (Lublin et al. 2014).

Outcome of the (untreated) target disease:

If left untreated, the majority of these RRMS patients will transition to a secondary progressive form characterized by worsening neurologic disability with or without occasional super-imposed relapses (relapsing or non-relapsing SPMS).

- Important co-morbidities:

Depression and anxiety disorder are the most prevalent comorbidities in patients with MS. Serious infections (SIs) (UTIs, gastrointestinal infections, respiratory infections) may be due to the bladder and bowel dysfunction experienced by MS patients, while an increased risk of respiratory infections may be because of inability to cough and clear the lungs or bulbar (brainstem) dysfunction and inability to protect the airway (i.e., aspiration).

- Adverse pregnancy outcomes in patients with multiple sclerosis:

Multiple sclerosis is three times more common in women than in men, and clinical onset often occurs in women aged between 20 and 40 years. Women with MS tend to be older than the general population (without MS) at the time of pregnancy diagnosis (Houtchens et al. 2018). Across MS studies with or without treatment at pregnancy, the rates for most adverse pregnancy outcomes were found to be comparable to that of general population (MacDonald et al. 2019, Oh et al. 2020, Soler et al. 2021).

A study using two large administrative databases (The Truven Health MarketScan Database [2011–2015] and the Nationwide Inpatient Sample [NIS: 2007–2011]) evaluated the adverse pregnancy outcomes in patients with or without MS in the United

States. In the Truven Health database, women with MS had an increased risk of preterm delivery (relative risk [RR]: 1.19; 95% confidence interval [CI] [1.04, 1.35]) while the risks of other outcomes were found to be similar for women with and without MS. In the NIS database, the risk of preterm delivery (RR: 1.30; 95% CI [1.16, 1.44]) was found to be increased in women with MS compared to without MS (MacDonald et al. 2019). Table 4 describes the rates of adverse pregnancy outcomes in women with or without MS.

Table 4 Pregnancy Outcomes Among United States Women with and without Multiple Sclerosis

	Truven Health MarketScan Database (2011-2015; n = 1,102,604)		**Nationwide Inpatient Sample (2007–2011; n = 4,186,816)**	
Pregnancy Outcomes	**Women with MS (n = 1,439) (%)**	**Women without MS (n = 1,101,165) (%)**	**Women with MS (n = 2,436) (%)**	**Women without MS (n = 4,184,380) (%)**
Preterm delivery	13.1	10.4	10.9	8.3
Pre-eclampsia	5.1	5.2	4.2	4.2
Chorioamnionitis	3.2	3.4	1.5	1.8
Postpartum hemorrhage	1.5	2.2	3.2	2.7
Stillbirth	-	0.6	0.6	0.7
Infant malformation	3.9	4.4	NA	NA
Poor fetal growth	8.9	8.8	2.4	2.1

MS = multiple sclerosis; NA = not available.

Source: McDonald et al. 2019

Another study that included patients with RRMS treated with alemtuzumab, reported the adverse pregnancy outcomes compared to the general population, and the overall MS population. The adverse pregnancy outcomes reported are presented in Table 5. There were 155 (67%) live births, with no congenital anomalies. The rate of spontaneous abortion in the RRMS group was comparable with the general population and the treatment-naïve MS patients. Stillbirths were found to be higher in the treatment-naïve MS patients (Oh et al. 2020).

Table 5 Pregnancy Outcomes in Relapsing-Remitting Multiple Sclerosis Patients Compared to General and Overall Multiple Sclerosis Patients

Pregnancy Outcomes	RRMS	General population	Overall MS population
Spontaneous abortion	22%	17%-22%	5%-21%
Stillbirth	0.4%	0.2%-0.6%	1%-2%
Elective abortion	11%	18%-23%	10%-27%

MS = multiple sclerosis; RRMS = relapsing-remitting MS.
Source: Oh et al. 2020

Another study was conducted in Chile between 2008 and 2018 to explore the pregnancy outcomes in women that conceived before (PreMS) and after MS diagnosis (PostMS). Overall pregnancy complications were found to be similar in both cohorts. The study found that PostMS patients had fewer pregnancies (mean 1.9±1.1 per woman in 54 women) compared to PreMS patients (mean 2.5±1.3 per woman in 97 women), (p=0.0003). First pregnancy at an older age (32.6±4.6 years in PostMS vs. 27.6±6,2 years in PreMS; p<0.001). No significant association was observed for major malformation, spontaneous abortion, pre-eclampsia, and premature delivery between both cohorts. Table 6 describes the rates of pregnancy complications in PreMS and PostMS cohorts (Soler et al. 2021).

Table 6 Pregnancy Complications in Women before and after Multiple Sclerosis Diagnosis

Pregnancy outcomes	Number of pregnancies in PreMS (n=223)	Number of pregnancies in PostMS (n=76)
Overall pregnancy complications	10%	10%
Major malformation	2.6%	2%
Abortion	12%	17%
Pre-eclampsia	1.8%	1.3%
Premature delivery	1.3%	0%

PreMS = pregnancy outcomes before multiple sclerosis diagnosis; PostMS = pregnancy outcomes before multiple sclerosis diagnosis.
Source: Soler et al. 2021

Treatment with DMTs in MS patients does not appear to be associated with adverse pregnancy outcomes as compared to no treatment with DMTs. A systematic review and meta-analysis of ten studies published between January 2000 and August 2019 evaluated pregnancy and neonatal outcomes in women with MS treated with (DMTs) compared to unexposed MS cohort. The results from this meta-analysis are summarized on Table 7, Table 8, Table 9. However, these results were mainly driven by interferon,

glatiramer acetate and natalizumab; therefore, it is not possible to generalize to other drugs such as fingolimod, azathioprine or rituximab. Given the diverse mechanisms by which these DMTs work, understanding each DMT individually is highly important; therefore, there is a need for studies with large sample sizes that present their results stratified by type of drug. Lopez-Leon et al, 2020.

Table 7 Adverse Pregnancy or Neonatal Outcomes in Unexposed vs Exposed DMTs Cohorts

Outcome	Unexposed DMTs cohort	Exposed DMTs cohort
Spontaneous abortions	10.9%	11.6%
Premature birth	12.1%	12.12%
Major congenital malformations	4.2%	3%

DMTs = disease-modifying therapies.
Source: Lopez-Leon et al. 2020

Table 8 Most Common Congenital Anomalies which Were Seen in the DMT-Treated Multiple Sclerosis Patients

Anomalies	Number of cases
Atrial septal defect	4
Polydactyly	4
Club foot	3
Down Syndrome	2
Ureteral duplication	2

DMTs = disease-modifying therapies.
Source: Lopez-Leon et al. 2020

Table 9 Relative Ratio Calculated for the Multiple Sclerosis Patients in the DMTs Treated Cohort Compared to the Untreated Cohort

	Relative Ratio
Spontaneous abortions (from eight studies)	1.14; 95% CI: 0.99–1.32
Preterm births (from seven studies)	0.93; 95% CI: 0.72–1.21
Major congenital malformations (from eight studies)	0.86; 95% CI: 0.47–1.56

CI = confidence interval; DMTs = disease-modifying therapies.
Source: Lopez-Leon et al. 2020

PART II: MODULE SII— NONCLINICAL PART OF THE SAFETY SPECIFICATION

As ocrelizumab is only known to bind to human and non-human primate CD20, the cynomolgus monkey was determined to be the only relevant species for use in the nonclinical toxicology program for ocrelizumab IV. The rats and minipigs were selected as appropriate species to assess local tolerance of a formulation suitable for ocrelizumab SC.

SII.1 TOXICITY:

SII.1.1 Local tolerance

Single-dose SC local tolerance studies were conducted in rats and minipigs over a period of 7 days to assess the tolerability of 40 mg/mL ocrelizumab with the addition of rHuPH20, human recombinant hyaluronidase enzyme PH20, in the proposed clinical SC formulation.

There were no macroscopic dermal observations or systemic effects attributed to ocrelizumab SC administration. SC administration was locally and systemically well tolerated in rats and minipigs. The results are in line with the toxicity profile for ocrelizumab IV.

Overall, in these local tolerance studies, there was microscopic evidence of concentration-dependent increases in inflammatory cell infiltration, edema, and fibrosis in SC tissue at the injection site. However, at an ocrelizumab concentration of 40 mg/mL, the proposed clinical SC, findings were limited to minimal mononuclear inflammatory cell infiltration in rats, and minimal to mild perivascular inflammatory cell infiltration and minimal to mild fibroplasia at the injection site in minipigs and the SC no observed adverse effect level was determined to be 40 mg/mL.

Relevance to human usage: Yes

Discussion: In the clinical development studies, treatment with ocrelizumab SC is associated with injection reactions (IR) that are categorized into systemic injection reactions and local injection reactions. Local symptoms are the ones occurring at the SC injection site, and systemic symptoms can be similar to the infusion-related reaction (IRR) symptoms with the IV infusions. Therefore, IRs were assessed as a new aspect of the important identified risk of IRRs, further described in Part II SVII.3.1.1.1 INFUSION-RELATED REACTIONS (observed with the IV formulation) and INJECTION REACTIONS (observed with the SC formulation).

SII.1.2 General toxicity

SII.1.2.1 B-cell depletion

Ocrelizumab was well tolerated by cynomolgus monkeys in nonclinical safety studies. In general, most ocrelizumab-related effects were consistent with pharmacologic depletion of B cells, which included decreases in lymphocytes and lymphoid atrophy (reduction in

the relative size and/or number of lymphoid germinal centers) in B cell regions of the spleen and lymph nodes. Immunohistochemical analyses of CD20 immunoreactivity showed depletion of B cells in the spleen (nearly complete), and mandibular lymph nodes (marked) of high-dose, ocrelizumab-treated terminal necropsy animals. These histological findings were largely absent in recovery animals. The no observed adverse effect level in the repeat-dose general toxicity studies was 100 mg/kg, the highest dose tested.

Relevance to human usage: Yes

Discussion:

B-cell depletion in blood and lymphoid tissues is consistent with the desired pharmacology and mode of action of ocrelizumab.

There was no increase in SIs associated with ocrelizumab treatment in clinical studies (in RMS patients, the rate of SIs was lower than for IFN, and in PPMS patients the rate was similar to placebo).

Ocrelizumab did not appear to have an effect on specific humoral immunity (antibody [Ab] titers) to common bacterial and viral antigens (Ag) (pneumonia, mumps, rubella, and varicella zoster) during the controlled treatment periods of clinical studies (over 2 years).

The safety of immunization with live or live-attenuated vaccines, following ocrelizumab therapy has not been studied and vaccination with live-attenuated or live vaccines is not recommended during treatment and until B-cell repletion.

In Study BN29739 (VELOCE), a randomized open-label study, RMS patients treated with ocrelizumab were able to mount humoral responses, albeit decreased, to tetanus toxoid, 23-valent pneumococcal polysaccharide, keyhole limpet hemocyanin neoantigen, and seasonal influenza vaccines. It is still recommended to vaccinate patients treated with ocrelizumab with seasonal influenza vaccines that are inactivated.

Physicians should review the immunization status of patients before starting treatment with ocrelizumab. Patients who require vaccination should complete their immunizations at least 6 weeks prior to initiation of ocrelizumab.

SII.1.3 Reproductive and developmental toxicity studies (neonates)

In an embryo-fetal development study in cynomolgus monkeys, there was no evidence of maternal toxicity, teratogenicity, or embryotoxicity following ocrelizumab treatment at 75/100 mg/kg (loading dose/study dose). Flow cytometric analyses demonstrated reductions in B cells (the anticipated pharmacological effect) in maternal and fetal peripheral blood.

In two pre- and postnatal development studies in cynomolgus monkeys, administration of ocrelizumab from gestation Day 20 to at least parturition was associated with glomerulopathy, lymphoid follicle formation in bone marrow, lymphoplasmacytic renal inflammation, and decreased testicular weight in offspring. The maternal doses administered in these studies resulted in maximum mean serum concentrations (C_{max}) that were 4.5- to 21-fold above those anticipated in the clinical setting.

There were five cases of neonatal moribundities, one attributed to weakness due to premature birth accompanied by opportunistic bacterial infection, one due to an infective meningoencephalitis involving the cerebellum of the neonate from a maternal dam with an active bacterial infection (mastitis) and three with evidence of jaundice and hepatic damage, with a viral etiology suspected, possibly a polyomavirus. The course of these five confirmed or suspected infections could have potentially been impacted by B-cell depletion. Newborn offspring of maternal animals exposed to ocrelizumab were noted to have depleted B-cell populations during the postnatal phase. Measurable levels of ocrelizumab were detected in milk (approximated 0.2% of steady state trough serum levels) during the lactation period.

Relevance to human usage: No

Discussion:

Exposure in utero to ocrelizumab and vaccination of neonates and infants with live or live-attenuated vaccines. 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-cell levels 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.

SII.1.3.1 Opportunistic infections:

In a pre- and postnatal development study in pregnant cynomolgus monkeys, one neonate in the 75/100 mg/kg group was found dead on post-birth Day 6, and another was euthanized on post-birth Day 138 in moribund condition. The cause of death or moribundity of these two neonates was in part attributed to opportunistic infections. In one animal with bacterial meningitis, weakness due to premature delivery and immaturity may have been a predisposing factor. The second animal became moribund while nursing from a dam diagnosed with concurrent bacterial (staphylococcal) mastitis and cause of death of this neonate was attributed to meningoencephalitis involving the cerebellum. Both of these infections may have been secondary to B-cell depletion

related to systemic exposure to ocrelizumab. In a separate pre- and post-natal development study in pregnant cynomolgus monkeys, two offspring were found dead on postnatal developments (PNDs) 10 and 13, respectively, and one offspring was euthanized on PND 12. Serum chemistry revealed hyperbilirubinemia along with increased liver enzymes, and yellowish discoloration of several organs/tissues of the whole body in these animals. Based on follow-up assessments with immunohistochemistry, electron microscopy and polymerase chain reaction, a viral etiology was presumed to be the cause of disease in these animals, possibly simian virus 40 (SV40). The suspected opportunistic infections in offspring may have been impacted by B-cell depletion.

Relevance to human usage: No

Discussion:

One infection was reported in a neonate born by a mother administered ocrelizumab during participation in the lupus nephritis (LN) Study WA20500. This prematurely born neonate developed respiratory distress requiring oxygen therapy for 5 days and sepsis (blood culture was positive for *Acinetobacter* and *Enterobacter*, while urine and cerebrospinal fluid [CSF] cultures were negative) on an unknown day of life and was discharged from hospital 4 weeks after birth. Certain strains of *Acinetobacte*r and *Enterobacter* can be opportunistic pathogens; however, *Acinetobacter* is also increasingly causing hospital-derived (nosocomial) infections. Since conception occurred nearly 10 months after the last dose (400 mg) of ocrelizumab, this fetus is not considered to have been transplacentally exposed to ocrelizumab. In the mother, B cell counts were normal 4 weeks before conception and during gestational week 6, while they were 57 cells/µL, i.e., below the lower limit of normal (LLN; 80 cells/ µL) during gestation week 20. The maternal B cell count on the day of delivery at 36 weeks gestation is unknown. No estimate can be made concerning the B-cell depletion/repletion status beyond the initial 6-month period following the last ocrelizumab infusion, when the patient is assumed to have been B cell depleted. In the absence of information on B cell count and immunoglobulin (Ig) status in the newborn at delivery, it cannot be ruled out whether or not this was an opportunistic infection and causality could not be assessed (Drug Safety Report [DSR] 1067126).

‘Infections’ are considered an important identified risk for ocrelizumab (see SVII.3.1).

SII.1.3.2 Additional developmental findings:

In the pre- and postnatal development study in pregnant cynomolgus monkeys, ocrelizumab-related changes in neonates included: glomerulopathy of unclear relationship to drug administration (29% of neonates in ocrelizumab groups), lymphoid follicle formation in the bone marrow (38% of neonates in ocrelizumab groups), and lymphoplasmacytic inflammation in the kidney (18% in the high dose [100 mg/kg] group).

Testicular weights (absolute and relative to brain weight) of the neonates were significantly decreased in the high dose group as compared to study control neonates. Histologically, this finding was limited to immature testes in all males in each group, including controls. Given the lack of differences in accessory reproductive organ weights (epididymis, prostate/ seminal vesicle weights), the small sample size and the age of neonates in this study, the toxicological significance of the testicular weight decrease on testis maturity remains unclear.

There was no evidence of teratogenicity or embryotoxicity in an embryo-fetal development study in cynomolgus monkeys.

An enhanced pre- and post-natal development study in cynomolgus monkeys, which was designed to further investigate fetal and infant outcome following ocrelizumab exposure during pregnancy, has been completed.

Relevance to human usage: Yes

Discussion:

Six cases describing structural malformations (small right renal cyst, benign nasopharyngeal neoplasm, and congenital positional feet contracture and limited hips abduction), functional deficits, or growth alterations have been identified on the Roche Global Safety Database. Based on single case review, no causal relationship between the structural malformations, functional deficits and growth alterations identified in the pregnancy cases reported and ocrelizumab administration could be established. All six cases had confounding factors or insufficient information for a medical assessment, and none was considered in utero exposed to ocrelizumab (DSR 1067126).

From all of the available information, no evidence for an increased risk of ocrelizumab for spontaneous/missed abortion, fetal death, induced abortion, premature birth, structural malformations, functional deficits, or growth abnormalities could be identified. A direct genotoxic effect of ocrelizumab is considered unlikely given that ocrelizumab is a large molecule and is therefore not expected to possess DNA damaging properties based on its physico-chemical properties. No information on B cell and immune globulin counts in the newborns of mothers exposed to ocrelizumab had been entered onto the Global Safety Database. Transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to anti-CD20 antibodies during pregnancy (DSR 1067126). The marketing authorization holder (MAH) does not believe the finding of testicular weight decrease has any relevance to human usage because it was not clearly drug-related and could have been influenced by the imbalance of animal immaturity in the study.

Of note, in discussions regarding pediatric development plans, the U.S. Food and Drug Administration (FDA) requested that the Sponsor conduct a juvenile animal toxicity study

in monkeys (Study 15-3109 “An 8-Week Multiple Dose Immunotoxicity Study of Ocrelizumab by Intravenous (IV) Injection in Juvenile Cynomolgus Monkeys with a 9-Month Recovery Period”) to support the planned pediatric study WA39085 (OPERETTA 1) “An Open Label Parallel Group Study to Evaluate Safety and Tolerability, Pharmacokinetics and Pharmacodynamic Effects of Ocrelizumab in Children and Adolescence with Relapsing Remitting Multiple Sclerosis. Study 15-3109 is now complete. Adverse findings that were attributed to ocrelizumab administration were limited to the high-dose (100 mg/kg/week) with two male cage mates that were found either moribund (post-partum day 148) or dead (post-partum day 78). Although no etiological agent was identified, an infective process was suspected. Clinical pathological findings suggestive of underlying endotoxemia, and histopathological findings consistent with the immunosuppression by ocrelizumab and/or systemic inflammation were observed in these males. Consistent with this was evidence of a pronounced inhibition of T-Cell-Dependent Antibody Response (TDAR) to keyhole limpet hemocyanin (KLH) primary vaccination and near complete depletion of B cells in lymph node tissues and peripheral blood. Although the degree of B-cell depletion and inhibition of TDAR at end of study were not substantively different from other monkeys in this high dose cohort, immunosuppression is likely to have played a role in the cause of morbidity and death of these two animals.

On 2 August 2017, the Sponsor received a partial clinical hold from FDA indicating that the studies in pediatric patients may not be initiated until the investigation related to the premature deaths in juvenile animal toxicology study has been concluded and a monitoring strategy in pediatric patients has been identified. On 29 March 2019, the Sponsor submitted a response package to FDA to address the partial clinical hold in pediatric studies, including the final juvenile toxicity report for Study 15-3109. Upon review of the response package, the FDA indicated on 26 April 2019 that the partial clinical hold was removed and that the Sponsor may proceed with the proposed pediatric study WA39085 (OPERETTA 1), which is currently ongoing.

Given that the findings in this study were limited to infant monkeys, which were significantly less mature than the current pediatric patient population in clinical trials (i.e., > 10 years old), and considering the totality of the safety data in adult humans, at this time there is no change in the benefit/risk in adults.

SII.1.4 Genotoxicity

Per International Conference on Harmonisation (ICH) S6 (R1) Guidance on the Nonclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, genotoxicity studies routinely performed for small molecules are not applicable to biotechnology-derived large molecules, such as ocrelizumab.

Relevance to human usage: No

Discussion:

A direct genotoxic effect of ocrelizumab is unlikely given that ocrelizumab is a large molecule and is therefore not expected to possess DNA damaging properties based on its physio-chemical properties.

SII.1.5 Carcinogenicity

No carcinogenicity studies have been conducted with ocrelizumab and none are planned due to lack of suitable nonclinical in vivo and in vitro approaches to malignancy risk assessment. Classical lifetime rodent bioassays, which are commonly used to assess carcinogenesis risk for small molecules, are considered inappropriate for biotherapeutics in general as these assays have largely been validated with genotoxic compounds and protein therapeutics are considered to have low genotoxic potential. Furthermore, lifetime studies in rodents with ocrelizumab are not viable given the lack of cross-reactivity with murine CD20.

In a female fertility study in cynomolgus monkeys, a nasal carcinoma was identified in 1 low-dose female animal at recovery necropsy, reaching from the tip of the nose to the orbita in the right nasal cavity. Clinical signs, attributed to this finding on review, were manifesting from study Day 164 onward (50 days into recovery period) and included progressive gasping; unsteady, noisy breathing; abnormal eye movements; teary eyes; swelling at the right eye or right lower eyelid; nasal discharge; and stress signs. As this was an advanced epithelial neoplasm in a single low-dose recovery animal and given the absence of abnormal proliferative findings in any other animals on this study, this finding was regarded as incidental and was not considered related to the test article. Furthermore, there was no evidence of hyperplastic or malignant lesions seen in any monkey from any other safety study conducted with ocrelizumab (n =126 monkeys with histopathological assessments).

No risk factors that are considered predictive of carcinogenic risk (e.g., chronic inflammation, aberrant proliferation, or dysplasia) were identified in nonclinical safety studies. Given the limitations of existing rodent models, the MAH believes additional nonclinical studies to assess malignancy risk are not warranted. Exploration of this potential risk is most appropriate in humans, as opposed to animal models.

Relevance to human usage: No

Discussion:

In the review of ocrelizumab clinical data, the MAH noted there was an imbalance in malignancies in the MS program, with an increased malignancy rate observed in the ocrelizumab group compared with the control groups (IFN or placebo). The only cluster identified, which drove the imbalance in malignancy, was for female breast cancer. There was no clinical or histological pattern observed with the reported breast cancer cases. Moreover, there is not a clear biological rationale why an increased risk of breast cancer would occur over that of multiple other solid tumor types.

The incidence rate of malignancy (including breast cancer) in the ocrelizumab rheumatoid arthritis (RA) program was balanced between ocrelizumab and placebo treatment groups and within the epidemiological data in patients with RA.

The risk of anti-CD20 B cell depleting agents in impeding the immune system's tumor surveillance, including less common types of breast cancer, lacks a clear mechanistic relationship. Further, clinical evidence from approximately 4.8 million patient exposures with rituximab (to September 2015) provides robust evidence that there is no increased malignancy risk, including breast cancer, associated with anti-CD20 treatment.

The extensive consolidated assessment of literature, epidemiology, clinical and safety data in oncology and non-oncology indications for rituximab conducted in 2014 did not point to an increased risk as compared to the known risks of malignancies and second malignancies in these populations. More recently in 2016, a specific assessment of the risk of breast cancer observed in the Swedish and British RA registries confirmed the results of this exhaustive review and no increased risk was seen with rituximab for female breast cancer.

Malignancies will continue to be monitored via routine pharmacovigilance (PV) activities and new reports received from any source will be evaluated thoroughly. The malignancies monitoring plan has been updated to clarify the ongoing assessment process, including removal of the reference to the biannual DSR on malignancies, since assessment outcomes will continue to be included in periodic aggregate reports or other safety evaluation reports required by PV regulations and the MAH internal processes. 'Malignancies including breast cancer' are considered an important potential risk for ocrelizumab (see SVII.3.1).

SII.2 GENERAL SAFETY PHARMACOLOGY:

General safety pharmacology

In the monkey studies, no effects on cardiovascular (CV) (ECG, blood pressure, and heart rate), respiratory (respiratory rate), and neurological endpoints or body temperature were identified.

Relevance to human usage: Yes

Discussion:

ECGs and neurological examinations performed during clinical studies with ocrelizumab and adverse events (AEs) reported were not indicative of any CV or neurological safety issues. These findings support the use of ocrelizumab in the proposed patient populations.

Mechanisms for drug interactions

No dedicated nonclinical drug interaction studies have been performed with ocrelizumab to date. Due to its nature as an Ab, ocrelizumab is not expected to have a direct effect on the activity or expression of cytochrome P450 enzymes or drug transporters.

Relevance to human usage: No

Discussion:

No formal drug-drug interaction (DDI) clinical studies have been conducted with ocrelizumab, as no DDIs are expected via the cytochromes or other metabolizing enzymes or transporters for a monoclonal Ab like ocrelizumab. Ocrelizumab is not expected to interact with other drugs through protein binding, renal or biliary excretion, or competition for common drug transporter proteins. Since ocrelizumab is administered by IV infusion, drug-food interactions are not anticipated. The occurrence of drug-drug and drug-food interactions will be monitored via routine PV activities. In Study BN29739, the impact of ocrelizumab treatment on immunization response was assessed. The study results showed that the humoral responses to the vaccines against tetanus (tetanus toxoid [TT]), pneumonia (23-valent pneumococcal polysaccharide vaccine [23-PPV]), influenza (seasonal influenza vaccine), and the KLH were decreased in adult RMS patients treated with ocrelizumab compared with those patients not treated with ocrelizumab. Nevertheless, RMS patients who received ocrelizumab and were peripherally B-cell depleted were able to mount humoral responses, albeit decreased, to clinically relevant vaccines (TT, 23-PPV, influenza) and the neoantigen KLH.

PART II: MODULE SIII— CLINICAL TRIAL EXPOSURE

Patient exposure in the clinical development program in MS is discussed in this section. Exposure data for the IV formulation and exposure data for the SC formulation are presented separately. The additional experience available from the studies in non-MS indications (such as RA), which are no longer pursued, for the IV formulation is presented where it is considered relevant.

SIII.1 PATIENT EXPOSURE TO OCRELIZUMAB SC FORMULATION

For the SC formulation, exposure and safety data included in this RMP are derived from the pivotal OCARINA II study and the supportive OCARINA I study. The ocrelizumab SC

development program followed the principle of pharmacokinetic (PK) bridging, i.e., if the systemic drug exposure after SC injection is comparable to the exposure after IV infusion, this results in comparable efficacy and safety (Shpilberg et al. 2013, Hourcade et al. 2014, Xu et al. 2023). This is supported by the extensive efficacy, safety, and immunogenicity data generated for the approved IV route of administration in clinical trials and in the post-marketing setting.

Data pooling between the two studies was not appropriate due to notable differences in study design and study population. Therefore, data from the two studies are presented separately within the RMP.

OCARINA II data include all patients who received at least one dose of 920 mg ocrelizumab SC, including patients initially randomized to 600 mg ocrelizumab IV who were switched to 920 mg ocrelizumab SC at Week 24. OCARINA I data include all patients who received at least one dose of ocrelizumab 1200 mg SC or 920 mg ocrelizumab SC excluding patients who were only administered doses lower than 920 mg.

A total of 312 patients were exposed to 920 mg or 1200 mg ocrelizumab SC, of which 181 in OCARINA II and 131 in OCARINA I. Of these 312 patients, 181 patients from OCARINA II and 118 patients from OCARINA I were exposed to at least one dose of 920 mg ocrelizumab SC, and 125 patients from OCARINA I were exposed to at least one dose of 1200 mg ocrelizumab SC. Overall, 506 injections of 920 mg ocrelizumab SC have been administered across the two studies (244 in OCARINA II and 262 in OCARINA I), and 346 injections of 1200 mg ocrelizumab SC have been administered in OCARINA I.

Patient exposure to ocrelizumab SC is presented by cumulative dose Table 10 (OCARINA II) and Table 12 (OCARINA I), and by treatment duration in Table 11 (OCARINA II) and Table 13 (OCARINA I).

Table 10 Exposure to Ocrelizumab SC in Patient Years by Cumulative Dose in OCARINA II

Number of Patients Exposed to Ocrelizumab SC and Exposure in Patient Years by Cumulative Dose for RMS and PPMS Population during OCR SC All Exposure Period (OCR SC All Exposure Analysis), Safety-evaluable - SC Set
Protocol: CN42097 (Clinical Cut-off Date: 10MAR2023)

Dose of exposure	OCR SC All (N=181)	PY
At least 1 dose	118 (65.2%)	29.94
At least 2 doses	63 (34.8%)	40.52
At least 3 doses	0	NE
Total	181 (100%)	70.46

PY: Total patient years at risk. Calculated as the sum over all patients of the time intervals (in years) from the first SC treatment to the end date.
End date is defined as the earliest between
- Start of other Disease modifying therapies, or commercial ocrelizumab
- End of the Treatment Phase (start of SFU)
- Withdrawal from study/death
- Withdrawal from treatment (start of SFU)
- CCOD

Program: root/clinical_studies/RO4964913/CDT30233/CN42097/data_analysis/CSR/prod/program/t_exp_cdose_py.sas
Output: root/clinical_studies/RO4964913/CDT30233/CN42097/data_analysis/CSR/prod/output/t_exp_cdose_py_SESC.out
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Table 11 Exposure to Ocrelizumab SC in Patient Years by Treatment Duration (in Months) in OCARINA II

Number of Patients Exposed to Ocrelizumab SC and Exposure in Patient Years by Treatment Duration (in Months) for RMS and PPMS Population during OCR SC All Exposure Period (OCR SC All Exposure Analysis), Safety-evaluable - SC Set
Protocol: CN42097 (Clinical Cut-off Date: 10MAR2023)

Duration of exposure	OCR SC All (N=181)	PY
< 1 month	19 (10.5%)	0.83
1 to < 3 months	24 (13.3%)	4.36
3 to < 6 months	84 (46.4%)	29.03
>= 6 months	54 (29.8%)	36.23

PY: Total patient years at risk. Calculated as the sum over all patients of the time intervals (in years) from the first SC treatment to the end date.
Duration of exposure is the end date minus the date of first SC treatment administration plus one day.
End date is defined as the earliest between
- Start of other Disease modifying therapies, or commercial ocrelizumab
- End of the Treatment Phase (start of SFU)
- Withdrawal from study/death
- Withdrawal from treatment (start of SFU)
- CCOD

Program: root/clinical_studies/RO4964913/CDT30233/CN42097/data_analysis/CSR/prod/program/t_exp_dur_py.sas
Output: root/clinical_studies/RO4964913/CDT30233/CN42097/data_analysis/CSR/prod/output/t_exp_dur_py_SESC.out
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Table 12 Exposure to Ocrelizumab SC in Patient Years by Cumulative Dose in OCARINA I

Number of Patients Exposed to Ocrelizumab SC and Exposure in Patient Years by Cumulative Dose, Safety-Evaluable Set, 920 or 1200 mg SC cohort (All Patients who Received at Least One Dose of Ocrelizumab 920 mg SC or 1200 mg SC)
Protocol: CN41144 (Clinical Cut-off Date: 27JAN2023)

Dose of exposure	All Patients (N=131)	PY
1 dose	3 (2.3%)	2.80
2 doses	4 (3.1%)	4.72
3 doses	21 (16.0%)	28.06
4 doses	31 (23.7%)	51.34
5 doses	31 (23.7%)	64.90
6 doses	32 (24.4%)	80.48
7 doses	9 (6.9%)	26.34
Total	131 (100%)	258.63

PY: Patient Years.

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Output: root/clinical_studies/RO4964913/CDT30233/CN41144/data_analysis/CSR/prod/output/t_exp_cdose_py_SE_SC.out
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Table 13 Exposure to Ocrelizumab SC in Patient Years by Treatment Duration (in Months) in OCARINA I

Number of Patients Exposed to Ocrelizumab SC and Exposure in Patient Years by Treatment Duration (in Months), Safety-Evaluable Set, 920 or 1200 mg SC cohort (All Patients who Received at Least One Dose of Ocrelizumab 920 mg SC or 1200 mg SC)
Protocol: CN41144 (Clinical Cut-off Date: 27JAN2023)

Duration of exposure	All Patients (N=131)	PY
<= 6	0	NE
> 6 - <= 12	5 (3.8%)	4.61
> 12 - <= 18	22 (16.8%)	27.51
> 18 - <= 24	43 (32.8%)	75.85
> 24 - <= 30	34 (26.0%)	77.77
> 30 - <= 36	26 (19.8%)	69.89
> 36 - <= 42	1 (0.8%)	3.00

PY: Patient Years.

Program: root/clinical_studies/RO4964913/CDT30233/CN41144/data_analysis/CSR/prod/program/t_exp_dur_py.sas
Output: root/clinical_studies/RO4964913/CDT30233/CN41144/data_analysis/CSR/prod/output/t_exp_dur_py_SE_SC.out
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Patients' demographics

Exposure data by age group and gender is presented in Table 14 (OCARINA II) and Table 16 (OCARINA I), whereas exposure data by race is presented in Table 15 (OCARINA II) and Table 17 (OCARINA I).

Table 14 Exposure to Ocrelizumab SC - by Age Group and Gender in OCARINA II[4]

Number of Patients Exposed to Ocrelizumab SC by Age Group and Gender for RMS and PPMS Population during OCR SC All Exposure Period (OCR SC All Exposure Analysis), Safety-evaluable - SC Set
Protocol: CN42097 (Clinical Cut-off Date: 10MAR2023)

	OCR SC All (N=181)			PY		
Age group (years)	Male	Female	Total	Male	Female	Total
<18	1 (1.5%)	0	1 (0.6%)	0.82	NE	0.82
18 - 65	64 (98.5%)	116 (100%)	180 (99.4%)	23.84	45.80	69.64
>65	0	0	0	NE	NE	NE
Cumulative total	65 (100%)	116 (100%)	181 (100%)	24.66	45.80	70.46

PY: Total patient years at risk. Calculated as the sum over all patients of the time intervals (in years) from the first SC treatment to the end date.
End date is defined as the earliest between
- Start of other Disease modifying therapies, or commercial ocrelizumab
- End of the Treatment Phase (start of SFU)
- Withdrawal from study/death
- Withdrawal from treatment (start of SFU)
- CCOD

Program: root/clinical_studies/RO4964913/CDT30233/CN42097/data_analysis/CSR/prod/program/t_exp_agg_py.sas
Output: root/clinical_studies/RO4964913/CDT30233/CN42097/data_analysis/CSR/prod/output/t_exp_agg_py_SESC.out
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[4] Note: One patient was recorded in the <18 age group according to the demographic summary, which is lower than the inclusion criteria (18–65 years). This is because the birth month and day were imputed as the middle of the birth year as only the birth year was collected in the country of enrollment. It was subsequently confirmed, by a query to the site, that the patient was in the 18-65 age group at the time of enrollment.

Table 15 Exposure to Ocrelizumab SC – by Race in OCARINA II

Number of Patients Exposed to Ocrelizumab SC by Race for RMS and PPMS Population during OCR SC All Exposure Period (OCR SC All Exposure Analysis), Safety-evaluable - SC Set
Protocol: CN42097 (Clinical Cut-off Date: 10MAR2023)

Race	OCR SC All (N=181)	PY
n	181 (100%)	70.46
American Indian or Alaska Native	0	NE
Asian	0	NE
Black or African American	7 (3.9%)	3.58
Native Hawaiian or other Pacific Islander	0	NE
White	164 (90.6%)	64.12
Multiple	3 (1.7%)	0.77
Unknown	7 (3.9%)	1.98

PY: Total patient years at risk. Calculated as the sum over all patients of the time intervals (in years) from the first SC treatment to the end date.
End date is defined as the earliest between
- Start of other Disease modifying therapies, or commercial ocrelizumab
- End of the Treatment Phase (start of SFU)
- Withdrawal from study/death
- Withdrawal from treatment (start of SFU)
- CCOD

Program: root/clinical_studies/RO4964913/CDT30233/CN42097/data_analysis/CSR/prod/program/t_exp_race_py.sas
Output: root/clinical_studies/RO4964913/CDT30233/CN42097/data_analysis/CSR/prod/output/t_exp_race_py_SESC.out
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Table 16 Exposure to Ocrelizumab SC - by Age Group and Gender in OCARINA I

Number of Patients Exposed to Ocrelizumab SC by Age Group and Gender, Safety-Evaluable Set, 920 or 1200 mg SC cohort (All Patients who Received at Least One Dose of Ocrelizumab 920 mg SC or 1200 mg SC)
Protocol: CN41144 (Clinical Cut-off Date: 27JAN2023)

	All Patients (N=131)			PY		
Age group (years)	Male	Female	Total	Male	Female	Total
<18	0	0	0	NE	NE	NE
18 - 65	39 (100%)	92 (100%)	131 (100%)	82.52	176.11	258.63
>65	0	0	0	NE	NE	NE
Cumulative total	39 (100%)	92 (100%)	131 (100%)	82.52	176.11	258.63

PY: Patient Years.

Program: root/clinical_studies/RO4964913/CDT30233/CN41144/data_analysis/CSR/prod/program/t_exp_agg_py.sas
Output: root/clinical_studies/RO4964913/CDT30233/CN41144/data_analysis/CSR/prod/output/t_exp_agg_py_SE_SC.out
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Table 17 Exposure to Ocrelizumab SC – by Race in OCARINA I

Number of Patients Exposed to Ocrelizumab SC by Race, Safety-Evaluable Set, 920 or 1200 mg SC cohort (All Patients who Received at Least One Dose of Ocrelizumab 920 mg SC or 1200 mg SC)
Protocol: CN41144 (Clinical Cut-off Date: 27JAN2023)

Race	All Patients (N=131)	PY
n	131 (100%)	258.63
American Indian or Alaska Native	0	NE
Asian	0	NE
Black or African American	25 (19.1%)	49.88
Native Hawaiian or other Pacific Islander	0	NE
White	105 (80.2%)	205.77
Multiple	1 (0.8%)	2.98
Unknown	0	NE

PY: Patient Years

Program: root/clinical_studies/RO4964913/CDT30233/CN41144/data_analysis/CSR/prod/program/t_exp_race_py.sas
Output: root/clinical_studies/RO4964913/CDT30233/CN41144/data_analysis/CSR/prod/output/t_exp_race_py_SE_SC.out
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Exposure in Special Population

The clinical development program for ocrelizumab SC formulation to date has limited specific exposure data for special population groupings.

SIII.2 PATIENT EXPOSURE TO OCRELIZUMAB IV FORMULATION

In order to provide a complete assessment of the safety of ocrelizumab in RMS and PPMS, the Sponsor pooled and analyzed the safety data from the MS studies, described as Pools A, B, and C below and in Table 18. Safety data from the controlled treatment period in the single Phase III study in PPMS (WA25406) are summarized separately. In addition, the Sponsor separately pooled and analyzed safety data from the RA studies, described as Pools D and E.

The following provides the rationale and description for the following pools:

- Pool A: Phase III RMS Controlled Treatment
- Pool B: MS All Exposure (RMS, RRMS, and PPMS)
- Pool C: Phase III RMS All Exposure
- PPMS (WA25406): Phase III PPMS Controlled Treatment
- Pool D: Phase II and Phase III RA Controlled Treatment
- Pool E: RA All Exposure

The pooling strategy was determined based on (1) pathophysiology of the disease, (2) concomitant medications and concomitant diseases, (3) similarity between populations in terms of age and general condition, (4) ocrelizumab posology and trial design, and (5) size of available dataset which would allow appropriate signal detection.

Of the non-MS ocrelizumab programs, the RA development program was the largest and longest running, providing a substantial body of ocrelizumab safety data from approximately 3000 patients treated in 9 studies for up to 5 years.

RA data or other non-MS data (LN, systemic lupus erythematosus [SLE], and non-Hodgkin's lymphoma [NHL]) were not pooled with the MS data because the safety profiles and doses were different across indications due to differences in disease and concomitant medications. Furthermore, there are considerable differences among these non-MS populations in terms of risks associated with underlying disease, dosing regimen, concomitant medications (including use of chronic immunosuppressive medications concomitantly, for example in the treatment of RA), and differences in study design.

Table 18 Studies Contributing Data to the Analysis Population

Pool	Population	Studies	Purpose of Pool
A	Phase III RMS Controlled Treatment	WA21092 WA21093	Pool A includes all available safety data from the 96-week double-blind controlled treatment period (including SFU data up to Week 96 for those patients who withdrew early). The purpose of Pool A is to compare the safety of ocrelizumab 600 mg relative to interferon beta-1a 44 µg within the RMS indication.
B	MS All Exposure	WA21493 WA21092 WA21093 WA25046	Pool B consists of all available data from the controlled and OLE periods of the MS program (RMS, RRMS, and PPMS) up to the CCOD of each study. Data are summarized as pooled "all exposure" data (i.e., no control arm). Data from all patients who received any part of an ocrelizumab infusion at any dose are included in this pool. Data from patients who were randomized to placebo or interferon beta-1a are included after the switch to OL ocrelizumab treatment. The purpose of this MS All Exposure pool is to evaluate the long-term safety of ocrelizumab across MS, therefore, the safety summaries will only display results obtained with ocrelizumab treatment for this pool. Pool B was modified for the analysis of laboratory parameters and for analyses of safety post last dose and includes all available data from the controlled and OLE periods of the Phase III studies WA21092, WA21093, and WA25046 only. Data from Phase II Study WA21493 were excluded. The Phase II data were excluded because after completion of the controlled treatment period, enrolled patients had to complete a treatment free observation period of at least 24 weeks or until B cells had repleted whichever occurred later followed by another 24 weeks of observation before entering the OLE period. Moreover, the OLE period was implemented by protocol amendment after some patients had already left the study leading to substantial gaps in patients' SFU. As a result, there was a variable treatment-free period before patients restarted ocrelizumab.
C	Phase III RMS All Exposure	WA21092 WA21093	Pool C is a subset of Pool B and consists of available data from the controlled and OLE periods from Phase III RMS Studies WA21092 and WA21093 through the CCOD for each study. Data from all patients who received any part of an ocrelizumab infusion at any dose are included in this pool. Data from patients who were randomized to interferon bea-1a are also included after the switch to OL ocrelizumab treatment. The purpose of Pool C is to evaluate the long-term safety of ocrelizumab across RMS pivotal studies as well as taking into consideration patients switching from interferon beta-1a to ocrelizumab during the OLE period. The safety summaries will only display results obtained with ocrelizumab treatment for this pool (i.e., no control arm).

Table 18 Studies Contributing Data to the Analysis Population (cont.)

Pool	Population	Studies	Purpose of Pool
PPMS	Phase III PPMS Controlled Treatment	WA25046	Includes all available safety data following double-blind treatment with either ocrelizumab or placebo for at least 120 weeks and when the predefined number of CDP events had occurred. All available SFU data up to the CCOD of the study (24 July 2015) are included.
D	RA Controlled Treatment	WA18230, ACT2847g JA21963, WA20494 WA20495, WA20496 WA20497	Pool D consists of all available safety data from the 7 placebo-controlled double-blind controlled treatment periods of RA studies, including SFU data up to the same time point for those patients who withdraw early. The purpose of Pool D is to provide combined comparative safety data of ocrelizumab at different doses relative to a placebo control within the RA indication. The Phase II Study ACT4562g (U.S.-only study) was not included within Pool D as the study was not placebo-controlled but instead included an active control arm (infliximab). Furthermore, the study was terminated when only 28 of the 290 planned patients had been enrolled thus adding little data beyond the overall substantial body of data. Study JA22003 was an OLE of Phase II Study JA21963 so is also not included in Pool D.
E	RA All Exposure	WA18230, ACT2847g WA20494, WA20495 WA20496, WA20497 JA21963, JA22003* ACT4562g	Pool E consists of all available safety data from patients exposed to ocrelizumab in all 9 RA studies (double-blind controlled treatment, OLE, and SFU periods). The purpose of Pool E is to provide longer term safety data of ocrelizumab treatment, regardless of dose, within the RA indication. Data from patients initially randomized to receive placebo or infliximab during the double-blind treatment periods will only be included after patients have switched to OL ocrelizumab.

CCOD = clinical cut-off date; CDP = confirmed disability progression; LN = lupus nephritis; MS = multiple sclerosis; NHL = Non-Hodgkin's lymphoma; OL=open-label; OLE = open-label extension; PPMS = primary progressive multiple sclerosis; RA = rheumatoid arthritis; RMP = risk management plan; RMS = relapsing multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SFU = safety follow-up; SLE = systemic lupus erythematosus; U.S. = United States.

Notes: In the Phase II/III RA studies (Pool D), patients were exposed to six different dosages of ocrelizumab (20 mg, 100 mg, 400 mg, 1000 mg, 1500 mg, and 2000 mg). The Phase III studies, which investigated only the 400 mg and 1000 mg dose levels, comprised 94% (3114 of 3322 patients) of patients in Pool D. As a result, only these treatment groups are discussed in detail within the RMP where relevant.

Data from Phase III studies in SLE (WA20499), LN (WA20500), and NHL (BO18414) were not pooled with the RA data, and were also not pooled with the MS data because of the considerable differences in the general health of these patients, concomitant medications (e.g., treatment with pulse steroids and high-dose steroid tapering) and study design. Results from these studies are presented separately where relevant.

SIII.2.1 Patient Exposure to Ocrelizumab in All Indications

A total of 5986 patients have been exposed to ocrelizumab in clinical studies in any indication (2726 patients in MS and 3260 patients in non-MS indications as of 22 January 2015 for Study WA21493, 2 April 2015 for Study WA21092; 12 May 2015 for Study WA21093; and 24 July 2015 for Study WA25046. Data are provided separately for MS and non-MS indications below.

SIII.2.1.1 Patient Exposure to Ocrelizumab in Multiple Sclerosis

Exposure to ocrelizumab and comparators in clinical studies in MS by number of doses is presented in Table 19, by cumulative doses in Table 20, and by treatment duration in Table 21. The exposure from the MA30143 substudy is presented in an untabulated manner below.

Pool A: A total of 825 RMS patients were exposed to at least one or part of an ocrelizumab infusion in Pool A contributing to a total of 1447.9 patient-years (PY) of exposure. The mean number of doses received was 3.8 resulting in a mean total cumulative dose of 2240 mg per patient. The median number of doses was 4 resulting in a median total cumulative dose of 2400 mg per patient.

Pool C: A total of 1448 RMS patients were exposed to at least one or part of an ocrelizumab infusion in Pool C contributing to a total of 2305.1 PY of exposure. The mean number of doses received was 3.9 resulting in a mean total cumulative dose of 2344 mg per patient. The median number of doses received was 4.0 resulting in a median total cumulative dose of 2400 mg per patient. The majority of patients (51.6%; 747 of 1448) were followed for more than 24 months (2 years), with 3.2% of patients (46 of 1448) followed for more than 42 months (3.5 years).

Study WA25046: A total of 486 PPMS patients in the controlled treatment period of Study WA25046 were exposed to at least one or part of an ocrelizumab infusion contributing to a total of 1416.4 PY of exposure. The mean number of doses received was 6.6 resulting in a mean total cumulative dose of 3868 mg per patient. The median number of doses received was 7.0 resulting in a median total cumulative dose of 4200 mg per patient. The majority of patients (66.3%; 322 of 486) were followed for more than 36 months (3 years), with 1.9% of patients (9 of 486) followed for more than 54 months (4.5 years).

Pool B: A total of 2147 RMS and PPMS patients in Pool B were exposed to at least one or part of an ocrelizumab infusion contributing to a substantial safety database for MS of 4484.5 PY of observation (including safety follow-up [SFU]). The mean number of doses received was 4.7 resulting in a mean total cumulative dose of 2825 mg per patient. The median number of doses received was 5.0 resulting in a median total cumulative dose of 3000 mg per patient. A total of 44.7% of patients (960 of 2147; 2953.0 PY) received at least six doses, 26.7% of patients (574 of 2147; 1968.1 PY) received at least seven doses, and 12.7% of patients (272 of 2147; 1046.1 PY) received at least eight doses. The maximum number of doses in Pool B was 11 (< 0.1% of patients; 1 of 2147). The

majority of patients (53.3%; 1147 of 2147) were followed for more than 30 months (2.5 years), with 0.4% of patients (10 of 2147) followed for more than 72 months (6 years), and $<$0.1% of patients (1 of 2147) followed for more than 78 months (6.5 years).

MA30143 substudy: A total of 579 patients in the MA30143 substudy were exposed to at least one Randomized Infusion of ocrelizumab at the time of the primary analysis (27 September 2019). In the conventional infusion group, 235 patients (81.6%) received one randomized infusion and 53 patients (18.4%) received two randomized infusions. In the shorter infusion group, 234 patients (80.4%) received one randomized infusion, 56 patients (19.2%) received two randomized infusions and one patient (0.3%) received three randomized infusions. Overall, the median duration of infusions was 215 minutes (range 195-350) and 120 minutes (range 109-255) in the conventional and the shorter infusion group, respectively.

Table 19 Exposure to Ocrelizumab IV and Comparators in Clinical Studies in Multiple Sclerosis – By Number of Doses

Number of Doses	RMS						PPMS				RMS and PPMS	
	Pool A (Phase III RMS Controlled Treatment)				Pool C (Phase III RMS All Exposure)		WA25046 (Phase III PPMS Controlled Treatment)				Pool B (MS All Exposure)	
	IFN (N = 826)		OCR (N = 825)		OCR (N = 1448)		PBO (N = 239)		OCR (N = 486)		OCR (N = 2147)	
	n (%)	PY	n (%)	PY	n (%)	PY	n (%)	PY	n (%)	PY	n (%)	PY
1	825 (99.9)	408.9	825 (100.0)	392.5	1448 (100.0)	647.4	239 (100.0)	118.2	486 (100.0)	236.5	2147 (100.0)	985.4
2	751 (90.9)	357.1	779 (94.4)	365.0	1169 (80.7)	462.3	227 (95.0)	111.5	465 (95.7)	222.8	1826 (85.0)	784.2
3	702 (85.0)	328.6	759 (92.0)	353.8	923 (63.7)	378.1	216 (90.4)	108.3	452 (93.0)	221.1	1561 (72.7)	816.6
4	663 (80.3)	304.2	732 (88.7)	336.6	762 (52.6)	393.2	201 (84.1)	94.9	439 (90.3)	208.5	1340 (62.4)	796.6
5	—	—	—	—	698 (48.2)	286.0	188 (78.7)	93.0	428 (88.1)	202.5	1224 (57.0)	535.2
6	—	—	—	—	457 (31.6)	109.2	170 (71.1)	69.4	406 (83.5)	165.6	960 (44.7)	319.8
7	—	—	—	—	196 (13.5)	28.7	116 (48.5)	41.3	295 (60.7)	100.5	574 (26.7)	160.2
8	—	—	—	—	31 (2.1)	0.2	72 (30.1)	19.6	182 (37.4)	49.2	272 (12.7)	68.9
9	—	—	—	—	—	—	28 (11.7)	3.5	72 (14.8)	9.5	108 (5.0)	16.0
10	—	—	—	—	—	—	2 (0.8)	0.1	7 (1.4)	0.3	17 (0.8)	1.5
11	—	—	—	—	—	—	—	—	—	—	1 (< 0.1)	0
Total PY	—	1399.0	—	1447.9	—	2305.1	—	659.8	—	1416.4	—	4484.5

Table 19 Exposure to Ocrelizumab IV and Comparators in Clinical Studies in Multiple Sclerosis – By Number of Doses (cont.)

IFN = interferon beta-1a; IV = intravenous; MS = multiple sclerosis; OCR = ocrelizumab; PBO = placebo; PPMS = primary progressive MS; PY = Patient-Years. RMS = relapsing forms of MS.

Notes: Patients who were exposed to at least one or part of an ocrelizumab infusion are summarized under the ocrelizumab group. Percentages are based on the number of patients in the treatment group. The initial 600 mg dose was administered as two separate IV infusions; first as a 300 mg infusion, followed 2 weeks later by a second 300 mg infusion. Depending on the study, subsequent doses of ocrelizumab were administered as either two separate IV infusions; first as a 300 mg infusion, followed 2 weeks later by a second 300 mg infusion; or a single 600 mg IV infusion every 6 months. The exposure in patient-years is calculated from the first infusion date to the last known to be alive date. Date last known to be alive is the last available complete date of treatment, last contact date, medication, laboratory or vital sign assessment, adverse event, early withdrawal visit, Magnetic Resonance Imaging date, or date of death. Study clinical cutoff dates are 22 January 2015 for Study WA21493, 2 April 2015 for Study WA21092; 12 May 2015 for Study WA21093; and 24 July 2015 for Study WA25046). Pool A and Pool C include Studies WA21092 and WA21093. Pool B includes all MS studies.

Sources: t_ex_ocr_cyc_all_spa; t_ex_ocr_cyc_all_spc; ah_t_ex_ocr_100py_cyc_SE_046; t_ex_ocr_cyc_all_spb2

Table 20 Exposure to Ocrelizumab IV in Multiple Sclerosis All Exposure Population (Pool B) – By Cumulative Doses

Number of Patients Exposed to	Pool B (MS All Exposure) OCR (N = 2147)	
	n (%)	PY
At least 1 dose	2147 (100.0)	4484.5
At least 2 doses	1826 (85.0)	4347.1
At least 3 doses	1561 (72.7)	4164.4
At least 4 doses	1340 (62.4)	3831.8
At least 5 doses	1224 (57.0)	3547.2
At least 6 doses	960 (44.7)	2953.0
At least 7 doses	574 (26.7)	1968.1
At least 8 doses	272 (12.7)	1046.1

IV = intravenous; MS = multiple sclerosis; OCR = ocrelizumab; PY = Patient-Years.

Notes: Patients who were exposed to at least one or part of an ocrelizumab infusion are summarized under the ocrelizumab group. Percentages are based on the number of patients in the treatment group. The initial 600 mg dose was administered as two separate IV infusions; first as a 300 mg infusion, followed 2 weeks later by a second 300 mg infusion. Depending on the study, subsequent doses of ocrelizumab were administered as either two separate IV infusions; first as a 300 mg infusion, followed 2 weeks later by a second 300 mg infusion; or a single 600 mg IV infusion every 6 months. The exposure in patient-years is calculated from the first infusion date to the last known to be alive date. Date last known to be alive is the last available complete date of treatment, last contact date, medication, laboratory or vital sign assessment, adverse event, early withdrawal visit, Magnetic Resonance Imaging date, or date of death. Study clinical cutoff dates are 22 January 2015 for Study WA21493, 2 April 2015 for Study WA21092; 12 May 2015 for Study WA21093; and 24 July 2015 for Study WA25046). Pool B includes all MS studies.

Source: t_ex_ocr_cyc_cum_all_spb2

Table 21 Exposure to Ocrelizumab IV in Clinical Studies in Multiple Sclerosis – By Treatment Duration

Treatment Duration (Months)	Pool C (Phase III RMS All Exposure) (N = 1448)		WA25046 (Phase III PPMS All Exposure) (N = 486)		Pool B (MS All Exposure) (N = 2147)	
	Patients n (%)	PY	Patients n (%)	PY	Patients n (%)	PY
≤ 6	280 (19.3)	82.1	11 (2.3)	3.0	302 (14.1)	87.3
> 6- ≤ 12	226 (15.6)	136.2	5 (1.0)	3.4	233 (10.9)	140.7
> 12- ≤ 18	149 (10.3)	154.1	10 (2.1)	11.9	162 (7.5)	169.6
> 18- ≤ 24	46 (3.2)	68.2	14 (2.9)	21.6	65 (3.0)	97.8
> 24- ≤ 30	217 (15.0)	466.2	10 (2.1)	20.5	241 (11.2)	515.7
> 30- ≤ 36	305 (21.1)	733.2	114 (23.5)	289.9	446 (20.8)	1089.9
> 36- ≤ 42	179 (12.4)	514.2	131 (27.0)	383.1	334 (15.6)	967.7
> 42- ≤ 48	46 (3.2)	151.0	115 (23.7)	388.1	179 (8.3)	602.4
> 48- ≤ 54	—	—	67 (13.8)	253.6	80 (3.7)	304.5
> 54- ≤ 60	—	—	9 (1.9)	37.7	38 (1.8)	164.8
> 60- ≤ 66	—	—	—	—	26 (1.2)	124.3
> 66- ≤ 72	—	—	—	—	31 (1.4)	162.6
> 72- ≤ 78	—	—	—	—	9 (0.4)	51.1
> 78	—	—	—	—	1 (< 0.1)	6.0
Total PY	—	2305.1	—	1412.9	—	4484.5

MS = multiple sclerosis; PPMS = primary progressive MS; PY = Patient-Years; RMS = relapsing forms of MS.

Notes: Patients who were exposed to at least one or part of an ocrelizumab infusion are summarized under the ocrelizumab group. Percentages are based on the number of patients in the treatment group. Treatment duration and exposure in patient-years are calculated from the first infusion date to the last known to be alive date. Date last known to be alive is the last available complete date of treatment, last contact date, medication, laboratory or vital sign assessment, adverse event, early withdrawal visit, Magnetic Resonance Imaging date, or date of death. Study clinical cutoff dates are 22 January 2015 for Study WA21493, 2 April 2015 for Study WA21092; 12 May 2015 for Study WA21093; and 24 July 2015 for Study WA25046). Pool C includes Studies WA21092 and WA21093. Pool B includes all MS studies. There is a minor discrepancy for exposure in PY for Study WA25046 between the controlled treatment and all exposure periods because there are patients who were given an incorrect medication (i.e., randomized to placebo but ocrelizumab was dispensed in error or vice versa). For controlled treatment period analysis, exposure was counted for the entire controlled treatment period and summarized to ocrelizumab if any ocrelizumab was given. For all exposure population, re-baseline was taken from the first dose of ocrelizumab, which is the reason of minor discrepancy.

Sources: t_ex_dur_all_spc; t_ex_dur2_all_spb2; t_ex_dur_all_spb2

SIII.2.1.2 Patient Exposure to Ocrelizumab in Non-Multiple Sclerosis Indications

An additional 3260 patients have been exposed to ocrelizumab in other indications that are no longer being pursued. The largest clinical development program in a non-MS indication was conducted in RA.

SIII.2.1.2.1 Rheumatoid Arthritis

Exposure to ocrelizumab in clinical studies in RA by number of doses is presented in Table 22, by cumulative doses in Table 23, and by treatment duration in Table 24.

Pool D: The vast majority (94%; 3114 of 3322 patients) of safety data in Pool D originates from Phase III trials investigating the safety and efficacy of ocrelizumab at the 400 mg and 1000 mg dose levels. Ocrelizumab was also investigated at other doses in small numbers of patients (20 mg n=36; 17.1 PY; 100 mg n=79; 34.5 PY; 1500 mg n=45; 21.6 PY; and 2000 mg n=48; 22.8 PY), who received only one dose of ocrelizumab.

A total of 1186 RA patients in the 400 mg group and 947 RA patients in the 1000 mg group were exposed to at least one or part of an ocrelizumab infusion, contributing to a total of 1004.1 and 906.3 PY of exposure, respectively. The mean number of doses received was 1.8 and 2.1 resulting in a mean total cumulative dose of 722 mg and 2020 mg per patient in the 400 mg and 1000 mg group, respectively. The median number of doses received was 2.0 and 2.0 resulting in a median total cumulative dose of 800 mg and 2000 mg per patient in the 400 mg and 1000 mg group, respectively. Follow-up time in Pool D is not presented, because it was cut at the end of the double blinded period and would not be truly reflecting the SFU duration.

Pool E: A total of 2926 RA patients were exposed to at least one or part of an ocrelizumab infusion in Pool E contributing to a substantial safety database for RA of 7323.9 PY of observation (including SFU). The mean number of doses received was 3.2 resulting in a mean total cumulative dose of 2492 mg per patient. The median number of doses received was 3, resulting in a median total cumulative dose of 2000 mg per patient. A total of 41.8% of patients (1222 of 2926; corresponding to 3725.7 PY of exposure) received at least four doses, 18.8% of patients (551 of 2926; 1804.2 PY) received at least five doses, 7.7% of patients (225 of 2926; 774.7 PY) received at least six doses, 3.3% of patients (96 of 2926; 348.0 PY) received at least seven doses, and 1.3% of patients (38 of 2926; 140.3 PY) received at least eight doses. The maximum number of doses in Pool E was 10 (0.1% of patients; 4 of 2926; corresponding to 6.5 PY of exposure). The majority of patients (68.8%; 2012 of 2926) were followed for more than 24 months (2 years), with 1.8% of patients (54 of 2926) followed for more than 60 months (5 years).

SIII.2.1.2.2 Studies in Other Populations

A total of 264 LN patients (Study WA20500), 23 SLE patients (Study WA20499), and 47 NHL patients (Study BO18414) were exposed to at least one or part of an ocrelizumab infusion.

Table 22 Exposure to Ocrelizumab IV in Clinical Studies in Rheumatoid Arthritis – By Number of Doses

Number of Doses	Pool D (RA Controlled Treatment)						Pool E (RA All Exposure)	
	PBO + DMARD (N = 981)		OCR 400 mg + DMARD (N = 1186)		OCR 1000 mg + DMARD (N = 947)		OCR (N = 2926)	
	n (%)	PY	n (%)	PY	n (%)	PY	n (%)	PY
1	981 (100.0)	465.2	1186 (100.0)	546.5	947 (100.0)	443.6	2926 (100.0)	2112.3
2	700 (71.4)	334.8	757 (63.8)	360.9	763 (80.6)	367.9	2305 (78.8)	1685.5
3	153 (15.6)	72.5	157 (13.2)	63.9	158 (16.7)	63.4	1895 (64.8)	1561.4
4	74 (7.5)	30.3	79 (6.7)	32.9	81 (8.6)	31.5	1222 (41.8)	1148.0
5	—	—	—	—	—	—	551 (18.8)	500.3
6	—	—	—	—	—	—	225 (7.7)	178.6
7	—	—	—	—	—	—	96 (3.3)	86.1
8	—	—	—	—	—	—	38 (1.3)	27.7
9	—	—	—	—	—	—	16 (0.5)	17.5
10	—	—	—	—	—	—	4 (0.1)	6.5
Total PY	—	902.7	—	1004.1	—	906.3	—	7323.9

DMARD = disease-modifying anti-rheumatic drug; OCR = ocrelizumab; PBO = placebo; PY = Patient-Years; RA = rheumatoid arthritis.

Notes: Patients who received any part of an ocrelizumab infusion at any dose are summarized under the ocrelizumab group. Percentages are based on the number of patients in the treatment group. Percentages are based on the number of patients in each treatment group. Depending on a study, a dose of ocrelizumab was administered as one or two separate intravenous infusions. The exposure in patient-years is calculated from the first infusion date to the last known to be alive date. Only doses of 400 mg and 1000 mg are shown in this table for Pool D; however, ocrelizumab was also investigated at other doses (20 mg, 100 mg, 1500 mg, and 2000 mg) in small numbers of patients. The RA development program encompassed Studies ACT2847g, WA18230, ACT4562g, JA21963, JA22003, WA20494g, WA20495g, WA20496g, and WA20497g sponsored by Roche; and Studies JA21963 and JA22003 sponsored by Chugai Pharmaceutical Company, Limited, Japan.

Sources: t_ex_ocr_cyc_all_spd; t_ex_ocr_cyc_all_spe

Table 23 Exposure to Ocrelizumab IV in Rheumatoid Arthritis All Exposure Population (Pool E) – By Cumulative Doses

Number of Patients Exposed to	Pool E (RA All Exposure) OCR (N = 2926)	
	n (%)	PY
At least 1 dose	2926 (100.0)	7323.9
At least 2 doses	2305 (78.8)	6342.6
At least 3 doses	1895 (64.8)	5422.0
At least 4 doses	1222 (41.8)	3725.7
At least 5 doses	551 (18.8)	1804.2
At least 6 doses	225 (7.7)	774.7
At least 7 doses	96 (3.3)	348.0
At least 8 doses	38 (1.3)	140.3

OCR = ocrelizumab; PY = Patient-Years; RA = rheumatoid arthritis.

Notes: Patients who received any part of an ocrelizumab infusion at any dose are summarized under the ocrelizumab group. Percentages are based on the number of patients in the treatment group. Depending on the study, a dose of ocrelizumab was administered as one or two separate IV infusions. The exposure in patient-years is calculated from the first infusion date to the last known to be alive date. The RA development program encompassed Studies ACT2847g, WA18230, ACT4562g, JA21963, JA22003, WA20494g, WA20495g, WA20496g, and WA20497g sponsored by Roche; and Studies JA21963 and JA22003 sponsored by Chugai Pharmaceutical Company, Limited, Japan.

Source: t_ex_ocr_cyc_cum_all_spe.

Table 24 Exposure to Ocrelizumab IV in Rheumatoid Arthritis All Exposure Population (Pool E) – By Treatment Duration

Treatment Duration (Months)	Pool E (RA All Exposure) OCR (N=2926)	
	n (%)	PY
≤6	79 (2.7)	20.9
>6-≤12	109 (3.7)	88.8
>12-≤18	342 (11.7)	451.2
>18-≤24	384 (13.1)	685.0
>24-≤30	592 (20.2)	1328.2
>30-≤36	599 (20.5)	1630.8
>36-≤42	375 (12.8)	1216.4
>42-≤48	185 (6.3)	690.8
>48-≤54	137 (4.7)	579.9
>54-≤60	70 (2.4)	329.9
>60	54 (1.8)	301.9
Total PY	—	7323.9

OCR=ocrelizumab; PY=Patient-Years; RA=rheumatoid arthritis.

Notes: Patients who received any part of an ocrelizumab infusion at any dose are summarized under the ocrelizumab group. Percentages are based on the number of patients in the treatment group. Depending on the study, a dose of ocrelizumab was administered as one or two separate intravenous infusions. The exposure in patient-years is calculated from the first infusion date to the last known to be alive date. The RA development program encompassed Studies ACT2847g, WA18230, ACT4562g, JA21963, JA22003, WA20494g, WA20495g, WA20496g, and WA20497g sponsored by Roche; and Studies JA21963 and JA22003 sponsored by Chugai Pharmaceutical Company, Limited, Japan.

Sources : t_ex_dur_all_spd ; t_ex_dur_all_spe

Patient Demography

Patient demography data are provided separately for MS and non-MS indications below.

Patient Demography in Multiple Sclerosis

Exposure to ocrelizumab in clinical studies in MS by age group and sex is presented in Table 25 and by race in Table 26. The demographic characteristics for the MA30143 substudy are presented in an untabulated manner below.

Pool A: The majority of RMS patients exposed to ocrelizumab in Pool A were female (65.6%; 541 of 825 patients), and were predominantly white (89.9%; 742 of 825 patients). The median age of patients was 38 years and age range was 18-56 years.

Pool C: The demographic characteristics in Pool C were consistent with that observed for Pool A. The majority of RMS patients exposed to ocrelizumab in Pool C were female (65.5%; 949 of 1448 patients), and were predominantly white (90.9%; 1316 of 1448 patients). The median age of patients was 38 years and age range was 18-58 years.

Study WA25046: Approximately half of the PPMS patients exposed to ocrelizumab in the controlled treatment period of Study WA25046 were female (49.4%; 240 of 486 patients), and were predominantly white (93.4%; 454 of 486 patients). The median age of patients was 46 years and age range was 20-56 years.

Pool B: The majority of RMS and PPMS patients exposed to ocrelizumab in Pool B were female (61.9%; 1328 of 2147 patients), and were predominantly white (91.9%; 1974 of 2147 patients), consistent with the epidemiology of MS. The median age of patients was 40 years and the age range was 18-58 years.

MA30143 substudy: The demographic characteristics of the MA30143 substudy patients were well balanced across the conventional and shorter infusion groups. The majority of patients were female (62.2−64.4% across infusion groups) and were predominantly White (84.1−87.6% across infusion groups) with median ages of 33.0 and 33.2 years across the infusion groups (range 19-56 years).

Table 25 Exposure to Ocrelizumab IV in Clinical Studies in Multiple Sclerosis – By Age Group and Sex

Age Group (Years)	Pool A (Phase III RMS Controlled Treatment) OCR (N=825)				WA25046 (Phase III PPMS Controlled Treatment) OCR (N=486)				Pool B (MS All Exposure) OCR (N=2147)			
	Female (n=541)		Male (n=284)		Female (n=240)		Male (n=246)		Female (n=1328)		Male (n=819)	
	n (%)	PY	n (%)	PY	n (%)	PY	n (%)	PY	n (%)	PY	n (%)	PY
<18	0	—	0	—	0	—	0	—	0	—	0	—
≥18 to <65	541 (100.0)	946.6	284 (100.0)	501.3	240 (100.0)	709.9	246 (100.0)	706.5	1328 (100.0)	2687.4	819 (100.0)	1797.1
≥65	0	—	0	—	0	—	0	—	0	—	0	—
Total PY	—	946.6	—	501.3	—	709.9	—	706.5	—	2687.4	—	1797.1

MS=multiple sclerosis; OCR=ocrelizumab; PPMS=primary progressive MS; PY=Patient-Years; RMS=relapsing forms of MS.

Notes: Percentages are based on the number of patients in the treatment by gender subgroup. Exposure in patient-years is calculated from the first infusion date to the last known to be alive date prior to reporting. Date last known to be alive is the last available complete date of treatment, last contact date, medication, laboratory or vital sign assessment, adverse event, early withdrawal visit, Magnetic Resonance Imaging date, or date of death. Study clinical cutoff dates are 22 January 2015 for Study WA21493, 2 April 2015 for Study WA21092; 12 May 2015 for Study WA21093; and 24 July 2015 for Study WA25046). Pool A includes Studies WA21092 and WA21093. Pool B includes all MS studies.

Sources: t_ex_ocr_100py_age_sex_all_spa; ah_t_ex_ocr_100py_age_sex_SE_046; t_ex_ocr_100py_age_sex2_all_spb2

Table 26 Exposure to Ocrelizumab IV in Clinical Studies in Multiple Sclerosis – By Race

Race	Pool A (Phase III RMS Controlled Treatment) OCR (N=825)		WA25046 (Phase III PPMS Controlled Treatment) OCR (N=486)		Pool B (MS All Exposure) OCR (N=2147)	
	Patients n (%)	PY	Patients n (%)	PY	Patients n (%)	PY
American Indian or Alaska Native	3 (0.4)	5.5	5 (1.0)	13.2	11 (0.5)	25.4
Asian	2 (0.2)	3.7	0 (0.0)	—	5 (0.2)	9.9
Black or African American	39 (4.7)	66.3	9 (1.9)	20.7	74 (3.4)	149.6
Multiple	9 (1.1)	16.7	0 (0.0)	—	18 (0.8)	23.5
Native Hawaiian or Other Pacific Islander	1 (0.1)	1.8	0 (0.0)	—	1 (<0.1)	2.4
Other	29 (3.5)	51.8	17 (3.5)	50.9	63 (2.9)	124.1
White	742 (89.9)	1302.1	454 (93.4)	1325.1	1974 (91.9)	4146.6
Unknown	—	—	1 (0.2)	3.0	1 (<0.1)	3.0
Total PY	—	1447.9	—	1416.4	—	4484.5

MS=multiple sclerosis; OCR=ocrelizumab; PPMS=primary progressive MS; PY=Patient-Years; RMS=relapsing forms of MS.

Notes: Percentages are based on the number of patients in the treatment group. Exposure in patient-years is calculated from the first infusion date to the last known to be alive date. Date last known to be alive is the last available complete date of treatment, last contact date, medication, laboratory or vital sign assessment, adverse event, early withdrawal visit, Magnetic Resonance Imaging date, or date of death. Study clinical cutoff dates are 22 January 2015 for Study WA21493, 2 April 2015 for Study WA21092; 12 May 2015 for Study WA21093; and 24 July 2015 for Study WA25046). Pool A includes Studies WA21092 and WA21093. Pool B includes all MS studies.

Sources: t_ex_ocr_100py_race_all_spa; ah_t_ex_ocr_100py_race_SE_046; t_ex_ocr_100py_race2_all_spb2

SIII.2.2 Patient Demography in Non-Multiple Sclerosis Indications

SIII.2.2.1 Rheumatoid Arthritis

Exposure to ocrelizumab in clinical studies in RA (Pool D and Pool E) by age group and sex is presented in Table 27 and by race in Table 28.

Pool D: The majority of patients exposed to ocrelizumab 400 mg were female (79.5%; 943 of 1186 patients), and were predominantly White (69.6%; 826 of 1186 patients). The median age of patients was 53 years, and the age range was 18-90 years. The majority of patients were ≥18 to <65 years old (84.1%; 998 of 1186 patients).

The majority of patients exposed to ocrelizumab 1000 mg were female (81.9%; 776 of 947 patients), and were predominantly White (68.5%; 649 of 947 patients). The median age of patients was 52 years, and the age range was 19-83 years. The majority of patients were ≥18 to <65 years old (85.6%; 811 of 947 patients).

Pool E: The demographic characteristics of Pool E were consistent with that of Pool D. The majority of RA patients exposed to ocrelizumab were female (80.0%; 2341 of 2926 patients), and were predominantly White (69.5%; 2034 of 2926 patients). The median age of patients was 53 years, and the age range was 18-90 years. The majority of patients were ≥18 to <65 years old (84.0%; 2459 of 2926 patients).

SIII.2.2.2 Studies in Other Populations

The majority of LN patients (Study WA20500) exposed to ocrelizumab were female (81.2%; 233 of 264 patients), and were predominantly white (48.1%; 127 of 264 patients). Patient age range was 16-69 years. The majority of patients were ≥18 to <65 years old (97.7%; 258 of 264 patients). A small percentage of patients were aged between ≥16 and <18 years old (1.9%; 5 of 264 patients), in line with study inclusion criteria, with the remaining 1 patient (0.4%) in the age group ≥65 years old.

The majority of SLE patients (Study WA20499) exposed to ocrelizumab were female (91.3%; 21 of 23 patients), and were predominantly white (65.2%; 15 of 23 patients). All patients were ≥18 to <65 years old (age range 24-62 years).

The majority of NHL patients (Study BO18414) exposed to ocrelizumab were male (59.6%; 28 of 47 patients), and were predominantly white (97.9%; 46 of 47 patients). Patient age range was 38-83 years. The majority of patients (74.5%; 35 of 47 patients) were ≥18 to <65 years old.

Table 27 Exposure to Ocrelizumab IV in Clinical Studies in Rheumatoid Arthritis – By Age Group and Sex

Age Group (Years)	Pool D (RA Controlled Treatment)								Pool E (RA All Exposure)			
	OCR 400 mg (N = 1186)				OCR 1000 mg (N = 947)				OCR (N = 2926)			
	Female (n = 943)		Male (n = 243)		Female (n = 776)		Male (n = 171)		Female (n = 2341)		Male (n = 585)	
	n (%)	PY	n (%)	PY	n (%)	PY	n (%)	PY	n (%)	PY	n (%)	PY
< 18	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	—	0 (0.0)	—	—
≥ 18 to < 65	801 (84.9)	676.8	197 (81.1)	166.4	671 (86.5)	649.5	140 (81.9)	138.2	1989 (85.0)	4927.4	470 (80.3)	1204.4
≥ 65	142 (15.1)	122.4	46 (18.9)	38.5	105 (13.5)	93.0	31 (18.1)	25.6	352 (15.0)	864.5	115 (19.7)	327.6
Total PY	—	799.3	—	204.8	—	742.4	—	163.9	—	5791.9	—	1532.0

OCR = ocrelizumab; N/A = not applicable; PY = Patient-Years; RA = rheumatoid arthritis.

Notes: Percentages are based on the number of patients in the treatment by gender subgroup. Exposure in patient-years is calculated from the first infusion date to the last known to be alive date. The RA development program encompassed Studies ACT2847g, WA18230, ACT4562g, JA21963, JA22003, WA20494g, WA20495g, WA20496g, and WA20497g sponsored by Roche; and Studies JA21963 and JA22003 sponsored by Chugai Pharmaceutical Company, Limited, Japan. Sources: t_ex_ocr_100py_age_sex_all_spd; t_ex_ocr_100py_age_sex_all_spe

Table 28 Exposure to Ocrelizumab IV in Clinical Studies in Rheumatoid Arthritis – By Race

Race	Pool D (RA Controlled Treatment)				Pool E (RA All Exposure)	
	OCR 400 mg (N = 1186)		OCR 1000 mg (N = 947)		OCR 400 mg (N = 1186)	
	Patients n (%)	PY	Patients n (%)	PY	Patients n (%)	PY
American Indian or Alaska Native	32 (2.7)	32.2	32 (3.4)	37.8	86 (2.9)	206.7
Asian	156 (13.2)	119.5	135 (14.3)	115.2	385 (13.2)	1031.1
Black or African American	74 (6.2)	58.2	48 (5.1)	50.3	178 (6.1)	400.6
Native Hawaiian or Other Pacific Islander	4 (0.3)	4.3	3 (0.3)	2.0	10 (0.3)	23.6
Other	94 (7.9)	85.1	80 (8.4)	81.1	233 (8.0)	533.9
White	826 (69.6)	704.8	649 (68.5)	619.9	2034 (69.5)	5128.1
Total PY	—	1004.1	—	906.3	—	7323.9

OCR = ocrelizumab; PY = Patient-Years; RA = rheumatoid arthritis.

Notes: Percentages are based on the number of patients in the treatment group. Exposure in patient-years is calculated from the first infusion date to the last known to be alive date. The RA development program encompassed studies ACT2847g, WA18230, ACT4562g, JA21963, JA22003, WA20494g, WA20495g, WA20496g, and WA20497g sponsored by Roche; and Studies JA21963 and JA22003 sponsored by Chugai Pharmaceutical Company, Limited, Japan.

Sources: t_ex_ocr_100py_race_all_spd; t_ex_ocr_100py_race_all_spe.

SIII.2.3 Exposure in Special Patient Populations

SIII.2.3.1 Pregnant/Lactating Women

A search of the Roche Global Safety Database using the pregnancy flag and the Standardized MedDRA Query (SMQ) Pregnancy and neonatal topics identified a total of 46 patients administered at least one ocrelizumab infusion who became pregnant during clinical study participation (15 MS patients [1.1% of female patients in Pool B], 21 RA patients [0.9% of female patients in Pool E], and 10 LN patients [4.3% of female LN patients]). These cases were included in DSR 1067126 (Review of pregnancy cases reported in clinical trials with ocrelizumab).

A search of the Roche Global Safety Database using the SMQ Pregnancy and neonatal topics, which includes the sub-SMQ Lactation related topics (including neonatal exposure through breast milk) did not identify any lactation cases reported in patients who participated in clinical studies with ocrelizumab.

SIII.2.3.2 Patients with Renal Impairment

Patients with renal impairment in MS studies were classified based on their calculated creatinine clearance (CRCL) at baseline, and pharmacokinetics was compared across categories within the population PK analysis: mild renal impairment: CRCL 50-90 mL/min; moderate renal impairment: CRCL 30-50 mL/min; and severe renal impairment: CRCL less than 30 mL/min. A total of 133 patients in the RMS program (14.1% of patients for which PK data are available) and 111 patients in the PPMS program (23% of patients for which PK data are available) had mild renal impairment with a CRCL of 50-90 mL/min. In addition, 1 patient in the RMS program (0.1% of patients for which PK data are available) had moderate renal impairment, i.e., between 30 and 50 mL/min.

SIII.2.3.3 Patients with Hepatic Impairment

Patients with elevated liver enzymes were included in the MS studies, and PK data was compared within the population PK analysis. At baseline, a total of 95 patients in the RMS program (10.1% of patients for which PK data are available) and 78 patients in the PPMS program (16.1% of patients for which PK data are available) had elevated ALT (above 35 U/L[5]), 25 patients in the RMS program (2.7% of patients for which PK data are available) and 22 patients in the PPMS program (4.6% of patients for which PK data are available) had elevated AST (above 35 U/L[5]), and 33 patients in the RMS program (3.5% of patients for which PK data are available) and 16 patients in the PPMS program (3.4% of patients for which PK data are available) had had elevated bilirubin (above 20.5 µmol/L[5]). The National Cancer Institute Organ Dysfunction Working Group classification was applied (i.e., total bilirubin and AST value at baseline) to categorize patients into normal, mild (78 patients), moderate (5 patients), and severe (2 patients) hepatic impairment.

[5] Normal ranges as per Merck Manual.

SIII.2.3.4 Patients with Cardiac Impairment

Patients with cardiac impairment in MS studies were identified using the SMQ Cardiac failure (narrow scope). Only 1 patient (<0.1%) with cardiac failure was exposed to ocrelizumab with a total of 3.7 PY of exposure. The reported term of this patient's medical history term was "cardiac failure 0 degree", and the patient did not experience any serious adverse event (SAE) during the study.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAM

Table 29 Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies	Exclusion of patients with a history of severe allergic or anaphylactic reactions to other humanized monoclonal antibodies was intended to mitigate the risk of hypersensitivity reaction in patients. Ocrelizumab contains a small number of murine-derived amino acid sequences from the original mouse antibody in the complementarity determining regions, it does not contain complete murine proteins.	No	Hypersensitivity to ocrelizumab or to any of the excipients is a potential risk (not important) and is included as a contraindication in the EU SmPC.
History of currently active primary or secondary immunodeficiency; previous treatment with immunosuppressants including B cell targeting therapies, total body irradiation or bone marrow transplantation; any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the study; low CD4 and/or total neutrophil counts (<300/µL, and $<1.5\times10^3$/µL, respectively), low serum IgG or IgM levels (18% and 8% below LLN, respectively)	To mitigate the risk of infections in patients with depleted B cells (immunosuppressed).	No	Patients with a severely immunocompromised state is contraindicated as per the EU SmPC.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
History of malignancy, including solid tumors and hematological malignancies, except basal cell carcinoma, in situ squamous cell carcinoma of the skin, and in situ carcinoma of the cervix that have been previously completely excised with documented, clear margins	Precautionary measure implemented in most non-oncology investigational studies, to ensure general safety of patients to be treated with the study drug in the clinical trial setting. Malignancies are serious risks impacting the patient's overall health. The pre-existing malignancy or its treatment may preclude patient from participating and stay in the study and could confound safety or efficacy assessment.	No	Malignancies are considered as an important potential risk. See Part II: Module SVII of the document for details. Known active malignancies is included as a contraindication in the EU SmPC.
Contraindications for, or intolerance to, oral or IV corticosteroids	Patients were given methylprednisolone 100 mg IV before each infusion of ocrelizumab to reduce the risk of IRRs.	No	The instruction in Section 4.2 (Posology and method of administration) of EU SmPC will sufficiently mitigate the risk.
CHF NYHA III or IV functional severity	Patients with severe CHF were excluded from study participation because IRRs in this patient population may theoretically lead to serious CV consequences, including fatal outcome.	No	The warning and precaution related to the management of IRRs in Section 4.4 (Special warnings and precautions for use) of EU SmPC will sufficiently mitigate the risk.
Currently active infection, active bacterial, viral, fungal, mycobacterial, or other infection excluding fungal infection of nail beds; infection requiring hospitalization or treatment with IV antibiotics within 4 weeks prior to baseline visit or oral antibiotics within 2 weeks prior to baseline visit; history or	To reduce the risk of severe infection and to mitigate the risk of exacerbation of infections, including hepatitis B infection reactivation, in patients with depleted B cells	No	Infections is an important identified risk. The MAH is of the opinion that the warnings and precautions on infections in Section 4.4 (Special warnings and precautions for use) of EU SmPC will be sufficient. "Active infection" is a contraindication in Section 4.3 of the EU SmPC.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
known presence of recurrent or chronic infection including hepatitis B			
Receipt of a live vaccine within 6 weeks prior to baseline visit; live vaccines were not permitted throughout the duration of the trials	To mitigate the risk of infections in patients with depleted B cells. Following immunotherapy patients have limited ability to mount an immune response to a live vaccination and are at increased risk of infection from the vaccination.	No	The warnings and precautions in Section 4.4 (Special warnings and precautions for use) and 4.6 (Fertility, pregnancy and lactation) of EU SmPC will sufficiently mitigate the risk.
Significant uncontrolled disease, such as CV, pulmonary, renal, hepatic, endocrine or gastrointestinal or any other significant disease that may preclude patient from participating in the study	Because these diseases may preclude patient from participating and staying in the study and would confound safety or efficacy assessments.	No	This was a standard clinical trial exclusion criterion to help minimize the risk of patients dropping out of the studies due to other health issues. Ocrelizumab was not found to have a clinically meaningful direct impact on these organs. ADRs listed in Section 4.8 (Undesirable effects) of the SmPC, namely infections and IRRs, may theoretically worsen a pre-existing organ dysfunction, e.g., respiratory tract infections may impair pulmonary function. Potential indirect effects secondary to ADRs are covered in the EU SmPC.

ADRs = adverse drug reaction; CD4 = cluster of differentiation 4; CHF= congestive heart failure; CV = cardiovascular; EU = European Union; IgG = Immunoglobulin G; IgM = Immunoglobulin M; IRRs = infusion related reactions; IV= intravenous; LLN= lower limit of normal; MAH = marketing authorization holder; NYHA = New York Heart Association; SmPC = Summary of Product Characteristics.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDERREPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

Table 30 Exposure of Special Populations Included or not in Clinical Trial Development Program[a]

Type of Special Population	Exposure
Pregnant women	46 patients[b]
Breastfeeding women[c]	Not included in the clinical development program.
Patients with relevant comorbidities	
Patients with moderate and severe hepatic impairment hepatic impairment	Not included in the clinical development program.
Patients with moderate and severe renal impairment	Not included in the clinical development program.
Patients with cardiovascular impairment	1 patient
Population with relevant different ethnic origin	Refer to Table 26 and Table 28 above.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Other	
Children:	Not included in the clinical development program.
Elderly aged ≥ 65 years:	Refer to Table 25 above.

[a] Summary based on the data in Part II Module SIII.2.3 Exposure in Special Patient Populations.

[b] Drug Safety Report 1067126.

[c] 29 breastfeeding women received ocrelizumab in an investigator initiated study on ocrelizumab transfer into breast milk (Anderson A, et al. 2023).

Use in Pregnancy and Lactation

MS is a chronic, inflammatory, demyelinating, neurodegenerative disease of the CNS that primarily affects women of childbearing potential, with onset typically between 20 and 40 years of age (Walton et al. 2021). As pregnant and lactating women have been historically excluded from pre-authorization clinical trials (FDA 2018; EMA 2019), labelling for most DMTs, including ocrelizumab label, precludes use during pregnancy, and generally discourages use while breastfeeding (LaHue et al. 2019).

Similarly, pregnant patients were excluded from ocrelizumab clinical trials. Pregnant patients and embryos and fetuses exposed to ocrelizumab in utero, as well as neonates and infants exposed to ocrelizumab via the breastfeeding mother are vulnerable patient populations. The safety concerns are expected to be different from the ones in the general patient population with MS, because both pregnant women and newborn babies have altered immune system due to physiological mechanisms, which may lead to increased risk of infections or altered immune response to vaccinations. These patient populations are in need of further benefit-risk characterization but a limited amount of data from the use of ocrelizumab in pregnant women is currently available.

In an embryo-fetal developmental study in cynomolgus monkeys, there was no evidence of maternal toxicity, teratogenicity, or embryotoxicity following ocrelizumab treatment at 75/100 mg/kg (loading dose/study dose). However, as IgG molecules are known to cross the placental barrier, and ocrelizumab causes depletion of B-cells in the fetuses of treated cynomolgus monkeys, ocrelizumab may cause B-cell depletion in the human fetus. For these reasons, ocrelizumab should not be administered to pregnant women (See section SVII 3.1.3.1).

B-cell levels in human neonates following maternal exposure to ocrelizumab have not been studied in clinical trials. A Phase IV open-label placental study (MN42988) will evaluate B cell levels in infants potentially exposed to ocrelizumab during pregnancy. A Phase IV open-label lactation study (MN42989), evaluating B cell levels in infants, over the first year of life, of lactating women receiving ocrelizumab post-partum was recently initiated too (Bove et al. 2020).

Two post-marketing commitment studies are currently ongoing (Study WA40063 and Study BA39732). BA39732 is a multi-source surveillance study (secondary data collection) assessing pregnancy and infant outcomes of pregnant women and babies exposed to ocrelizumab in utero treatment for MS (at least during their first year of life). WA40063 is the ocrelizumab Pregnancy registry study (primary data collection), aiming to assess and characterize the frequency of maternal, fetal, and infant outcomes among women with MS exposed to ocrelizumab during the 6 months before last menstrual period or at any time during pregnancy.

In post-marketing surveillance and registry data recorded up to 12 July 2023, 3253 MS pregnancies were reported in women treated with ocrelizumab (Hellwig K, et al. ECTRIMS 2023 [P061]), an increase of approximately 62% over the previous year (n=2020; Oreja Guevara et al. 2022). Characterizing the safety of ocrelizumab in pregnancy and breastfeeding is therefore becoming increasingly relevant. Updated data do not suggest an increased risk of adverse pregnancy outcomes with ocrelizumab use with or without *in utero* exposure and remain in line with previous reports and expected epidemiological ranges (Lopez-Leon S, et al. 2020; CDC 2008). Refer to Section SI.1 Multiple sclerosis for additional epidemiological data comparing general and MS population.

Cumulative post-marketing surveillance and registry data suggest that ocrelizumab use in pregnancy is not associated with an increased risk of adverse pregnancy outcomes (Dobson et al. 2021; Kümpfel et al. 2021; Ciplea et al. 2020), compared to the expected rates in MS cohorts (Lopez-Leon et al. 2020) or in the general population (CDC 2008; EUROCAT 2021). Data from 29 lactating women receiving ocrelizumab at 0.1-36 weeks postpartum indicate minimal transfer and very low ocrelizumab concentrations in breastmilk. Ocrelizumab concentration in breastmilk was analyzed up to 90 days after the first post-partum infusion of ocrelizumab. The median average concentration of ocrelizumab in breast milk was low at 0.08 (0.05-0.4) μg/mL. Based on the average concentration, the relative infant dose (RID) was 0.1 (0.07-0.7) %. Ocrelizumab was virtually undetectable in breast milk by 90 days post-infusion. [Anderson A, et al. 2023]. Follow-up of 30 breastfed infants describe normal growth and development up to 1 year.

Absence of an ocrelizumab association with an increased risk of adverse pregnancy and infant outcomes is further supported by the most recent annual aggregate analysis of 2,089 pregnancy cases with no safety concern identified for any risk of ocrelizumab associated with spontaneous/missed abortion, fetal death, stillbirth, induced abortion, premature birth, structural malformations, functional deficits, or growth abnormalities. The review of the cases did not reveal any safety signal or safety concern regarding ocrelizumab use in pregnancy and lactation that would warrant any changes to the label or the RMP.

While clinical outcomes reported for pregnancies are reassuring to date, there is a need for more granular information on biological effects that could influence rarer, or longer-term, risks (e.g., prolonged B cell depletion/repletion, susceptibility to certain type of infections, impaired immunization response). There is limited data on whether placental transfer of ocrelizumab occurs in women who are administered ocrelizumab within 6 months before conception or during the first trimester of pregnancy. Furthermore, if *in utero* exposure occurs, it is unknown whether it affects the development of B cells in the fetus, the neonatal adaptive immune response, or the response to vaccines in the first year. In addition, it is unclear whether the infant's ability to fight infections, or growth and development, are impacted by potential *in utero* exposure. Similar questions remain for infants who are breastfed while their mothers receive ocrelizumab.

Annual interim reports will continue to be produced by the MAH on data collected from the EU Post Authorization Safety Study (PASS) BA39732, with the complete analysis of data expected to be performed and submitted in line with the PV milestones in Part III.3.

Additionally, a U.S. post-marketing commitment registry (WA40063) is conducted by the MAH, for which interim reports are also annually produced, and two clinical investigational studies (MN42988 and MN42989) have recently been initiated. For all studies, complete analysis of data will be performed upon study completion and submitted to the regulatory authorities in line with the applicable regulatory requirements.

The pregnancy and lactation events will continue to be monitored as part of routine signal detection activities and data on maternal, fetal and infant outcomes will continue to be collected via the above-mentioned EU and U.S. post-marketing commitments (Study BA39732 and Study WA40063), as well as the two interventional clinical studies (MN42988 and MN42989).

PART II: MODULE SV— POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

As ocrelizumab SC is not yet approved in any country, the cumulative post-authorization exposure provided below is for the IV formulation only and it is based on the data presented in the latest Periodic Benefit Risk Evaluation Report (PBRER) (data lock point [DLP] 27 March 2023).

SV.1.1 Method used to calculate exposure

The market exposure data presented below for the European Economic Area (EEA) and Rest of World (RoW) are estimated based on total number of ocrelizumab vials sold.

In the United States, patient estimates are based on a combination of new patient start forms, submitted to access solutions (AS), and primary market research on AS utilization rate.

Calculation of the estimated total patient exposure numbers and total patient-years (PYs) in each region is based on the following assumptions:

European Economic Area and Rest of World Methodology Assumptions:

The volume sold in EEA and RoW is sourced from Roche supply chain and financial systems (Controlling Profitability Analysis). The sales data are provided on a monthly basis; therefore, the exposure is available from the international birth date (IBD) (28 March 2017) to the nearest DLP, i.e. 31 March 2023.

Each ocrelizumab dose comprises two vials of 300 mg each (600 mg per dose).

Persistence Assumption

Persistence rates indicate the proportion of patients remaining on therapy after each dose based on a proxy for ocrelizumab. The current assumption from the average of available data from the countries estimates 97% of patients remaining on therapy from first to second dose ex-U.S. In the U.S., current assumption estimates 81% of patients remaining on therapy from 1st to 2nd dose.

Overall exposure is calculated in PYs on ocrelizumab. Market exposure data provides estimates on new patients starting treatment each month in the period. For each new patient, the exposure is estimated starting in the middle of the first month since date of actual exposure within the month is not accurately available (month average estimate)

until end of the period (March 2023), up to a maximum of 12 months. For each continuing patient, the exposure is estimated starting in the middle of the first month since date of actual exposure within the month is not accurately available (month average estimate) until end of the period (March 2023), up to a maximum of 12 months. This methodology is aligned with Global Safety and Reporting Team recommendation.

The demographic breakdown is based on U.S. Symphony Health (SHA) claims data and U.S. primary market research:

- The breakdown by MS type (RMS and PPMS) is based on primary market research using chart audits (based on >1,500 individual patient charts submitted by neurologists over the time period of April 2017 – February 2020);
- The breakdown by sex is based on U.S. SHA claims data as of 28 February 2020;
- The breakdown by age is based on U.S. SHA claims data as of 28 February 2020.

In the demographic data, the breakdown by MS type simply reflects PPMS and RMS.

Limitations to the EU and RoW Methodology

The market exposure data for ocrelizumab is based on volume sold. It is acknowledged that some of this volume may be retained in stock by third parties. For RoW and EEA ex-EU5, a constant steady state of 5% stocks was assumed. For the EU5 countries (Germany, France, Italy, Spain, and United Kingdom) country specific stock assumptions were assumed, since the level of stocks may vary significantly by supplier and country and therefore, may have an impact on overall patient exposures.

The retreatment interval based on U.S. claims data represents patients who are receiving continuing doses. Current assumptions may need to be revised once RWD for EEA/RoW exists to assess average time between doses.

For demographic breakdowns, U.S. assumptions have been applied to ex-U.S. exposures. This is due to lack of reliable data from countries in this region. Following the European Medicines Agency (EMA) approval, these breakdowns may be restated with results from primary market research in major ex-U.S. markets.

Regarding overall estimated exposures in PYs, the approach previously described provides a realistic estimate at the early phase of commercialization of the product. For future estimations, this approach may require revision.

During the course of coronavirus disease 2019 (COVID-19) pandemic and lockdowns, there was a lack of reliable data to assess the pandemic impact especially for ex-U.S. COVID-19 may also have long-term impact on certain parameters such as retreatment

intervals, and assumptions may need to be revised once relevant data becomes available.

United States Methodology Assumptions:

In the U.S., patient estimates are based on a combination of new patient start forms, submitted to AS, and primary market research on AS utilization rate.

Consistent with the EEA and RoW data, the exposures reported represent data through 31 March 2023.

New patient start forms are submitted to AS and reported on a daily basis. These forms account for approximately 70% of all ocrelizumab new patient starts and have been adjusted to account for AS utilization rate among practices in the U.S.

An incremental 12% bulk-up is applied to account for non-commercial vials (Genentech Access to Care Foundation). This assumption is based on the volume of vials that are sent through the third-party distributor responsible for free good distribution.

The demographic breakdown is based on claims data and primary market research:

- The breakdown by MS type (RMS and PPMS) is based on primary market research using chart audits (based on $>$1,500 individual patient charts submitted by neurologists over the time period of April 2017 – February 2020);
- The breakdown by sex is based on U.S. SHA claims data as of 28 February 2020;
- The breakdown by age is based on U.S. SHA claims data as of 28 February 2020.

Overall exposure is calculated in PYs on ocrelizumab. Market exposure data provides estimates on new patients starting treatment each month in the period. For each new patient, the exposure is estimated starting in the middle of the first month since date of actual exposure within the month is not accurately available (month average estimate) until end of the period (March 2023), up to a maximum of 12 months. For each continuing patient, the exposure is estimated starting in the middle of the first month since date of actual exposure within the month is not accurately available (month average estimate) until end of the period (March 2023), up to a maximum of 12 months. This methodology is aligned with Global Safety and Reporting Team recommendation.

Limitations to the U.S. Methodology

As noted previously, claims data does not represent 100% capture rate of treated patients, and final patients are adjusted to account for this capture rate.

Additionally, direct insight is not available into the number of non-commercial patients treated (Genentech Access to Care Foundation) as a result, these assumptions are based on volume data provided by the distributor of free goods.

Regarding overall estimated exposures in PYs, the approach previously described provides a realistic estimate at the early phase of commercialization of the product. For future estimations, this approach may require revision.

In the demographic data, the breakdown by MS type simply reflects PPMS and RMS.

During the course of COVID-19 pandemic and lockdowns, there was a lack of reliable data to assess the pandemic impact especially for ex-U.S. COVID-19 may also have long-term impact on certain parameters such as retreatment intervals, and assumptions may need to be revised once relevant data becomes available.

SV.1.2 Exposure

Since the IBD (28 March 2017) until 31 March 2023, an estimated cumulative total of 302,199 patients have received ocrelizumab IV from marketing experience. This corresponds to an estimated 721,879 PYs of exposure since IBD (see Annex 7).

PART II: MODULE SVI— ADDITIONAL E.U. REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Misuse for Illegal Purposes

Radio-labelled ocrelizumab biodistribution studies in animals concluded that ocrelizumab does not significantly penetrate the brain, which is consistent with the expected distribution pattern of Ab therapeutics (Yu and Watts 2013). Ex vivo tissue binding studies revealed that ocrelizumab specific binding is consistent with the known pattern of B cell distribution in humans and nonhuman primates. Furthermore, numerous nonclinical studies with ocrelizumab demonstrated that there were no observed behavioral changes suggestive of abuse potential. A thorough review of the clinical datasets in MS and RA concluded there was no indication of abuse-related AEs associated with ocrelizumab. As a class, there is no known association between anti-CD20 monoclonal antibodies (mAbs) and drug abuse potential.

Based on the mechanistic, bio-distribution, tissue binding, nonclinical and clinical data, consistent with approved anti-CD20 B-cell depleting Ab therapies, the MAH believes ocrelizumab does not have CNS activity associated with abuse potential and therefore does not require additional abuse-related studies.

PART II: MODULE SVII— IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

No new safety concerns have been identified since this module of the RMP was last submitted.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1 Information on important identified risks

SVII.3.1.1.1 INFUSION-RELATED REACTIONS (observed with the IV formulation) and INJECTION REACTIONS (observed with the SC formulation)

Potential mechanisms:

The most likely mechanism for an IRR or a systemic IR is a type 2 hypersensitivity reaction where cytokines are released from an effector cell following ligation of low affinity Fc receptors by ocrelizumab-opsonized B cells. This mechanism is plausible in initial exposure cases.

Type 3 hypersensitivity reactions mediated by the formation of mAbs and anti-drug antibodies (ADAs) complexes may also occur in patients who have previously been exposed to ocrelizumab and have evidence of ADAs, though such reactions would be likely to occur more than 24 hours after the infusion and/or injection. Based on currently available data, there is no evidence for such complex formation in patients exposed to ocrelizumab.

A type 1 hypersensitivity reaction could also occur (acute allergic reaction to drug). Severe IRRs may be clinically indistinguishable from type 1 (IgE-mediated) acute hypersensitivity reactions. A type 1 hypersensitivity reaction may present during any infusion and/or injection, although typically would not present during the first infusion.

The clinical symptoms are similar regardless of the mechanism.

Local IRs are irritative local reactions seen commonly at the injection sites of subcutaneously administered biologics, caused by the proinflammatory actions of the substances. Inappropriate injection techniques, injection close to blood vessels, the chemical and physical properties of the injected drug and a reaction to the vehicle component are several causes described in the literature resulting in irritative reactions (Thomaidou and Ramot 2019).

Evidence source(s) and strength of evidence:

Clinical studies of ocrelizumab: WA21092, WA21093, WA25046, WA21493, BN29739, MN30035, MA30005, WA20494, WA20495, WA20496, WA20497, WA18230,

ACT2847g, GA00931, JA21963, JA22003, WA20499, WA20500, BO18414, MA30143 substudy, CN41144, and CN42097.

Characterization of the risk:

Data from the ocrelizumab SC investigational program is provided in the subheadings below (frequency observed on ocrelizumab, seriousness/outcomes, severity and nature of risk, and impact on quality of life) in an untabulated manner. Data presented in Table 31 - Table 34 is only for ocrelizumab IV.

In OCARINA II, all IR events reported in patients who received at least one dose of 920 mg ocrelizumab SC, including patients initially randomized to 600 mg ocrelizumab IV who were switched to 920 mg ocrelizumab SC at Week 24 are presented.

In OCARINA I, all IR events reported in patients who received at least one dose of 1200 mg ocrelizumab SC are presented separately from patients who received at least one dose of ocrelizumab 920 mg SC. Only 6 of 118 patients who received ocrelizumab 920 mg SC did not previously receive ocrelizumab 1200 mg SC; thus, the majority of patients in the 920 mg SC analysis set are also in the 1200 mg SC analysis set.

Background Incidence/Prevalence:
Infusion-related reactions are known to occur with the IV administration of mAbs. Rates of IRRs are specific to the mAb and a comparison of incidence rates reported for different mAbs would not be meaningful.

The local IRs incidence rates occurring with the administration of mAb vary, depending on the biologic agent, from 0.5% to 40% (Thomaidou and Ramot 2019).

A total of 6.5% of RMS patients administered ocrelizumab placebo in Pool A and 12.1% of PPMS patients administered ocrelizumab placebo in Study WA25046 experienced an IRR at first infusion.

A total of 9.7% of RMS patients administered ocrelizumab placebo in Pool A and 25.5% of PPMS patients administered ocrelizumab placebo experienced an IRR at any infusion. With the PPMS dosing regimen, the total number of IRRs experienced in the PPMS study was higher compared with the RMS studies.

Frequency observed on ocrelizumab:
In the ocrelizumab SC investigational program, IRs were the most frequently reported events.

In OCARINA II, of the 181 patients, 86 (47.6%) patients experienced a total of 106 events of IR, 81 (44.8%) patients experienced 99 events of local IRs and 22 (12.2%) patients experienced 23 events of systemic IRs.

In OCARINA I, of the 125 patients who received at least one dose of ocrelizumab 1200 mg SC, 94 (75.2%) patients experienced 201 events of IRs, 90 (72%) patients experienced 167 events of local IRs, and 25 (20%) patients experienced 34 events of systemic IRs. Of the 118 patients who received at least one dose of ocrelizumab 920 mg SC, 68 (57.6%) experienced 112 events of IRs, 62 (52.5%) experienced 112 events of local IRs, and 13 (11%) experienced 14 events of systemic IRs.

The percentage of patients in clinical studies with ocrelizumab IV in MS (RMS population: Pool A and Pool C; PPMS population: Study WA25046, MA30143 substudy population), with at least one IRR overall and by infusion (to Dose 6 inclusive) is summarized in Table 31.

Infusion-related reactions were the most frequently reported AE in MS patients treated with ocrelizumab IV.

In the controlled treatment period of the RMS Phase III studies (Pool A), IRRs were reported by 34.3% of patients in the ocrelizumab group and 9.7% of patients in the interferon group. The percentage (30.3%) of patients who experienced an IRR remained stable with additional exposure to ocrelizumab during open label treatment (this includes patients initially randomized to the interferon group who transitioned to ocrelizumab during the open label extension (OLE) (Pool C).

In the PPMS Phase III study, IRRs were reported by 39.9% of patients in the ocrelizumab group and 25.5% of patients in the placebo group.

At the time of the primary analysis of the MA30143 substudy, 23.1% of patients in the conventional infusion group and 24.6% of patients in the shorter infusion group experienced an IRR at their first Randomized Dose of ocrelizumab (Dose 2, 3, 4, 5, or 6). The incidence of IRRs between the two groups was comparable (Table 32).

For RMS patients, who received two separate infusions of ocrelizumab for the first dose and single infusions for each subsequent dose, the incidence was highest for the first infusion of the first dose (Dose 1, Infusion 1; 27.5% of patients) and decreased thereafter (4.7% to 13.7% of patients). For PPMS patients, who received two separate infusions for all doses, the incidence was also highest for the first infusion of the first dose (Dose 1, Infusion 1; 27.4% of patients) and decreased thereafter (1.1% to 11.6% of patients). The typical pattern of highest incidence of IRRs with the first infusion followed by subsequent decreases with each subsequent dose was similar with both regimens. In both RMS and PPMS studies, IRRs were noted with each ocrelizumab infusion, albeit with decreasing frequency with subsequent dosing.

IRRs profiles per infusion were similar in both RMS and PPMS studies, but because of overall more infusions with the 2 × 300 mg regimen in the PPMS study, the total number of IRRs in PPMS patients was higher.

Analyses of Pool A and C data showed no notable differences in the incidence of IRRs in patients with a history of CV disease.

Overall, the data support the hypothesis that dividing the dose of ocrelizumab beyond the first dose does not provide a meaningful benefit for the patient. In fact, the infusions being double, the incidence of IRRs increases.

Table 31 Percentage of Patients with at Least One Infusion Related Reaction Overall and by Infusion to Dose 6 Inclusive

Infusion[a]	Pool A (Phase III RMS Controlled Treatment)		Pool C (Phase III RMS All Exposure)	WA25046 (Phase III PPMS Controlled Treatment)	
	IFN (N=826)	OCR (N=825)	OCR (N=1448)	PBO (N=239)	OCR (N=486)
Overall	80/826 (9.7%)	283/825 (34.3%)	439/1448 (30.3%)	61/239 (25.5%)	194/486 (39.9%)
Dose 1 Infusion 1	54/825 (6.6%)	227/825 (27.5%)	347/1448 (24.0%)	29/239 (12.1%)	133/486 (27.4%)
Dose 1 Infusion 2	21/815 (2.6%)	38/806 (4.7%)	62/1420 (4.4%)	14/235 (6.0%)	35/477 (7.3%)
Dose 2 Infusion 1	15/751 (2.0%)	107/779 (13.7%)	127/1169 (10.9%)	18/227 (7.9%)	54/465 (11.6%)
Dose 2 Infusion 2	—	—	—	10/219 (4.6%)	23/449 (5.1%)
Dose 3 Infusion 1	8/702 (1.1%)	73/759 (9.6%)	78/923 (8.5%)	13/216 (6.0%)	52/452 (11.5%)
Dose 3 Infusion 2	—	—	—	10/210 (4.8%)	22/437 (5.0%)
Dose 4 Infusion 1	12/663 (1.8%)	57/732 (7.8%)	60/762 (7.9%)	11/201 (5.5%)	29/439 (6.6%)
Dose 4 Infusion 2	—	—	0/4 (0.0%)	8/197 (4.1%)	13/430 (3.0%)
Dose 5 Infusion 1	—	—	64/698 (9.2%)	9/188 (4.8%)	30/428 (7.0%)
Dose 5 Infusion 2	—	—	16/694 (2.3%)	3/178 (1.7%)	19/414 (4.6%)
Dose 6 Infusion 1	—	—	26/457 (5.7%)	5/170 (2.9%)	27/406 (6.7%)
Dose 6 Infusion 2	—	—	—	2/159 (1.3%)	15/382 (3.9%)

IFN=interferon beta-1a (Rebif); MS=multiple sclerosis; OCR=ocrelizumab; PBO=placebo; PPMS=primary progressive MS; RMS=relapsing forms of MS.

Notes: Percentages for Overall are based on the total number of patients (N). Percentages for each Infusion are based on the number of patients who received that Infusion. IRRs and related symptoms experienced by a patient during the infusion, 1 hour post infusion while the patient was still in the clinic, or within 24 hours after the completion of the infusion while the patient was not in the clinic were reported on a dedicated IRR eCRF form. In order not to miss any IRR, investigators were asked to confirm whether any event reported on the AE eCRF forms with onset date on the day of an infusion or on the next day after the completion of an infusion did not represent IRRs. Furthermore, investigators were asked to confirm that vital sign changes observed during and post-infusion did not represent an IRR. The clinical cutoff dates are 2 April 2015 for Study WA21092; 12 May 2015 for Study WA21093; and 24 July 2015 for Study WA25046.

Table 31 Percentage of Patients with at Least One Infusion Related Reaction Overall and by Infusion to Dose 6 Inclusive (cont.)

[a] Dosing in the controlled treatment period of Study WA21092 and WA21093: Dose 1: 2 x ocrelizumab or placebo 300 mg IV infusions separated by 2 weeks, subsequently 1 x ocrelizumab or placebo 600 mg infusion every 24 weeks. Dosing in the OLE phase: Dose 1: 2 x ocrelizumab 300 mg IV infusions separated by 2 weeks, subsequently 1 x ocrelizumab 600 mg infusion every 24 weeks. Dosing in the controlled treatment period of Study WA25046: 2 x ocrelizumab or placebo 300 mg IV infusions separated by 2 weeks. Sources: t_ae_irr_inf_all_spa; t_ae_irr_inf_all_spc; t_ae_irr_int_inf_CNTR_SE_046

Table 32 Percentage of Patients with at Least One Infusion Related Reaction Overall and by Infusion to Dose 6 Inclusive (MA30143 substudy)

Infusion	MA30143 (Shorter Infusion Substudy)	
	Conventional (N=291)	Shorter (N=289)
Overall	67 (23.1%)	71 (24.6%)
Dose 2	54 (27.3%)	54 (27.1%)
Dose 3	3 (12.5%)	2 (9.1%)
Dose 4[1]	8 (14.5%)	15 (27.8%)
Dose 5	2 (15.4%)	0
Dose 6	-[2]	0

All doses belong to the first Randomized Dose.
All patients received only conventional infusion up to the first Randomized Dose, and those randomized to shorter infusion received the shorter infusion for the first time at the first Randomized Dose.
[1]There was an apparent imbalance in the proportion of IRRs between the infusion groups, for patients who received their first randomized dose as Dose 3 or 4. This can be attributed to the smaller number of patients who received their first Randomized Doses at Doses 3 and 4, and the much smaller number of patients with previous IRR who received Dose 3 (1 patient from the conventional infusion group and 2 patients from the shorter infusion group) and Dose 4 (3 patients from the conventional infusion group and 9 patients from the shorter infusion group)
[2]No patients in the conventional group had the first Randomized Dose at Dose 6.
Source: t_ae_irr_sum_IT_IA_27SEP2019_30143

Seriousness/Outcomes:
In the clinical studies with ocrelizumab SC, all IRs reported were non-serious.

In OCARINA II, 85 of the 86 patients who experienced an IR (including local and systemic IRs) recovered except for one patient (with a local IR) who was recovering at the time of database cut off.

In OCARINA I, all patients who received at least one dose of 1200 mg or 920 mg and experienced an IR (including local and systemic IRs) recovered, except for one patient, who received at least one dose of ocrelizumab 920 mg SC and experienced a systemic IR, who was recovering at the time of the database cut off.

The outcomes of IRRs reported in clinical studies with ocrelizumab in MS (RMS population: Pool A and Pool C; PPMS population: Study WA25046) overall and by infusion (to Dose 6 inclusive) are summarized in Table 33. The outcomes of IRRs reported in the MA30143 substudy are presented in an untabulated manner below.

Very few IRRs reported by patients treated with ocrelizumab were considered serious. One RMS patient in Pool A (0.1%; 1 of 825 patients) reported a serious IRR (Grade 4 in intensity) during the first infusion (Infusion 1, Dose 1) with the symptom of

bronchospasm. This patient was withdrawn per protocol. There were no additional serious IRRs reported in the OLE phases of the RMS Phase III studies. Five PPMS patients in Study WA25046 (1.0%; 5 of 486 patients) had IRRs that were reported as serious; none was Grade 4 in intensity.

No patients in MA30143 substudy reported any serious IRRs in the conventional and shorter infusion groups in association with the first Randomized Dose and across all Randomized doses.

From the total number of patients who experienced any IRR at the time of the primary analysis of the MA30143 substudy, 66/67 [98.5%] patients in the conventional infusion group and 70/71 [98.6%] patients in the shorter infusion group reported the outcome as Recovered/Resolved. One patient (1/67 [1.5%]) in the conventional infusion group reported the outcome as Recovering/Resolving (IRR symptom: headache) and one patient (1/71 [1.4%]) in the shorter infusion group reported the outcome as Not Recovered/Not Resolved (IRR symptom: back pain).

No IRRs that led to a fatal outcome were reported in MS studies.

Table 33 Infusion Related Reactions by Outcome Overall and by Infusion to Dose 6 Inclusive

Infusion[a]	Outcome	Pool A		Pool C	WA25046	
		IFN (N = 826)	OCR (N = 825)	OCR (N = 1448)	PBO (N = 239)	OCR (N = 486)
Overall	Fatal	0	0	0	0	0
	Not recovered/Not resolved	0	0	3/793 (0.4%)	3/145 (2.1%)	0
	Recovered/Resolved	108/110 (98.2%)	503/505 (99.6%)	788/793 (99.4%)	142/145 (97.9%)	485/485 (100.0%)
	Recovered/Resolved with sequelae	2/110 (1.8%)	2/505 (0.4%)	2/793 (0.3%)	0	0
	Recovering/Resolving	0	0	0	0	0
	Unknown	0	0	0	0	0
Dose 1 Infusion 1	Fatal	0	0	0	0	0
	Not recovered/Not resolved	0	0	1/349 (0.3%)	1/29 (3.4%)	0
	Recovered/Resolved	53/54 (98.1%)	228/228 (100.0%)	348/349 (99.7%)	28/29 (96.6%)	133/133 (100.0%)
	Recovered/Resolved with sequelae	1/54 (1.9%)	0	0	0	0
	Recovering/Resolving	0	0	0	0	0
	Unknown	0	0	0	0	0
Dose 1 Infusion 2	Fatal	0	0	0	0	0
	Not recovered/Not resolved	0	0	0	0	0
	Recovered/Resolved	20/21 (95.2%)	38/38 (100.0%)	63/63 (100.0%)	14/14 (100.0%)	35/35 (100.0%)
	Recovered/Resolved with sequelae	1/21 (4.8%)	0	0	0	0
	Recovering/Resolving	0	0	0	0	0
	Unknown	0	0	0	0	0
Dose 2 Infusion 1	Fatal	0	0	0	0	0
	Not recovered/Not resolved	0	0	0	0	0
	Recovered/Resolved	15/15 (100.0%)	107/108 (99.1%)	127/128 (99.2%)	18/18 (100.0%)	54/54 (100.0%)
	Recovered/Resolved with sequelae	0	1/108 (0.9%)	1/128 (0.8%)	0	0
	Recovering/Resolving	0	0	0	0	0
	Unknown	0	0	0	0	0

Infusion[a]	Outcome	Pool A		Pool C	WA25046	
		IFN (N = 826)	OCR (N = 825)	OCR (N = 1448)	PBO (N = 239)	OCR (N = 486)
Dose 2 Infusion 2	Fatal				0	0
	Not recovered/Not resolved				0	0
	Recovered/Resolved				10/10(100.0%)	23/23 (100.0%)
	Recovered/Resolved with sequelae	-	-	-	0	0
	Recovering/Resolving				0	0
	Unknown				0	0
Dose 3 Infusion 1	Fatal	0	0	0	0	0
	Not recovered/Not resolved	0	0	0	1/13 (7.7%)	0
	Recovered/Resolved	8/8 (100.0%)	73/73 (100.0%)	78/78 (100.0%)	12/13 (92.3%)	52/52 (100.0%)
	Recovered/Resolved with sequelae	0	0	0	0	0
	Recovering/Resolving	0	0	0	0	0
	Unknown	0	0	0	0	0
Dose 3 Infusion 2	Fatal				0	0
	Not recovered/Not resolved				0	0
	Recovered/Resolved				10/10(100.0%)	22/22 (100.0%)
	Recovered/Resolved with sequelae	-	-	-	0	0
	Recovering/Resolving				0	0
	Unknown				0	0
Dose 4 Infusion 1	Fatal	0	0	0	0	0
	Not recovered/Not resolved	0	0	1/61 (1.6%)	0	0
	Recovered/Resolved	12/12 (100.0%)	57/58 (98.3%)	59/61 (96.7%)	11/11 (100.0%)	29/29 (100.0%)
	Recovered/Resolved with sequelae	0	1/58 (1.7%)	1/61 (1.6%)	0	0
	Recovering/Resolving	0	0	0	0	0
	Unknown	0	0	0	0	0

Infusion[a]	Outcome	Pool A		Pool C	WA25046	
		IFN (N = 826)	OCR (N = 825)	OCR (N = 1448)	PBO (N = 239)	OCR (N = 486)
Dose 4 Infusion 2	Fatal Not recovered/Not resolved Recovered/Resolved Recovered/Resolved with sequelae Recovering/Resolving Unknown	-	-	-	0 0 1/8 (12.5%) 7/8 (87.5%) 0 0	0 0 13/13 (100.0%) 0 0 0
Dose 5 Infusion 1	Fatal Not recovered/Not resolved Recovered/Resolved Recovered/Resolved with sequelae Recovering/Resolving Unknown	-	-	0 0 64/64 (100.0%) 0 0 0	0 0 9/9 (100.0%) 0 0 0	0 0 30/30 (100.0%) 0 0 0
Dose 5 Infusion 2	Fatal Not recovered/Not resolved Recovered/Resolved Recovered/Resolved with sequelae Recovering/Resolving Unknown	-	-	0 0 16/16 (100.0%) 0 0 0	0 0 3/3 (100.0%) 0 0 0	0 0 19/19 (100.0%) 0 0 0
Dose 6 Infusion 1	Fatal Not recovered/Not resolved Recovered/Resolved Recovered/Resolved with sequelae Recovering/Resolving Unknown	-	-	0 1/26 (3.8%) 25/26 (96.2%) 0 0 0	0 0 5/5 (100.0%) 0 0 0	0 0 28/28 (100.0%) 0 0 0

Infusion[a]	Outcome	Pool A		Pool C	WA25046	
		IFN (N = 826)	OCR (N = 825)	OCR (N = 1448)	PBO (N = 239)	OCR (N = 486)
Dose 6 Infusion 2	Fatal	-	-	-	0	0
	Not recovered/Not resolved				0	0
	Recovered/Resolved				2/2 (100.0%)	15/15 (100.0%)
	Recovered/Resolved with sequelae				0	0
	Recovering/Resolving				0	0
	Unknown				0	0

IFN = interferon beta-1a (Rebif); OCR = ocrelizumab; PBO = placebo.

Notes: Percentages for overall total patients with at least one IRR based on number of patients that received any infusion. For total patients with at least one IRR, percentages are based on the number of patients that received the infusion. For total number of IRRs, multiple occurrences of the same AE in an individual are counted separately. For frequency counts by outcome, multiple occurrences of the same AE in an individual are counted separately. Percentages for each outcome are based on the total number of IRR at each infusion. IRRs and related symptoms experienced by a patient during the infusion, 1 hour post infusion while the patient was still in the clinic, or within 24 hours after the completion of the infusion while the patient was not in the clinic were reported on a dedicated IRR eCRF form. In order not to miss any IRR, investigators were asked to confirm whether any event reported on the AE eCRF forms with onset date on the day of an infusion or on the next day after the completion of an infusion did not represent IRRs. Furthermore, investigators were asked to confirm that vital sign changes observed during and post-infusion did not represent an IRR. The clinical cutoff dates are 2 April 2015 for Study WA21092; 12 May 2015 for Study WA21093; and 24 July 2015 for Study WA25046.

[a] Dosing in the controlled treatment period of Study WA21092 and WA21093: Dose 1: 2 x ocrelizumab or placebo 300 mg IV infusions separated by 2 weeks, subsequently 1 x ocrelizumab or placebo 600 mg infusion every 24 weeks. Dosing in the OLE phase: Dose 1: 2 x ocrelizumab 300 mg IV infusions separated by 2 weeks, subsequently 1 x ocrelizumab 600 mg infusion every 24 weeks. Dosing in the controlled treatment period of Study WA25046: 2 x ocrelizumab or placebo 300 mg IV infusions separated by 2 weeks.

Sources: ah_t_ae_irr_out_ev_all_spa; ah_t_ae_irr_out_ev_all_spc; ah_t_ae_irr_ocm_ev_CNTR_SE_046.

Severity and Nature of Risk:
In the clinical studies with ocrelizumab SC, the majority of IRs (including local and systemic IRs) were Grade 1 or 2.

In the OCARINA II study, of the 86 patients who experienced at least one IR with any injection, 66 (76.7%) had IRs of Grade 1 highest severity and 20 (23.3%) had IRs of Grade 2 highest severity. Of the 81 patients who experienced at least one local IR with any injection, 63 (77.8%) had local IRs of Grade 1 highest severity and 18 (22.2%) had local IRs of Grade 2 highest severity. Of the 22 patients who experienced at least one systemic IR with any injection, 10 (45.5%) had local IRs of Grade 1 highest severity and 12 (54.5%) had local IRs of Grade 2 highest severity.

In the OCARINA I study, all events (both local and systemic IRs) were assessed as Grade 1 or 2 except for one systemic IR assessed as Grade 3 (the patient was previously treated with ocrelizumab IV prior to study; after the first injection of ocrelizumab 1200 mg SC, the patient experienced symptoms of dyspnea and wheezing, 4 hours following completion of ocrelizumab 1200 mg SC).

The IRs observed with ocrelizumab SC were local symptoms such as erythema, pain, swelling and pruritus or systemic symptoms such as headache and nausea.

The intensity of IRRs in patients in clinical studies with ocrelizumab IV in MS (RMS population: Pool A and Pool C; PPMS population: Study WA25046) overall and by infusion (to Dose 6 inclusive) is summarized in Table 34. The intensity of IRRs in patients in the MA30143 substudy are presented in an untabulated manner below.

The majority of IRRs (>90% of patients who experienced an IRR) in both RMS and PPMS studies were of Grade 1 or 2 in intensity and the intensity of IRRs decreased with subsequent dosing. Grade 3 IRRs were reported in 2.4% (20 of 825 patients) of RMS patients receiving ocrelizumab and 1.2% (6 of 486 patients) of PPMS patients receiving ocrelizumab. Most were associated with the first infusion (Dose 1, Infusion 1); however, Grade 3 IRRs were also observed with doses beyond the first infusion. One serious Grade 4 IRR was reported in a RMS patient during the first infusion (Dose 1, Infusion 1). No PPMS patients had Grade 4 IRRs. There were no Grade 5 IRRs. The severity and symptoms of IRRs were similar between RMS and PPMS, for Dose 1 (where two 300 mg infusions were administered 2 weeks apart in both RMS and PPMS studies), and from Dose 2 onward (where this regimen continued in PPMS compared with a regimen of single 600 mg infusions in RMS).

At the time of the primary analysis of the MA30143 substudy, the majority of the IRRs, at all Randomized Doses, were mild (Grade 1) or moderate (Grade 2) and two IRRs were severe (Grade 3) in intensity, with one severe IRR in each group. Of the two Grade 3 IRRs, one IRR was experienced by a patient in the shorter infusion group at the first Randomized Dose, and the other IRR was experienced by a patient in the conventional

infusion group at the second Randomized Dose. There were no Grade 4 or serious IRRs observed in this substudy.

Overall, across all studies, the most common symptoms associated with IRRs were laryngeal inflammation, arthralgia, back pain, fatigue, pruritus, rash, throat irritation, flushing, pyrexia, and headache. The symptoms reported at the first infusion of ocrelizumab were representative of symptoms experienced with subsequent infusions and were consistent with the overall IRR profile. The symptoms associated with the Grade 3 IRRs in the ocrelizumab group were generally consistent with those of the overall IRR symptom profile. In RMS patients, the symptoms included rash, pruritus, oropharyngeal pain, urticaria, angioedema, throat irritation, bronchospasm, arthralgia, back pain, and hypotension. In PPMS patients, the symptoms included oropharyngeal pain, agitation, fatigue, flushing, throat irritation, rash, pyrexia, tachycardia, angioedema, and laryngeal edema. ECG QT prolongation was reported in one patient. Some patients reported more than one symptom associated with their IRR.

Also, the term ‘anaphylaxis’ was introduced to Section 4.4 of EU Summary of Product Characteristics (SmPC) among the possible symptoms of infusion-related reactions.

Justification for the inclusion:

To assist FDA evaluation of anaphylaxis as a potential signal following post-marketing cases captured in the FDA Adverse Event Reporting System database (FDA request for information dated 28 January 2019), the MAH performed a comprehensive analysis of cases retrieved by Anaphylactic reaction MedDRA narrow SMQ. Data search was conducted both in clinical trials (cutoff date ranging from 1 June 2018 to 24 August 2018) and in the post-marketing setting (cutoff date of 22 January 2019). The analysis of the safety data from nine clinical studies in 4501 patients exposed to ocrelizumab for a total of 12558.9 PYs, revealed one SAE (anaphylactic reaction secondary to Solumedrol) and two non-serious AEs (circulatory collapse and anaphylactic reaction). The non-serious circulatory collapse AE was not considered as anaphylaxis based on lack of temporal relationship (2 months after the last infusion of ocrelizumab) and it was reported as related to the patient’s incurred illness. The non-serious anaphylactic reaction was reported as related to peanut allergy in a patient with documented allergy to peanuts. The reaction lacked temporal relationship (occurred 5 months after the last infusion of ocrelizumab) and treatment with ocrelizumab was maintained after this event. The reported rate for SAE of anaphylaxis is 0.008 events per 100 PYs while the reported rate for all AEs (serious and non-serious) is 0.024 events per 100 PYs. The search of the global Roche Safety Database identified 49 additional serious cases from the post-marketing setting, where discrepancies between the reported terms and symptoms experienced are not unexpected. Among the total 50 serious cases, 24 were suggestive of IRRs, 7 had sufficient evidence for alternative explanations other than ocrelizumab and the remaining 19 contained insufficient information to allow for a medical assessment. Of the 24 cases suggestive of IRRs, the majority (22/24) were assessed as

IRRs because they occurred at the first infusion. Therapy with ocrelizumab could be maintained in the majority of the cases (reporting symptoms suggestive of IRR) where information on treatment continuation was reported. Based on the review of individual case details, it was concluded that none of the evaluated cases represent anaphylaxis due to ocrelizumab, but rather represent IRRs with ocrelizumab, or anaphylaxis due to another identifiable cause, or contained insufficient information to make a medical assessment. The symptoms of IRRs were consistent with those reported in the clinical development program with ocrelizumab. Hence, anaphylaxis does not constitute a new safety signal and the MAH proposed to add anaphylaxis to the symptoms of IRRs in the reference safety information.

Most IRRs in ocrelizumab-treated patients were reported during the infusion, rather than after the infusion while the patient was in the clinic, or 24 hours post infusion when the patient was no longer in the clinic. The intensity of IRR (mostly Grade 1 or 2) was generally consistent regardless of when they occurred. In RMS, there were more reports of Grade 3 IRRs with onset during the infusion (16 patients) compared with IRRs reported with onset after the infusion while the patient was still in the clinic (2 patients), or 24 hours post infusion when the patient was no longer in the clinic (2 patients). The single Grade 4 IRR was reported with onset during infusion. In PPMS, five of the 6 Grade 3 IRRs in the ocrelizumab group were reported with onset during infusion. The remaining Grade 3 IRR was reported with onset within 24 hours post infusion when the patient was no longer in the clinic. In the MA30143 substudy, one of the 2 Grade 3 IRRs was reported with onset during infusion and 1 was reported with onset 24h post infusion (1 patient in each infusion group).

In the pivotal studies (RMS, PPMS), the most frequently reported symptoms of IRRs with onset reported during infusion were pruritus, rash, flushing, and throat irritation. IRR symptoms reported with onset one hour after the completion of infusion were generally consistent with those reported during infusion. In the MA30143 substudy, the most frequently reported symptoms of IRRs with onset during infusion were throat irritation, oropharyngeal pain, and dysphagia, while the most frequently reported symptoms of IRRs with onset occurring within 24 hours post-infusion were fatigue, headache, and nausea. The IRR symptoms were consistent with the overall AE profile for IRRs and did not lead to identification of any new signals.

Table 34 Infusion Related Reactions by Most Extreme Intensity (Grade) Overall and by Infusion to Dose 6 Inclusive

Infusion[a]	Intensity (Grade)	Pool A		Pool C	WA25046	
		IFN (N = 826)	OCR (N = 825)	OCR (N = 1448)	PBO (N = 239)	OCR (N = 486)
Overall	1	57/826 (6.9%)	179/825 (21.7%)	275/1448 (19.0%)	38/239 (15.9%)	129/486 (26.5%)
	2	22/826 (2.7%)	83/825 (10.1%)	138/1448 (9.5%)	19/239 (7.9%)	59/486 (12.1%)
	3	1/826 (0.1%)	20/825 (2.4%)	25/1448 (1.7%)	4/239 (1.7%)	6/486 (1.2%)
	4	0/826 (0.0%)	1/825 (0.1%)	1/1148 (0.1%)	0/239 (0.0%)	0/486 (0.0%)
	5	0/826 (0.0%)	0/825 (0.0%)	0/1448 (0.0%)	0/239 (0.0%)	0/486 (0.0%)
Dose 1 Infusion 1	1	42/825 (5.1%)	151/825 (18.3%)	232/1448 (16.0%)	22/239 (9.2%)	98/486 (20.2%)
	2	11/825 (1.3%)	61/825 (7.4%)	95/1448 (6.6%)	7/239 (2.9%)	31/486 (6.4%)
	3	1/825 (0.1%)	14/825 (1.7%)	19/1448 (1.3%)	0/239 (0.0%)	4/486 (0.8%)
	4	0/825 (0.0%)	1/825 (0.1%)	1/1448 (0.1%)	0/239 (0.0%)	0/486 (0.0%)
	5	0/825 (0.0%)	0/825 (0.0%)	0/1448 (0.0%)	0/239 (0.0%)	0/486 (0.0%)
Dose 1 Infusion 2	1	14/815 (1.7%)	29/806 (3.6%)	50/1420 (3.5%)	11/235 (4.7%)	30/477 (6.3%)
	2	7/815 (0.9%)	9/806 (1.1%)	12/1420 (0.8%)	3/235 (1.3%)	4/477 (0.8%)
	3	0/815 (0.0%)	0/806 (0.0%)	0/1420 (0.0%)	0/235 (0.0%)	1/477 (0.2%)
	4	0/815 (0.0%)	0/806 (0.0%)	0/1420 (0.0%)	0/235 (0.0%)	0/477 (0.0%)
	5	0/815 (0.0%)	0/806 (0.0%)	0/1420 (0.0%)	0/235 (0.0%)	0/477 (0.0%)

Infusion[a]	Intensity (Grade)	Pool A		Pool C	WA25046	
		IFN (N = 826)	OCR (N = 825)	OCR (N = 1448)	PBO (N = 239)	OCR (N = 486)
Dose 2 Infusion 1	1	11/751 (1.5%)	84/779 (10.8%)	96/1169 (8.2%)	14/227 (6.2%)	39/465 (8.4%)
	2	4/751 (0.5%)	20/779 (2.6%)	28/1169 (2.4%)	3/227 (1.3%)	15/465 (3.2%)
	3	0/751 (0.0%)	3/779 (0.4%)	3/1169 (0.3%)	1/227 (0.4%)	0/465 (0.0%)
	4	0/751 (0.0%)	0/779 (0.0%)	0/1169 (0.0%)	0/227 (0.0%)	0/465 (0.0%)
	5	0/751 (0.0%)	0/779 (0.0%)	0/1169 (0.0%)	0/227 (0.0%)	0/465 (0.0%)
Dose 2 Infusion 2	1	-	-	-	10/219 (4.6%)	39/465 (8.4%)
	2				0/219 (0.0%)	15/465 (3.2%)
	3				0/219 (0.0%)	0/465 (0.0%)
	4				0/219 (0.0%)	0/465 (0.0%)
	5				0/219 (0.0%)	0/465 (0.0%)
Dose 3 Infusion 1	1	7/702 (1.0%)	56/759 (7.4%)	61/923 (6.6%)	9/216 (4.2%)	39/452 (8.6%)
	2	1/702 (0.1%)	14/759 (1.8%)	14/923 (1.5%)	4/216 (1.9%)	13/452 (2.9%)
	3	0/702 (0.0%)	3/759 (0.4%)	3/923 (0.3%)	0/216 (0.0%)	0/452 (0.0%)
	4	0/702 (0.0%)	0/759 (0.0%)	0/923 (0.0%)	0/216 (0.0%)	0/452 (0.0%)
	5	0/702 (0.0%)	0/759 (0.0%)	0/923 (0.0%)	0/216 (0.0%)	0/452 (0.0%)
Dose 3 Infusion 2	1	-	-	-	7/210 (3.3%)	19/437 (4.3%)
	2				3/210 (1.4%)	3/437 (0.7%)
	3				0/210 (0.0%)	0/437 (0.0%)
	4				0/210 (0.0%)	0/437 (0.0%)
	5				0/210 (0.0%)	0/437 (0.0%)

Infusion[a]	Intensity (Grade)	Pool A		Pool C	WA25046	
		IFN (N = 826)	OCR (N = 825)	OCR (N = 1448)	PBO (N = 239)	OCR (N = 486)
Dose 4 Infusion 1	1	9/663 (1.4%)	44/732 (6.0%)	46/762 (6.0%)	8/201 (4.0%)	26/439 (5.9%)
	2	3/663 (0.5%)	13/732 (1.8%)	14/762 (1.8%)	3/201 (1.5%)	3/439 (0.7%)
	3	0/663 (0.0%)	0/732 (0.0%)	0/762 (0.0%)	0/201 (0.0%)	0/439 (0.0%)
	4	0/663 (0.0%)	0/732 (0.0%)	0/762 (0.0%)	0/201 (0.0%)	0/439 (0.0%)
	5	0/663 (0.0%)	0/732 (0.0%)	0/762 (0.0%)	0/201 (0.0%)	0/439 (0.0%)
Dose 4 Infusion 2	1			0/4 (0.0%)	4/197 (2.0%)	12/430 (2.8%)
	2			0/4 (0.0%)	2/197 (1.0%)	1/430 (0.2%)
	3	-	-	0/4 (0.0%)	2/197 (1.0%)	0/430 (0.0%)
	4			0/4 (0.0%)	0/197 (0.0%)	0/430 (0.0%)
	5			0/4 (0.0%)	0/197 (0.0%)	0/430 (0.0%)
Dose 5 Infusion 1	1			50/698 (7.2%)	7/188 (3.7%)	23/428 (5.4%)
	2			14/698 (2.0%)	2/188 (1.1%)	7/428 (1.6%)
	3	-	-	0/698 (0.0%)	0/188 (0.0%)	0/428 (0.0%)
	4			0/698 (0.0%)	0/188 (0.0%)	0/428 (0.0%)
	5			0/698 (0.0%)	0/188 (0.0%)	0/428 (0.0%)
Dose 5 Infusion 2	1			13/694 (1.9%)	3/178 (1.7%)	13/414 (3.1%)
	2			3/694 (0.4%)	0/178 (0.0%)	6/414 (1.4%)
	3	-	-	0/694 (0.0%)	0/178 (0.0%)	0/414 (0.0%)
	4			0/694 (0.0%)	0/178 (0.0%)	0/414 (0.0%)
	5			0/694 (0.0%)	0/178 (0.0%)	0/414 (0.0%)

Infusion[a]	Intensity (Grade)	Pool A		Pool C	WA25046	
		IFN (N = 826)	OCR (N = 825)	OCR (N = 1448)	PBO (N = 239)	OCR (N = 486)
Dose 6 Infusion 1	1	-	-	21/457 (4.6%)	2/170 (1.2%)	21/406 (5.2%)
	2			5/457 (1.1%)	3/170 (1.8%)	6/406 (1.5%)
	3			0/457 (0.0%)	0/170 (0.0%)	0/406 (0.0%)
	4			0/457 (0.0%)	0/170 (0.0%)	0/406 (0.0%)
	5			0/457 (0.0%)	0/170 (0.0%)	0/406 (0.0%)
Dose 6 Infusion 2	1	-			1/159 (0.6%)	13/382 (3.4%)
	2				0/159 (0.0%)	2/382 (0.5%)
	3				1/159 (0.6%)	0/382 (0.0%)
	4				0/159 (0.0%)	0/382 (0.0%)
	5				0/159 (0.0%)	0/382 (0.0%)

IFN = interferon beta-1a (Rebif); OCR = ocrelizumab; PBO = placebo.

Notes: Percentages for Overall are based on the total number of patients (N). Percentages for each Infusion are based on the number of patients who received that Infusion. Multiple events in one individual are counted only once (AE with most extreme intensity is used). IRRs and related symptoms experienced by a patient during the infusion, 1 hour post infusion while the patient was still in the clinic, or within 24 hours after the completion of the infusion while the patient was not in the clinic were reported on a dedicated IRR eCRF form. In order not to miss any IRR, investigators were asked to confirm whether any event reported on the AE eCRF forms with onset date on the day of an infusion or on the next day after the completion of an infusion did not represent IRRs. Furthermore, investigators were asked to confirm that vital sign changes observed during and post-infusion did not represent an IRR. The clinical cutoff dates are 2 April 2015 for Study WA21092; 12 May 2015 for Study WA21093; and 24 July 2015 for Study WA25046.

[a] Dosing in the controlled treatment period of Study WA21092 and WA21093: Dose 1: 2 x ocrelizumab or placebo 300 mg IV infusions separated by 2 weeks, subsequently 1 x ocrelizumab or placebo 600 mg infusion every 24 weeks. Dosing in the OLE phase: Dose 1: 2 x ocrelizumab 300 mg IV infusions separated by 2 weeks, subsequently 1 x ocrelizumab 600 mg infusion every 24 weeks. Dosing in the controlled treatment period of Study WA25046: 2 x ocrelizumab or placebo 300 mg IV infusions separated by 2 weeks.

Sources: t_ae_irr_int_inf_all_spa; t_ae_irr_int_inf_all_spc; t_ae_irr_int_inf_CNTR_SE_046.

Impact on quality of life:

The IRs observed with ocrelizumab SC were all non-serious in nature and had local symptoms such as erythema, pain, swelling and pruritus, or systemic symptoms such as headache and nausea. All events were assessed as non-serious. None led to treatment discontinuations and the full dose of ocrelizumab SC was always administered. The majority of events required no treatment. All but two events resolved at the time of the database cutoff. With repeated injections the incidence of IRs decreased, and fewer patients required symptomatic treatment, this trend of the risk decreasing with subsequent doses being observed across the ocrelizumab SC investigational program. Given this, IRs are unlikely to have any long-term impact on patients' QOL.

If there are signs of a life-threatening IR, the injection should be stopped immediately, and the patient should receive appropriate treatment. Ocrelizumab treatment must be permanently discontinued in these patients.

If a patient experiences a severe IR, the injection should be interrupted immediately, and the patient should receive symptomatic treatment. The injection should be completed only after all symptoms have resolved.

Patients may experience considerable discomfort during an IRR. These reactions may present as pruritus, rash, urticaria, erythema, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, tachycardia and anaphylaxis. However, since symptoms are likely to be of mild to moderate intensity and resolve completely following the infusion, typical IRRs are unlikely to have long-term impact on QOL. If a patient experiences a mild to moderate IRR, the infusion rate should be reduced to half the rate at the onset of the event. This reduced rate should be maintained for at least 30 minutes. If tolerated, the infusion rate may then be increased according to the patient’s initial infusion rate. No infusion adjustment is necessary for subsequent new infusions unless the patient experiences an IRR.

If a patient experiences a severe IRR or a complex of flushing, fever, and throat pain symptoms, the infusion should be interrupted immediately, and the patient should receive symptomatic treatment. The infusion should be restarted only after all symptoms have resolved. The initial infusion rate at restart should be half of the infusion rate at the time of onset of the reaction. No infusion adjustment is necessary for subsequent new infusions unless the patient experiences an IRR.

Life-threating IRRs, such as acute hypersensitivity or acute respiratory distress syndrome, can significantly impact patient’s QOL. If a life-threatening IRR occurs, ocrelizumab must be immediately stopped and the patient should receive appropriate supportive treatment. Ocrelizumab must be permanently discontinued in these patients.

Although fatal IRRs were not observed in clinical studies with ocrelizumab, IRRs can theoretically result in a fatal outcome (e.g., hypotension in a patient with cardiac impairment).

Risk factors and risk groups:

Symptoms of IRs have been more frequently reported with the first injection.

IRRs and IRs occur most frequently on first exposure to ocrelizumab in patients with no history of prior opportunities for sensitization.

In patients receiving ocrelizumab IV, 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 (with the exception of Dose 1, Infusion 2). The addition of analgesics/antipyretics to oral antihistamines did not appear to have additional benefit.

Dosing intervals other than 6-monthly have not been systematically studied in MS and it is not known whether delaying dosing beyond the dosing schedule of 6-monthly would be associated with an increased rate of IRRs beyond what was observed with the first infusion.

The low number of patients with treatment-induced ADAs did not allow for an evaluation of the impact of ADAs on rate and intensity of IRRs.

Preventability:

The likelihood of occurrence of IRR or IR and its severity are not predictable. Although IRRs and IRs have been more frequently reported during the first infusion, an IRR or IRs may occur during any infusion, and patients who did not have an IRR or IR during the first infusion can still have an IRR or IR at later infusions. IRRs or IRs can occur within 24 hours of the infusion/injection.

To reduce the frequency and severity of local and systemic IRs the following two pre-medications are to be administered shortly before each ocrelizumab injection: 20 mg oral dexamethasone (or equivalent) together with an oral antihistamine (e.g., desloratadine or equivalent). In addition, premedication with an antipyretic (e.g., paracetamol) may also be considered shortly before each administration.

Similarly, to further reduce the frequency and severity of IRRs, patients receiving ocrelizumab IV must be premedicated with 100 mg IV methylprednisolone (or an equivalent) approximately 30 minutes prior to each ocrelizumab infusion to reduce the frequency and severity of IRRs. Additional premedication with an antihistaminic drug (e.g., diphenhydramine) is also mandatory approximately 30-60 minutes before each

infusion of ocrelizumab. The addition of an antipyretic (e.g., paracetamol) may also be considered approximately 30-60 minutes prior to each infusion of ocrelizumab.

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

Impact on the benefit-risk balance of the product:

All but one event of IR (both local and systemic IRs) reported from both studies were of Grade 1 or 2. One IR event of Grade 3 was reported in OCARINA I. The EU SmPC for ocrelizumab SC lays out the appropriate resources and measures for post-injection monitoring for the dose administration.

The majority of IRRs ($>$90% of patients who experienced an IRR) in both RMS and PPMS studies were of Grade 1 or 2 in intensity and the intensity of IRRs decreased with subsequent dosing. Grade 3 IRRs were reported in 2.4% of RMS patients receiving ocrelizumab and 1.2% of PPMS patients receiving ocrelizumab and most were associated with the first infusion. One serious Grade 4 IRR was reported in a RMS patient during the first infusion, while no PPMS patients had Grade 4 IRRs.

At the time of the primary analysis of the MA30143 substudy, the safety results did not show any significant or meaningful differences in safety profile between the conventional and shorter infusion groups.

The main observed risk associated with shorter infusion administration, IRRs, were mostly of mild or moderate intensity and were manageable by standard measures. No Grade 4 or serious IRR were reported. There were no IRRs that led to permanent discontinuation from ocrelizumab treatment, and the outcome for the vast majority of IRRs in each infusion group was reported as recovered.

There were no Grade 5 (fatal) IRRs in clinical studies with ocrelizumab.

The incidence of IRRs during or within 24 hours following the end of the first Randomized Dose, the primary endpoint of the study, was comparable between the conventional and the shorter infusion group. When looking at all randomized doses, the IRR incidences were also similar between the two groups. IRRs were not treatment limiting. IRRs were manageable with prophylactic treatment, infusion adjustments, and symptomatic treatment.

The EU SmPC for ocrelizumab IV states that treatment should be initiated and supervised by an experienced healthcare professional with access to appropriate medical support to manage severe reactions such as serious IRRs and premedication consisting of methylprednisolone (or an equivalent), an antihistamine and an antipyretic administered. This should reduce the risk of patients developing IRRs, and in case

patients nevertheless develop IRRs, increase the likelihood of prompt treatment and quick recovery. The impact of IRRs on the benefit-risk balance of ocrelizumab is considered low due to the low incidence of severe or serious cases of IRRs and preventive measures.

Public health impact:

No impact on public health is anticipated. This is due to the population treated and the limitations placed upon administration of ocrelizumab by virtue of the warnings and precautions. Ocrelizumab for IV administration is provided as a solution for infusion and because of the nature of this pharmaceutical form will always be administered by an experienced healthcare professional with access to appropriate medical support to manage severe reactions such as serious IRRs. Use outside of controlled environments by non-healthcare professionals is not anticipated.

SVII.3.1.1.2 INFECTIONS

Potential mechanisms:

The precise mechanisms through which ocrelizumab exerts its therapeutic clinical effects in MS are not fully elucidated but involve immunomodulation through the reduction in the number and function of B cells. Since B cells play an important role in maintaining normal immune response by their involvement in humoral defense, Ag presentation, and coordination of T-cell activity, patients may be at an increased risk of infection or infection reactivation following administration of ocrelizumab.

Evidence source(s) and strength of evidence:

Clinical studies of ocrelizumab: WA21092, WA21093, WA25046, WA21493, BN29739, MN30035, MA30005, WA20494, WA20495, WA20496, WA20497, WA18230, ACT2847g, GA00931, JA21963, JA22003, WA20499, WA20500, BO18414, WA40404, BA39730, ML29966, MN39158, MA30143, CN41144, and CN42097.

Characterization of the risk:

Data from the SC investigational program is provided in the subheadings below (frequency with 95% CI, seriousness/outcomes, severity and nature of risk) in an untabulated manner. Data presented in Table 35 - Table 46 is only for ocrelizumab IV.

Background Incidence/Prevalence:

Patients Exposed to Placebo:

The overall rate of infections in the placebo group of the PPMS Study WA25046 was 76.1 events per 100PY (95% CI: 69.6, 83.0); the rate of SIs was 4.2 events per 100PY (95% CI: 2.8, 6.1); refer to Table 35 and Table 36 , respectively.

A literature review conducted by Laser Analytica with the objective to identify studies (clinical trials and observational studies) with any information on occurrence of infections in patients with any type of MS and to estimate event rates using available exposure information showed that rates of SIs in MS patients exposed to placebo in clinical studies ranged from 0 to 4.97 (95%CI: 0, 14.7) per 100PY. The highest estimated rate of 4.97 per 100PY was based on a study with low cumulative exposure of 20PY (Laser Analytica Report 2016).

Patients Exposed to Other Disease-Modifying Therapies:

The overall rate of infections in the interferon group in Pool A (as there was no placebo group) was 69.1 events per 100PY (95% CI: 64.8, 73.6); the rate of SIs was 2.4 events per 100PY (1.7, 3.4); refer Table 35 and Table 36 , respectively.

The literature review conducted by Laser Analytica showed that rates of SIs in MS patients exposed to interferons in clinical and observational studies ranged from 0 to 7.72 (95%CI: 0, 18.43) per 100PY. The highest estimated rate of 7.72 events per 100PY was based on a clinical study with low cumulative exposure of 26PY. Furthermore, estimated rates of SIs per 100PY ranged from 0.14 (95%CI: 0, 0.41) to 4.27 (95%CI: 0, 10.2) in fingolimod-exposed patients, 1.08 (95%CI: 0.33, 1.84) to 2.4 (95%CI: 0.74, 4.06) in alemtuzumab-exposed patients, 0.53 (95%CI: 0, 1.13) to 1.46 (95%CI: 0.56, 2.37) in dimethyl-fumarate-exposed patients, 0 to 2.36 (95%CI: 1.41, 3.3) in natalizumab-exposed patients, and 0.91 (95%CI: 0.18, 1.64) to 2.58 (95%CI: 1.23, 3.93) in teriflunomide-exposed patients (Laser Analytica Report 2016).

Epidemiological Data:

In a Swedish registers-based study, MS was associated with an increased hospital admission risk for all infections (RR: 4.26 [95% CI: 4.13-4.40]), with the highest risk reported for UTIs (RR: 8.22 [95% CI: 7.71-8.77]). Among the subset of MS patients identified through the MS Register, the highest risk of infection-related hospital admission was observed for the primary and secondary progressive phenotypes (Montgomery et al. 2013).

Frequency with 95% CI:

In the clinical studies with ocrelizumab SC, of the181 patients from OCARINA II study, 47 (26.0%, 95% CI: 19.75, 32.99) experienced 70 events of infections. Of the 131 patients who received 920 mg or 1200 mg ocrelizumab SC from OCARINA I, 89 (67.9%, 95% CI: 59.23, 75.82) experienced 186 events of infections.

The incidence of infections and SIs reported in clinical studies with ocrelizumab IV in MS patients (Pool A, Study WA25046, Pool B) overall and by dose is summarized in Table 35 and Table 36, respectively. The incidence of SIs reported in clinical studies with ocrelizumab in RA (Pool D and Pool E) overall and by dose is summarized in

Table 37 . The rate of infections in RMS patients treated with ocrelizumab in Pool A (85.4 events per 100PY [95% CI: 80.7, 90.3]) was higher than in RMS patients treated with interferon (69.1 events per 100PY [95% CI: 64.8, 73.6]). The rate of infections in PPMS patients treated with ocrelizumab in Study WA25046 (76.5 events per 100PY [95% CI: 72.0, 81.2]) was similar to that in PPMS patients treated with placebo (76.1 events per 100PY [95% CI: 69.6, 83.0]). With open label treatment (Pool B), there was no increase in the rate of infections with additional exposure to ocrelizumab (77.7 events per 100PY [95% CI: 75.2, 80.4]).

Upper respiratory tract infections and UTIs, per predefined baskets of AEs, were the most frequently reported (>10% of patients) types of infections in all MS patients treated with ocrelizumab (Pool B).

In both the RMS (Pool A) and PPMS (Study WA25046) populations during controlled treatment, the rates of UTIs, 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 or placebo). In RMS patients, more upper respiratory tract infections and more herpes infections (non-disseminated herpes virus related, oral or genital, as well as herpes zoster) were reported in the ocrelizumab group compared with the interferon group. In PPMS patients, more oral herpetic infections were reported in the ocrelizumab group compared with the placebo group (refer to Table 39).

No opportunistic infections were reported by any MS patient treated with ocrelizumab and there were no fevers of unknown origin.

Event rates for most types of infections were generally stable with no consistent increase or decrease between doses of ocrelizumab, with the exception of upper respiratory tract infection which was reported at a higher rate following Dose 1 and then declined over time.

The rate of SIs in MS patients treated with ocrelizumab (Pool B) was low (2.3 events per 100 PY [95% CI: 1.9, 2.8]). In RMS patients (Pool A), the rate of SIs in the IFN group was higher (2.4 events per 100PY [95% CI: 1.7, 3.4]) than in the ocrelizumab group (1.2 events per 100PY [95% CI: 0.7, 2.0]). In PPMS patients (Study WA25046), the rate of SIs was balanced between the placebo (4.2 events per 100PY [95% CI: 2.8, 6.1]) and ocrelizumab (3.7 per events 100PY [95% CI: 2.8, 4.9]) groups (refer to Table 36). This higher rate of SIs in both arms of the PPMS study (compared with RMS patients) may reflect the severity of the disease.

In RA patients (Table 40), an imbalance in serious and opportunistic infections was observed, including, but not limited to, atypical pneumonia and pneumocystis jirovecii

pneumonia, varicella pneumonia, tuberculosis, and histoplasmosis. In rare cases, some of these infections were fatal.

In Pool D, the rate of SIs was higher in the 1000 mg group (7.3 events per 100PY [95% CI: 5.6, 9.3]) compared with the 400 mg (5.2 events per 100PY [95% CI: 3.9, 6.8]) or placebo (4.0 events per 100PY [95% CI: 2.8, 5.5]) group (refer to Table 37) SIs were observed more frequently in patients with other comorbidities, chronic use of immunosuppressants/steroids, or from Asia. The higher rate of serious and opportunistic infections in the RA trials compared with the MS trials may be explained by a higher prevalence of risk factors for infection (e.g., chronic steroid use, medical history of CV events, medical history of infections, medical history of respiratory complications, use of high disease-modifying antirheumatic drugs (DMARDs); specifically anti-tumor necrosis factor in the RA study population, leading to a higher absolute risk compared with the MS study population. In the MS population, where patients were treated with ocrelizumab as monotherapy, with intermittent use of steroids for symptomatic treatment of relapse, without significant numbers of Asian patients, and no Asian clinical trial sites, there was no imbalance in SIs observed.

Although the data are limited, SIs were also reported in 3 patients in the SLE trial and in 64 patients in the LN trial. Among the 3 patients from the SLE trial, two patients developed opportunistic infections (cytomegalovirus retinitis and pneumocystis jiroveci pneumonia).

Table 35 Number of Infections per 100 Patient-Years Overall and by Dose to Dose 7 – Clinical Studies in Multiple Sclerosis

Dose	Pool A (Phase III RMS Controlled Treatment)		WA25046 (Phase III PPMS Controlled Treatment)		Pool B (MS All Exposure)
	IFN (N = 826)	OCR (N = 825)	PBO (N = 239)	OCR (N = 486)	OCR (N = 2147)
Overall	69.1 (64.8, 73.6)	85.4 (80.7, 90.3)	76.1 (69.6, 83.0)	76.5 (72.0, 81.2)	77.7 (75.2, 80.4)
Dose 1	74.8 (66.7, 83.7)	101.7 (91.9, 112.2)	99.8 (82.6, 119.6)	89.2 (77.6, 102.1)	93.4 (87.4, 99.6)
Dose 2	72.5 (64.0, 81.9)	89.9 (80.4, 100.1)	87.0 (70.5, 106.1)	75.9 (64.9, 88.2)	82.5 (76.3, 89.1)
Dose 3	71.5 (62.7, 81.3)	81.1 (72.0, 91.1)	72.9 (57.7, 90.9)	81.9 (70.4, 94.7)	70.7 (65.0, 76.7)
Dose 4	53.9 (46.0, 62.8)	66.3 (57.8, 75.5)	64.3 (49.2, 82.5)	72.4 (61.3, 84.9)	60.9 (55.6, 66.6)
Dose 5	—	—	68.8 (53.0, 87.9)	72.1 (60.9, 84.8)	83.3 (75.8, 91.4)
Dose 6	—	—	67.8 (49.8, 90.1)	67.0 (55.1, 80.7)	72.2 (63.2, 82.2)
Dose 7	—	—	50.8 (31.5, 77.7)	75.7 (59.6, 94.7)	79.3 (66.1, 94.3)

IFN = interferon beta-1a (Rebif); MS = multiple sclerosis; OCR = ocrelizumab; PBO = placebo; PPMS = primary progressive MS; RMS = relapsing forms of MS.

Note: Adverse events were identified as infections in the following way: events coded to the SOC Infections and Infestations or events from other MedDRA body systems if identified by the investigator as infections in the eCRF form (i.e., with pathogen information provided). Multiple occurrences of the same AE in one patient will be counted multiple times. 95% CI is calculated using an exact method based on the Poisson distribution. The clinical cutoff dates are 22 January 2015 for Study WA21493, 2 April 2015 for Study WA21092; 12 May 2015 for Study WA21093; and 24 July 2015 for Study WA25046.

Sources: t_ae_100py_profile_all_spa; t_ae_100py_cyc_INFECT_spa; t_ae_100py_IVSER_INFECT_CNTR_SE_046; t_ae_100py_cyc_INFECT_CNTR_SE_046; t_ae_100py_profile_all_spb2; t_ae_100py_cyc_INFECT_spb2

Table 36 Number of Serious Infections per 100 Patient-Years Overall and by Dose to Dose 7 – Clinical Studies in Multiple Sclerosis

Dose	Pool A (Phase III RMS Controlled Treatment)		WA25046 (Phase III PPMS Controlled Treatment)		Pool B (MS All Exposure)
	IFN (N=826)	OCR (N=825)	PBO (N=239)	OCR (N=486)	OCR (N=2147)
Overall	2.4 (1.7, 3.4)	1.2 (0.7, 2.0)	4.2 (2.8, 6.1)	3.7 (2.8, 4.9)	2.3 (1.9, 2.8)
Dose 1	1.7 (0.7, 3.5)	1.0 (0.3, 2.6)	1.7 (0.2, 6.1)	3.4 (1.5, 6.7)	2.0 (1.2, 3.1)
Dose 2	2.5 (1.2, 4.8)	1.6 (0.6, 3.6)	4.5 (1.5, 10.5)	2.2 (0.7, 5.2)	2.2 (1.3, 3.5)
Dose 3	2.7 (1.3, 5.2)	0.9 (0.2, 2.5)	5.5 (2.0, 12.1)	4.5 (2.2, 8.3)	2.3 (1.4, 3.6)
Dose 4	3.0 (1.4, 5.6)	1.5 (0.5, 3.5)	8.4 (3.6, 16.6)	3.4 (1.4, 6.9)	1.6 (0.9, 2.8)
Dose 5	—	—	4.3 (1.2, 11.0)	4.9 (2.4, 9.1)	2.8 (1.6, 4.6)
Dose 6	—	—	4.3 (0.9, 12.6)	6.0 (2.9, 11.1)	4.4 (2.4, 7.4)
Dose 7	—	—	0 (0, 8.9)	0 (0, 3.7)	1.9 (0.4, 5.5)

IFN = interferon beta-1a (Rebif); MS = multiple sclerosis; OCR = ocrelizumab; PBO = placebo; PPMS = primary progressive MS; RMS = relapsing forms of MS.

Notes: Adverse events were identified as infections in the following way: events coded to the SOC Infections and Infestations or events from other MedDRA body systems if identified by the investigator as infections in the eCRF form (i.e., with pathogen information provided). Serious infections were identified in the following ways: infections assessed by investigators as serious and those non-SIs that were treated with IV anti-infectives. Multiple occurrences of the same AE in one patient will be counted multiple times. 95% CI is calculated using an exact method based on the Poisson distribution. The clinical cutoff dates are 22 January 2015 for Study WA21493; 2 April 2015 for Study WA21092; 12 May 2015 for Study WA21093; and 24 July 2015 for Study WA25046.

Sources: t_ae_100py_profile_all_spa; t_ae_100py_cyc_INFECT_IVSER_spa; t_ae_100py_IVSER_INFECT_CNTR_SE_046; t_ae_100py_cyc_IVSER_INFECT_CNTR_SE_046; t_ae_100py_profile_all_spb2; t_ae_100py_cyc_INFECT_IVSER_spb2.

Table 37 Number of Serious Infections per 100 Patient-Years Overall and by Dose to Dose 7 – Clinical Studies in Rheumatoid Arthritis

Dose	Pool D (Phase II/III RA Controlled Treatment)			Pool E (RA All Exposure)
	PBO (N = 981)	OCR 400 mg (N = 1186)	OCR 1000 mg (N = 947)	OCR (N = 2926)
Overall	4.0 (2.8, 5.5)	5.2 (3.9, 6.8)	7.3 (5.6, 9.3)	4.3 (3.9, 4.8)
Dose 1	4.5 (2.8, 6.9)	5.5 (3.7, 7.8)	9.5 (6.8, 12.8)	6.1 (5.1, 7.3)
Dose 2	3.3 (1.6, 5.9)	4.2 (2.3, 6.9)	6.0 (3.8, 9.1)	5.6 (4.5, 6.8)
Dose 3	5.5 (1.5, 14.1)	3.1 (0.4, 11.3)	0 (0, 5.8)	2.8 (2.0, 3.7)
Dose 4	0 (0, 12.2)	15.2 (4.9, 35.5)	6.4 (0.8, 23.0)	2.4 (1.6, 3.5)
Dose 5	—	—	—	1.6 (0.7, 3.2)
Dose 6	—	—	—	2.2 (0.6, 5.7)
Dose 7	—	—	—	7.0 (2.6 15.2)

OCR = ocrelizumab; PBO = placebo; RA = rheumatoid arthritis.

Notes: Adverse events were identified as infections in the following way: events coded to the SOC Infections and Infestations or events from other MedDRA body systems if identified by the investigator as infections in the eCRF form (i.e., with pathogen information provided). Serious infections were identified in the following ways: infections assessed by investigators as serious and those non-SIs that were treated with IV anti-infectives. Multiple occurrences of the same AE in one patient will be counted multiple times. 95% CI is calculated using an exact method based on the Poisson distribution.

Sources: t_ae_100py_profile_all_spd; t_ae_100py_cyc_INFECT_IVSER_spd; tt_ae_100py_profile_all_spe; t_ae_100py_cyc_INFECT_IVSER_spe.

Table 38 Number of Infections per 100 Patient-Years by Basket – Clinical Studies in Multiple Sclerosis

Infection Basket	Pool A (Phase III RMS Controlled Treatment)		WA25046 (Phase III PPMS Controlled Treatment)		Pool B (MS All Exposure)
	IFN (N = 826)	OCR (N = 825)	PBO (N = 239)	OCR (N = 486)	OCR (N = 2147)
URTI	33.1 (30.2, 36.3)	41.3 (38.1, 44.7)	31.1 (27.0, 35.6)	30.6 (27.8, 33.7)	35.6 (33.9, 37.4)
UTI	12.2 (10.4, 14.1)	13.5 (11.6, 15.5)	20.2 (16.9, 23.9)	18.5 (16.3, 20.9)	14.8 (13.7, 16.0)
Skin infections	3.9 (3.0, 5.1)	5.5 (4.4, 6.9)	5.2 (3.6, 7.2)	5.4 (4.3, 6.8)	4.9 (4.3, 5.6)
LRTI	3.4 (2.5, 4.5)	5.4 (4.3, 6.7)	3.9 (2.6, 5.8)	4.1 (3.1, 5.3)	4.8 (4.2, 5.5)
GI tract infections	5.7 (4.5, 7.0)	5.9 (4.7, 7.3)	5.3 (3.7, 7.4)	3.6 (2.7, 4.7)	4.6 (3.9, 5.2)
HSV-associated infections	2.4 (1.7, 3.4)	4.6 (3.5, 5.8)	2.9 (1.7, 4.5)	2.1 (1.4, 2.9)	3.6 (3.1, 4.2)
Infectious biliary disorders	0.3 (0.1, 0.7)	0.5 (0.2, 1.0)	0.2 (0, 0.8)	0 (0, 0.3)	0.2 (0.1, 0.4)
Sepsis/SIRS (broad)	0.2 (0, 0.6)	0.1 (0, 0.4)	0.6 (0.2, 1.6)	0.4 (0.1, 0.8)	0.2 (0.1, 0.3)
Sepsis/ SIRS (narrow)	0.2 (0, 0.6)	0.1 (0, 0.4)	0.6 (0.2, 1.6)	0.3 (0.1, 0.7)	0.1 (0, 0.3)
CNS infections	0 (0, 0.3)	0 (0, 0.3)	0.3 (0, 1.1)	0.1 (0, 0.5)	0 (0, 0.1)

CNS = central nervous system; GI = gastrointestinal; HSV = herpes virus; IFN = interferon beta-1a (Rebif); LRTI = lower respiratory tract infections; MS = multiple sclerosis; OCR = ocrelizumab; PBO = placebo; PPMS = primary progressive MS; RMS = relapsing forms of MS; SIRS = systemic inflammatory response syndrome; URTI = upper respiratory tract infection; UTI = urinary tract infections.

Notes: Adverse events were identified as infections in the following way: events coded to the SOC Infections and Infestations or events from other MedDRA body systems if identified by the investigator as infections in the eCRF form (i.e., with pathogen information provided). Multiple occurrences of the same AE in one patient will be counted multiple times. 95% CI is calculated using an exact method based on the Poisson distribution. The clinical cutoff dates are 22 January 2015 for Study WA21493, 2 April 2015 for Study WA21092; 12 May 2015 for Study WA21093; and 24 July 2015 for Study WA25046.

Sources: t_ae_100py_cyc_type_all_spa; t_ae_100py_cyc_type_INFB_CNTR_SE_046; t_ae_100py_cyc_type_all_spb2.

Table 39 Number of Serious Infections per 100 Patient-Years by Basket – Clinical Studies in Multiple Sclerosis

Infection Basket	Pool A (Phase III RMS Controlled Treatment)		WA25046 (Phase III PPMS Controlled Treatment)		Pool B (MS All Exposure)
	IFN (N=826)	OCR (N=825)	PBO (N=239)	OCR (N=486)	OCR (N=2147)
UTI	0.2 (0.0, 0.6)	0.1 (0.2, 0.5)	1.5 (0.7, 2.8)	1.2 (0.7, 1.9)	0.7 (0.7, 1.0)
GI tract infections	0.6 (0.3, 1.2)	0.4 (0.2, 0.9)	0.5 (0.1, 1.3)	0.6 (0.3, 1.2)	0.5 (0.3, 0.7)
LRTI	0.1 (<0.1, 0.5)	0.1 (0.0, 0.5)	0.6 (0.2, 1.6)	0.8 (0.4, 1.4)	0.4 (0.3, 0.7)
Skin infections	0.2 (0.0, 0.6)	0.2 (<0.1, 0.6)	0.5 (0.1, 1.3)	0.5 (0.2, 1.0)	0.3 (0.2, 0.5)
Infectious biliary disorders	0.1 (<0.1, 0.5)	0.4 (0.1, 0.8)	0.2 (<0.1, 0.8)	0.1 (<0.1, 0.5)	0.2 (0.1, 0.4)
Sepsis/SIRS (broad)	0.1 (<0.1, 0.4)	0.1 (<0.1, 0.4)	0.6 (0.2, 1.6)	0.2 (<0.1, 0.6)	0.1 (<0.1, 0.3)
Sepsis/ SIRS (narrow)	0.1 (<0.1, 0.4)	0.1 (<0.1, 0.4)	0.6 (0.2, 1.6)	0.2 (<0.1, 0.6)	0.1 (<0.1, 0.2)
URTI	0.1 (0.0, 0.4)	0.1 (<0.1, 0.4)	0.2 (<0.1, 0.8)	0 (0, 0.3)	0.1 (<0.1, 0.3)
HSV-associated infections	0.0 (0.0, 0.3)	0.1 (<0.1, 0.4)	0 (0, 0.6)	0 (0, 0.3)	0.1 (<0.1, 0.2)
CNS infections	0.0 (0.0, 0.3)	0.0 (0.0, 0.3)	0.3 (<0.1, 1.1)	0 (0, 0.3)	0 (0, 0.1)

CNS = central nervous system; GI = gastrointestinal; HSV = herpes virus; LRTI = lower respiratory tract infections; MS = multiple sclerosis; OCR = ocrelizumab; PBO = placebo; PPMS = primary progressive MS; RMS = relapsing forms of MS; SIRS = systemic inflammatory response syndrome; URTI = upper respiratory tract infection; UTI = urinary tract infections.

Notes: Adverse events were identified as infections in the following way: events coded to the SOC Infections and Infestations or events from other MedDRA body systems if identified by the investigator as infections in the eCRF form (i.e., with pathogen information provided). Serious infections were identified in the following ways: infections assessed by investigators as serious and those non-SIs that were treated with IV anti-infectives. Multiple occurrences of the same AE in one patient will be counted multiple times. 95% CI is calculated using an exact method based on the Poisson distribution.

Sources: t_ae_100py_ type_IVSER_spa; t_ae_100py_cyc_type_IVSER_INFB_CNTR_SE_046; t_ae_100py_cyc_type_IVSER_spb2.

Table 40 Number of Serious Infections per 100 Patient-Years by Basket – Clinical Studies in Rheumatoid Arthritis

Infection basket	Pool D (Phase II/III RA Controlled Treatment)			Pool E (RA All Exposure)
	PBO (N = 981)	OCR 400 mg (N = 1186)	OCR 1000 mg (N = 947)	OCR (N = 2926)
LRTI	1.2 (0.6, 2.2)	1.9 (1.1, 3.0)	1.9 (1.1, 3.0)	1.3 (1.0, 1.6)
UTI	0.3 (0.1, 1.0)	0.8 (0.3, 1.6)	1.0 (0.5, 1.9)	0.6 (0.5, 0.9)
GI tract infections	0.3 (0.1, 1.0)	0.9 (0.4, 1.7)	1.2 (0.6, 2.2)	0.6 (0.4, 0.8)
Skin infections	0.6 (0.2, 1.3)	0.3 (0.1, 0.9)	1.1 (0.5, 2.0)	0.5 (0.4, 0.7)
Sepsis/SIRS (broad)	0.1 (<0.1, 0.6)	0.3 (0.1, 0.9)	0.4 (0.1, 1.1)	0.4 (0.3, 0.6)
Sepsis/ SIRS (narrow)	0 (0, 0.4)	0.3 (0.1, 0.9)	0.2 (0, 0.8)	0.3 (0.2, 0.5)
URTI	0.2 (<0.1, 0.8)	0.1 (<0.1, 0.6)	0.4 (0.1, 1.1)	0.2 (0.1, 0.3)
HSV-associated infections	0.1 (<0.1, 0.6)	0.1 (<0.1, 0.6)	0.3 (0.1, 1.0)	0.2 (0.1, 0.3)
CNS infections	0 (0, 0.4)	0 (0, 0.4)	0.2 (<0.1, 0.8)	0.1 (<0.1, 0.2)
Infectious biliary disorders	0.1 (<0.1, 0.6)	0.1 (<0.1, 0.6)	0 (0, 0.4)	0.1 (<0.1, 0.2)

CNS = central nervous system; GI = gastrointestinal; HSV = herpes virus; LRTI = lower respiratory tract infections; OCR = ocrelizumab; PBO = placebo; RA = rheumatoid arthritis; SIRS = systemic inflammatory response syndrome; URTI = upper respiratory tract infection; UTI = urinary tract infections.

Notes: Adverse events were identified as infections in the following way: events coded to the SOC Infections and Infestations or events from other MedDRA body systems if identified by the investigator as infections in the eCRF form (i.e., with pathogen information provided). Serious infections were identified in the following ways: infections assessed by investigators as serious and those non-SIs that were treated with IV anti-infectives. Multiple occurrences of the same AE in one patient will be counted multiple times. 95% CI is calculated using an exact method based on the Poisson distribution.

Sources: t_ae_100py_cyc_type_IVSER_spd; t_ae_100py_cyc_type_IVSER_spe.

Seriousness/Outcomes:

In the clinical studies with ocrelizumab SC, the majority of events were non-serious.

All events reported in patients receiving ocrelizumab SC in OCARINA II were non-serious, and all were reported as recovered.

In OCARINA I, 13 (9.9%) patients receiving ocrelizumab SC 920 mg or 1200 mg experienced at least one serious AE. For 88 (67.2%) patients, the outcome of at least one event was reported as recovered. Two (1.5 %) patients had at least one event recovered with sequelae, and one (0.8%) patient each had an event recovering/resolving, unresolved, or with fatal outcome.

The outcomes of infections and SIs reported in clinical studies with ocrelizumab IV in MS (Pool A, Study WA25046, Pool B) are summarized in Table 41 and Table 42 respectively. The outcomes of SIs reported in clinical studies with ocrelizumab in RA (Pool D and Pool E) are summarized in Table 43.

A total of 1.8% (15 of 825) of RMS patients treated with ocrelizumab in Pool A, 2.1% (31 of 1448) of RMS patients treated with ocrelizumab in Pool C, and 7.6% (37 of 486) of PPMS patients treated with ocrelizumab in Study WA25046 experienced SIs. This higher rate of SIs in PPMS patients (compared with RMS patients) may reflect the severity of the disease. Overall, SIs were experienced by 3.8% (81 of 2147) of patients treated with ocrelizumab in Pool B (6.9%; 81 of 1181 of patients treated with ocrelizumab who had infections). The majority of SIs resolved within 4 weeks.

There were no fatal infections among RMS patients treated with ocrelizumab. In the PPMS Study WA25046, fatal infection was reported in two patients (0.4%) in the ocrelizumab group during the controlled treatment period, one case of pneumonia and one case of pneumonia aspiration. These events were not considered by the investigators as related to treatment.

Overall, less than 0.1% (2 of 2147) of MS patients treated with ocrelizumab had SIs that led to a fatal outcome (Pool B).

A total of 0.5% of RA patients (15 of 2926) treated with ocrelizumab in Pool E had SIs that led to a fatal outcome.

Although the data are limited, among the 3 patients from the SLE trial who developed SIs, 2 patients developed opportunistic infections (cytomegalovirus retinitis and pneumocystis jiroveci pneumonia) and both died (due to upper respiratory infection and pneumocystis, respectively). Among the 64 patients in the LN trial who developed a serious infection, 8 patients died from the serious infection (due to Legionella infection, pneumonia, sepsis, urosepsis, or septic shock). Of the 10 fatal infection cases, all patients were treated with immunosuppressants which likely contributed to their fatal outcome.

Table 41 Infections by Outcome – Clinical Studies in Multiple Sclerosis

Outcome	Pool A (Phase III RMS Controlled Treatment)		WA25046 (Phase III PPMS Controlled Treatment)		Pool B (MS All Exposure)
	IFN (N = 826)	OCR (N = 825)	PBO (N = 239)	OCR (N = 486)	OCR (N = 2147)
Fatal	0	0	0	2/1080 (0.2%)	2/3480 (< 0.1%)
Not recovered/Not resolved	3/966 (0.3%)	6/1237 (0.5%)	8/499 (1.6%)	23/1080 (2.1%)	48/3480 (1.3%)
Recovered/Resolved	946/966 (97.9%)	1213/1237 (98.1%)	485/499 (97.2%)	1046/1080 (96.9%)	3374/3480 (97.0%)
Recovered/Resolved with sequelae	13/966 (1.3%)	11/1237 (0.9%)	4/499 (0.8%)	5/1080 (0.5%)	31/3480 (0.9%)
Recovering/Resolving	3/966 (0.3%)	3/1237 (0.2%)	0	4/1080 (0.4%)	21/3480 (0.6%)
Unknown	1/966 (0.1%)	4/1237 (0.3%)	2/499 (0.4%)	0	4/3480 (0.1%)

IFN = interferon beta-1a (Rebif); MS = multiple sclerosis; OCR = ocrelizumab; PBO = placebo; PPMS = primary progressive MS; RMS = relapsing forms of MS.

Notes: Percentages are based on the total number of events. For frequency counts by outcome, multiple occurrences of the same AE in an individual are counted separately. Adverse events were identified as infections in the following way: events coded to the SOC Infections and Infestations or events from other MedDRA body systems if identified by the investigator as infections in the eCRF form (i.e., with pathogen information provided). For frequency counts by outcome, multiple occurrences of the same AE with the same outcome in an individual are counted only once. The clinical cutoff dates are 22 January 2015 for Study WA21493, 2 April 2015 for Study WA21092; 12 May 2015 for Study WA21093; and 24 July 2015 for Study WA25046.

Sources: ah_t_ae_out_ev_INFECT_spa; ah_t_ae_ocm_ev_INFECT_CNTR_SE_046; ah_t_ae_out_ev_INFECT_spb2.

Table 42 Serious Infections by Outcome – Clinical Studies in Multiple Sclerosis

Outcome	Pool A (Phase III RMS Controlled Treatment)		WA25046 (Phase III PPMS Controlled Treatment)		Pool B (MS All Exposure)
	IFN (N = 826)	OCR (N = 825)	PBO (N = 239)	OCR (N = 486)	OCR (N = 2147)
Fatal	0	0	0	2/53 (3.8%)	2/104 (1.9%)
Not recovered/Not resolved	0	0	0	1/53 (1.9%)	2/104 (1.9%)
Recovered/Resolved	32/34 (94.1%)	16/18 (88.9%)	27/28 (96.4%)	45/53 (84.9%)	92/104 (88.5%)
Recovered/Resolved with sequelae	2/34 (5.9%)	2/18 (11.1%)	0	2/53 (3.8%)	5/104 (4.8%)
Recovering/Resolving	0	0	0	3/53 (5.7%)	3/104 (2.9%)
Unknown	0	0	1/28 (3.6%)	0	0

IFN = interferon beta-1a (Rebif); MS = multiple sclerosis; OCR = ocrelizumab; PBO = placebo; PPMS = primary progressive MS; RMS = relapsing forms of MS.

Notes: Percentages are based on the total number of events. For frequency counts by outcome, multiple occurrences of the same AE in an individual are counted separately. Adverse events were identified as infections in the following way: events coded to the SOC Infections and Infestations or events from other MedDRA body systems if identified by the investigator as infections in the eCRF form (i.e., with pathogen information provided). Serious infections were identified in the following ways: infections assessed by investigators as serious and those non-SIs that were treated with IV anti-infectives. For frequency counts by outcome, multiple occurrences of the same AE with the same outcome in an individual are counted only once. The clinical cutoff dates are 22 January 2015 for Study WA21493, 2 April 2015 for Study WA21092; 12 May 2015 for Study WA21093; and 24 July 2015 for Study WA25046.

Sources: ah_t_ae_out_ev_INFECT_IVSER_spa; ah_t_ae_ocm_ev_IVSER_INFECT_CNTR_SE_046; ah_t_ae_out_ev_INFECT_IVSER_spb2

Table 43 Serious Infections by Outcome – Clinical Studies in Rheumatoid Arthritis

Outcome	Pool D (Phase II/III RA Controlled Treatment)			Pool E (RA All Exposure)
	PBO (N = 981)	OCR 400 mg (N = 1186)	OCR 1000 mg (N = 947)	OCR (N = 2926)
Fatal	0	2/52 (3.8%)	4/66 (6.1%)	19/317 (6.0%)
Not recovered/Not resolved	0	4/52 (7.7%)	3/66 (4.5%)	13/317 (4.1%)
Recovered/Resolved	32/36 (88.9%)	42/52 (80.8%)	57/66 (86.4%)	265/317 (83.6%)
Recovered/Resolved with sequelae	3/36 (8.3%)	3/52 (5.8%)	2/66 (3.0%)	12/317 (3.8%)
Recovering/Resolving	0	0	0	0
Unknown	0	1/52 (1.9%)	0	1/317 (0.3%)
Missing	1/36 (2.8%)	0	0	7/317 (2.2%)

OCR = ocrelizumab; PBO = placebo; RA = rheumatoid arthritis.

Notes: Percentages are based on the total number of events. For frequency counts by outcome, multiple occurrences of the same AE in an individual are counted separately. Adverse events were identified as infections in the following way: events coded to the SOC Infections and Infestations or events from other MedDRA body systems if identified by the investigator as infections in the eCRF form (i.e., with pathogen information provided). Serious infections were identified in the following way: infections assessed by investigators as serious and those non-SIs that were treated with IV anti-infectives. For frequency counts by outcome, multiple occurrences of the same AE with the same outcome in an individual are counted only once.

Sources: ah_t_ae_out_ev_INFECT_IVSER_spd; ah_t_ae_ev_INSIVA_spe.

Severity and Nature of Risk:

In the clinical studies with ocrelizumab SC in MS patients, the majority of events were Grade 1 or Grade 2.

In OCARINA II, 19 (10.5%) patients experienced infections of Grade 1 highest severity and 28 (15.5%) patients experienced infections of Grade 2 highest severity.

In OCARINA I, 25 (19.1%) patients experienced infections of Grade 1 highest severity, 48 (36.6.%) patients experienced infections of Grade 2 highest severity, 15 (11.5%) of Grade 3 highest severity and 1 (0.8%) was of Grade 5 (an SAE of COVID-19 pneumonia in a patient treated with 1200 mg ocrelizumab SC during the dose escalation phase).

The most frequently reported infections in patients receiving ocrelizumab SC were consistent with the ones previously known with ocrelizumab IV. No infections at the injection site were reported.

The intensity (grades) of infections and SIs reported in clinical studies with ocrelizumab IV in MS are summarized in Table 44 and Table 45, respectively. The intensity of SIs reported in clinical studies with ocrelizumab in RA (Pool D and Pool E) is summarized in Table 46.

In the RMS and PPMS controlled treatment populations, the majority ($>$90% across groups) of infections in ocrelizumab-treated patients were of Grade 1 or 2 in intensity. The majority of SIs ($\geq$73% across groups) were of Grade 2 or 3 in intensity. There were no Grade 5 infections among RMS patients treated with ocrelizumab. In the PPMS Study WA25046, Grade 5 infection was reported in two patients (0.4%) in the ocrelizumab group during the controlled treatment period, one case of pneumonia and one case of pneumonia aspiration.

The majority ($\geq$77% across groups) of SIs in RA patients in each treatment group in Pool D and in Pool E were classified by the Investigators as Grade 2 or 3 in intensity. There were two Grade 5 events (0.2% of patients) among RA patients treated with ocrelizumab 400 mg and four Grade 5 events (0.4% of patients) among patients treated with ocrelizumab 1000 mg in Pool D. In Pool E, there were 14 Grade 5 events (0.5% of patients).

Table 44 Infections by Most Extreme Intensity (Grade) – Clinical Studies Multiple Sclerosis

Intensity (Grade)	Pool A (Phase III RMS Controlled Treatment)		WA25046 (Phase III PPMS Controlled Treatment)		Pool B (MS All Exposure)
	IFN (N = 826)	OCR (N = 825)	PBO (N = 239)	OCR (N = 486)	OCR (N = 2147)
1	204 (24.7%)	215 (26.1%)	77 (32.2%)	186 (38.3%)	441 (20.5%)
2	205 (24.8%)	242 (29.3%)	121 (50.6%)	260 (53.5%)	652 (30.4%)
3	32 (3.9%)	24 (2.9%)	19 (7.9%)	26 (5.3%)	76 (3.5%)
4	0	2 (0.2%)	1 (0.4%)	8 (1.6%)	10 (0.5%)
5	0	0	0	2 (0.4%)	2 (<0.1%)

IFN = interferon beta-1a (Rebif); MS = multiple sclerosis; OCR = ocrelizumab; PBO = placebo; PPMS = primary progressive MS; RMS = relapsing forms of MS.

Notes: Adverse events were identified as infections in the following way: events coded to the SOC Infections and Infestations or events from other MedDRA body systems if identified by the investigator as infections in the eCRF form (i.e., with pathogen information provided). Multiple events in one individual are counted only once (AE with most extreme intensity is used). The clinical cutoff dates are 22 January 2015 for Study WA21493, 2 April 2015 for Study WA21092; 12 May 2015 for Study WA21093; and 24 July 2015 for Study WA25046).

Sources: t_ae_int_INFECT_spa; ah_t_ae_int_INFECT_CNTR_SE_046; t_ae_int_INFECT_spb2

Table 45 Serious Infections by Most Extreme Intensity (Grade) – Clinical Studies in Multiple Sclerosis

Intensity (Grade)	Pool A (Phase III RMS Controlled Treatment)		WA25046 (Phase III PPMS Controlled Treatment)		Pool B (MS All Exposure)
	IFN (N=826)	OCR (N=825)	PBO (N=239)	OCR (N=486)	OCR (N=2147)
1	2 (0.2%)	1 (0.1%)	1 (0.4%)	0	5 (0.2%)
2	11 (1.3%)	4 (0.5%)	7 (2.9%)	12 (2.5%)	26 (1.2%)
3	18 (2.2%)	8 (1.0%)	12 (5%)	15 (3.1%)	38 (1.8%)
4	0	2 (0.2%)	1 (0.4%)	8 (1.6%)	10 (0.5%)
5	0	0	0	2 (0.4%)	2 (<0.1%)

IFN = interferon beta-1a (Rebif); MS = multiple sclerosis; OCR = ocrelizumab; PBO = placebo; PPMS = primary progressive MS; RMS = relapsing forms of MS.

Note: Adverse events were identified as infections in the following way: events coded to the SOC Infections and Infestations or events from other MedDRA body systems if identified by the investigator as infections in the eCRF form (i.e., with pathogen information provided). Serious infections were identified in the following ways: infections assessed by investigators as serious and those non-SIs that were treated with IV anti-infectives. Multiple events in one individual are counted only once (AE with most extreme intensity is used. The clinical cutoff dates are 22 January 2015 for Study WA21493, 2 April 2015 for Study WA21092; 12 May 2015 for Study WA21093; and 24 July 2015 for Study WA25046).

Sources: t_ae_int_INFECT_IVSER_spa; ah_t_ae_int_INFECT_IVSER_CNTR_SE_046; t_ae_int_INFECT_IVSER_spb2.

Table 46 Serious Infections by Most Extreme Intensity (Grade) – Clinical Studies in Rheumatoid Arthritis

Intensity (Grade)	Pool D (Phase II/III RA Controlled Treatment)			Pool E (RA All Exposure)
	PBO (N=981)	OCR 400 mg (N=1186)	OCR 1000 mg (N=947)	OCR (N=2926)
1	4 (0.4%)	6 (0.5%)	3 (0.3%)	17 (0.6%)
2	17 (1.7%)	16 (1.3%)	16 (1.7%)	84 (2.9%)
3	10 (1.0%)	14 (1.2%)	23 (2.4%)	98 (3.3%)
4	1 (0.1%)	1 (<0.1%)	0	7 (0.2%)
5	0	2 (0.2%)	4 (0.4%)	14 (0.5%)

OCR = ocrelizumab; PBO = placebo; RA = rheumatoid arthritis.

Notes: Multiple events in one individual are counted only once (AE with most extreme intensity is used). Adverse events were identified as infections in the following way: events coded to the SOC Infections and Infestations or events from other MedDRA body systems if identified by the investigator as infections in the eCRF form (i.e., with pathogen information provided). Serious infections were identified in the following way: infections assessed by investigators as serious and those non-SIs that were treated with IV anti-infectives.

Sources: t_ae_int_INFECT_ser_spd; t_ae_int_INFECT_ser_spe.

Impact on quality of life:

Although the impact on patient QOL depends on the specific pathogen, many infections in immunocompromised patients are life threatening or require prolonged hospitalization and anti-infective therapy. Hence, the impact on QOL is likely to be substantial.

Most opportunistic infections are associated with substantial morbidity and mortality. Some are irreversible and/or associated with serious long-term sequelae, disability and dependence. Hence, most opportunistic infections have a major impact on QOL.

Risk factors and risk groups:

Previous or concomitant immunotherapy, and/or corticotherapy can be important contributing factors. Exploratory analyses were conducted to identify prognostic and treatment-emergent risk factors for infections and SIs. Ocrelizumab in combination with concomitant immunosuppressive medications (e.g., chronic steroids, non-biologic and biologic DMARDS, mycophenolate mofetil, cyclophosphamide, azathioprine has been studied in other autoimmune conditions. Risk factors for SIs were only explored for RA because of the too low event number in the MS studies. In the studies in patients with RA, an imbalance in SIs was observed, including, but not limited to, atypical pneumonia and pneumocystis jirovecii pneumonia, varicella pneumonia, tuberculosis, histoplasmosis in the ocrelizumab-immunosuppressant group. In rare cases, some of these infections were fatal. SIs were reported more frequently in the 1000 mg dose group compared to the 400 mg dose group or immunosuppressant-placebo group. Risk

factors for SIs in these trials included other comorbidities, chronic use of immunosuppressants/steroids, and patients from Asia. In conclusion, data from the RA cohort indicated that ocrelizumab treatment might increase the risk of SIs for Asian patients/patients in Asia on chronic steroid treatment, notably on the ocrelizumab 1000 mg dose. However, these observations do not reach statistical significance and are confounded with Asian region, lower body weight, as well as increased drug exposure. In the MS population, where patients were treated with ocrelizumab as monotherapy, with intermittent use of steroids for symptomatic treatment of relapse, without significant numbers of Asian patients and no Asian clinical trial sites, there was no imbalance in SIs observed.

B-cell depletion is an expected pharmacologic effect of ocrelizumab, which might result in decreased Ig levels in some ocrelizumab-treated patients. A clinical feature of decreased Ig relates to predisposition toward infections.

In the active-controlled (RMS) studies, the proportion of patients reporting at baseline IgG, IgA and IgM < LLN in the ocrelizumab treatment arm was 0.5%, 1.5% and 0.1% respectively. Following treatment, the proportion of ocrelizumab-treated patients reporting IgG, IgA and IgM < LLN at 96 weeks was 1.5%, 2.4% and 16.5% respectively.

In the placebo-controlled (PPMS) study, the proportion of patients reporting at baseline IgG, IgA and IgM < 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 < LLN at 120 weeks was 1.1%, 0.5% and 15.5% respectively.

The rate of SIs below and above a pre-defined LLN for each type of Ig in the pooled Phase III studies; WA21092, WA21093 and WA25046; at 07 Jan 2019 clinical cut-off date (CCOD) were analyzed.

Rates of SIs during episodes of IgA<LLN are similar to rates of SIs during episodes of IgA>LLN, but rates of SIs during episodes of IgM or IgG <LLN (IgG <LLN: 5.48/100PY, 95% CI (3.00, 9.20); IgM<LLN: 3.54/100PY, 95% CI (2.77, 4.47)) were higher than rates observed during episodes >LLN for the respective Igs (IgG≥LLN: 2.14/100PY, 95% CI (1.86, 2.45); IgM≥LLN: 1.89/100PY, 95% CI (1.60, 2.22)) (DSR 1096448).

Patients with preexisting hypogammaglobulinemia prior to the start of treatment with ocrelizumab or who received previous or concomitant treatment with immunosuppressive or other immunomodulatory drugs may be at a greater risk of serious infection.

In the MS studies, mean and median levels of neutrophils did not change during treatment with ocrelizumab. Most events were of Grade 1 and 2 neutropenia without any temporal pattern associated with infections.

Preventability:

Ocrelizumab administration must be delayed in patients with an active infection until the infection is resolved.

When initiating ocrelizumab after an immunosuppressive therapy or initiating an immunosuppressive therapy after ocrelizumab, the potential for overlapping pharmacodynamics (PD) effects should be taken into consideration. The prescriber should exercise caution when prescribing ocrelizumab taking into consideration the pharmacodynamics of other MS DMTs. Ocrelizumab has not been studied in combination with other MS DMTs.

Anti-CD20 Ab therapy may trigger hepatitis B virus (HBV) reactivation in patients with a history of HBV infection. Similarly, immunomodulatory therapy may trigger reactivation of latent herpes virus in patients with a history of herpes infection (Kappos 2010).

HBV screening should be performed in all patients before initiation of treatment with ocrelizumab as per local guidelines. Patients with active HBV (i.e., an active infection confirmed by positive results for hepatitis B surface antigen [HBsAg] and anti HB testing) should not be treated with ocrelizumab. Patients with positive serology (i.e. negative for HBsAg and positive for hepatitis B core antibody (HBcAb+); carriers of HBV [positive for surface Ag, HBsAg+]) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Impact on the benefit-risk balance of the product:

During the controlled treatment period of the clinical trials in RMS and PPMS patients, the majority ($>$90% across groups) of infections in ocrelizumab-treated patients were of Grade 1 or 2 in intensity. In MS patients, Grade 1 and 2 upper respiratory tract infections and UTIs were the most common infections reported with ocrelizumab. The majority of SIs ($\geq$73% across groups) were of Grade 2 or 3 in intensity. There were no Grade 5 infections among RMS patients treated with ocrelizumab. In the PPMS Study WA25046, Grade 5 infection was reported in two patients (0.4%, pneumonia and pneumonia aspiration, respectively) in the ocrelizumab group during the controlled treatment period. The overall proportion of patients with MS treated with ocrelizumab experiencing a serious infection was similar to comparators used in the clinical trials. There were no fatal infections among RMS patients treated with ocrelizumab. Overall, less than 0.1% (2 of 2147) of MS patients treated with ocrelizumab had SIs that led to a fatal outcome. Most infections reported with ocrelizumab were not treatment limiting and resolved within 14 days.

It is recommended in the EU SmPC to verify the patient's immune status before dosing since severely immunocompromised patients should not be treated and similarly, ocrelizumab administration must be delayed in patients with an active infection until the infection is resolved. Furthermore, HBV screening should be performed in all patients

before initiation of treatment with ocrelizumab. Although infections belong to the AEs reported most frequently with ocrelizumab, the impact of infections on the benefit-risk balance of ocrelizumab is considered low since the majority was of Grade 1 or 2 in intensity.

Public health impact:

Minimal public health impact is foreseen. 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 the start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

SVII.3.1.2 Information on important potential risks

SVII.3.1.2.1 MALIGNANCIES INCLUDING BREAST CANCER

Potential mechanisms:

Mechanistically, B cells influence the course of tumor surveillance; however, their role is controversial with outcomes highly impacted by the model of B cell deficiency, tumor type, and the role of specific B cell subsets in tumor surveillance. The contrasting and often conflicting roles of B cell subsets on the process of tumor surveillance leads to a significant uncertainty regarding the impact of depleting CD20 mAbs on tumor development, progression and overall incidence. This is in contrast to the well-established positive role of T and natural killer (NK) cells in tumor surveillance (Gajewski 2013; Marcus 2014). The specific biological plausibility to an increased risk of malignancies including breast cancer remains unlikely.

Evidence source(s) and strength of evidence:

Clinical studies of ocrelizumab: WA21092, WA21093, WA25046, WA21493, BN29739, MN30035, MA30005, WA20494, WA20495, WA20496, WA20497, WA18230, ACT2847g, GA00931, JA21963, JA22003, WA20499, WA20500, BO18414, WA40404, BA39730, MA30143, MN39158, MN39159, ML29966, CN41144, and CN42097.

Characterization of the risk:

Data from the SC investigational program is provided in the subheadings below (frequency with 95% CI, seriousness/outcomes, severity and nature of risk) in an untabulated manner. Data presented in Table 47 - Table 54 is only for ocrelizumab IV.

Background Incidence/Prevalence:

Multiple Sclerosis

Published studies on MS population have reported a similar or somewhat lower risk of any cancer compared to the general population (Nielsen et al. 2006; Kingwell et al. 2012b). A literature-based meta-analysis involving almost 55,000 MS patients, mainly from Europe, reported a somewhat lower risk of cancer in MS compared to the general population (RR=0.91; 95% CI: 0.87, 0.95) (Catala-Lopez 2014). In the same study, no association with breast cancer was reported in the MS population (RR=1.02; 95% CI: 0.88, 1.18). The risk of cancer in the PPMS population is still uncertain, and so far contradictory results have been reported (Lebrun et al. 2008; Kingwell et al. 2012b).

Incidence rates of malignancies, malignancies excluding nonmelanoma skin cancer (NMSC), and female breast cancer in MS population reported in the control groups (placebo/ IFN beta-1a) of Phase III clinical trials with ocrelizumab, placebo arms of clinical studies with other DMTs, and epidemiological studies are presented in Table 47.

Table 47 Incidence Rates for Any Malignancy, Malignancy excluding Non-Melanoma Skin Cancer, and Breast Cancer in Multiple Sclerosis Population (Epidemiological and Clinical Study Data)

Malignancy type	Incidence rate per 100PY (95% CI)	Population	Reference
Clinical study data – pooled comparator groups of Phase III studies with ocrelizumab			
Any malignancy	0.20 (0.05, 0.50)[a]	Pooled crude IR for the control groups (PBO/ IFN) in Phase III clinical trials with ocrelizumab	Refer to table footer
Any malignancy excluding NMSC	0.10 (0.01, 0.35)		
Female breast cancer	0 (0, 0.29)[a]		
Clinical study data – placebo groups of studies with other DMTs			
Any malignancy	0.50 (0.36, 0.67)[b]	Analysis of placebo groups of MS clinical studies (for breast cancer, age range mostly 18-55 years)	Laser Analytica Report 2016
Any malignancy excluding NMSC	0.33 (0.20, 0.50)		
Female breast cancer	0.16 (0.06, 0.32)[b]		
Epidemiological data			
Any malignancy (not specified; probably excluding NMSC and in situ)	0.67 (0.63-0.71)[c]	Danish MS patients	Nielsen et al. 2006
Any malignancy excluding NMSC	0.37 (0.32, 0.43)[c]	Patients with MS in British Columbia, Canada	Kingwell et al. 2012b

Malignancy type	Incidence rate per 100PY (95% CI)	Population	Reference
Female breast cancer	0.28 (0.27, 0.28)[c]	UK women 50 – 55 years old	Cancer Research UK, 2015
	0.21 (0.18-0.23)[c]	Danish MS patients	Nielsen et al. 2006
	0.14 (0.11-0.16)[c]	Patients with MS in British Columbia, Canada	Kingwell et al. 2012b

CI = confidence interval; DMTs = disease-modifying therapies; IFN = interferon; IR = incidence rate; MS = multiple sclerosis; NMSC = non melanoma skin cancer; PBO = placebo; PY = patient-years; UK = United Kingdom.

[a] Incidence rate based on first event only (i.e., patients with multiple events are counted once only); the denominator is the exposure in patient years. For patients with the pre-defined malignancy events, the exposure is from the first Dose up to the onset of the event.

[b] A variety of sources were identified through the literature search. The sources reported either the number of events or the number of patients affected. Since no patient level data was available, it is unknown how many events occurred in one patient during the study, and whether only first events or multiple events were reported. As a result, calculations were different from study to study.

[c] Estimated based on the number of events, and follow up time (in PY) reported in the references. Sex specific incidence rates were estimated taking into account the sex distribution reported in the publications.

Sources for data from ocrelizumab studies:
t_ae_100py_bscmo_MAL_ph3_spa;t_ae_100py_bscmo_BC_female_ph3_spa;
t_ae_100py_bscmo_MAL_EXMSMAL_ph3_spa.

Other Disease-Modifying Therapies:

The literature review by Laser Analytica showed that the estimate rate of malignancies (including NMSC) per 100PY in interferon-exposed MS patients (mostly patients with RRMS or relapsing SPMS) ranged from 0 to 3.72 (95% CI: 0, 11.01). Moreover, the estimated rates of malignancies per 100PY in MS patients (mostly patients with RRMS or relapsing SPMS) ranged from 0 to 2.24 (95% CI: 1.06, 3.41) in fingolimod-exposed patients, 0.24 (95% CI: 0, 0.57) and 0.92 (95% CI: 0, 1.95) in alemtuzumab-exposed patients, 0 to 0.29 (95% CI: 0, 0.7) in dimethyl-fumarate-exposed patients, 0.06 (95% CI: 0, 0.14) to 1.37 (95% CI: 0, 3.28) in natalizumab-exposed patients, and 0.16 (95% CI: 0, 0.46) in teriflunomide-exposed patients (Laser Analytica Report 2016).

The estimated rate of breast cancer per 100PY in MS patients (mostly patients with RRMS or relapsing SPMS) ranged from 0 to 0.52 (95% CI: 0, 1.23) in fingolimod-exposed patients, 0 to 0.14 (95% CI: 0, 0.43) in dimethyl-fumarate-exposed patients, and 0.04 (95% CI: 0.01, 0.06) to 0.88 (95% CI: 0, 2.62) in natalizumab-exposed patients. No cases of breast cancer were reported in interferon-exposed patients, alemtuzumab-exposed patients, as well as in teriflunomide-exposed patients (Laser Analytica Report 2016).

Rheumatoid Arthritis (to Contextualize Pool E Data)

The incidence rates of malignancies in RA population reported in epidemiological studies are presented in Table 48.

Table 48 Incidence Rates for Any Cancer and Breast Cancer in Rheumatoid Arthritis Population

Incidence rate per 100PY	Cancer type	Population	Reference
General Epidemiology			
1.13 (1.11, 1.15)	Any cancers excluding NMSC	RA patients (mainly Western populations)	DSR 1061959
1.27 (1.21, 1.33)	Any cancers excluding lymphatic and hematopoietic cancers	Danish RA patients	Mellemkjaer et al. 1996
1.30 (1.19, 1.41)	Any cancers excluding NMSC	U.S. RA patients	Wolfe et al. 2007
1.37 (1.18, 1.58)	Any cancers excluding NMSC	British RA patients (biologic naïve cohort)	Mercer et al. 2012
0.19 (0.18, 0.20)	Breast cancer (incidence for men and women combined)	RA patients (mainly Western populations)	DSR 1042848
0.13 (0.10, 0.15)	Breast cancer (incidence for men and women combined)	Danish RA patients	Mellemkjaer et al. 1996
0.21 (0.17, 0.26)	Breast cancer (incidence for men and women combined)	U.S. RA patients	Wolfe et al. 2007
0.31 (0.21, 0.45)	Female breast cancer	British RA patients (biologic naïve cohort)	Mercer et al. 2012
0.22 (0.15, 0.29)	Breast cancer (incidence for men and women combined)	British RA patients (biologic naïve cohort)	BSRBR report 2016
0.25	Female breast cancer	Swedish RA patients (biologic naïve cohort)	ARTIS report 2016
Rituximab-exposed			
1.45 (0.19, 2.70)	Any cancers	French RA patients	DSR 1061959

Incidence rate per 100PY	Cancer type	Population	Reference
1.98 (1.63, 2.37)	Any cancers	British RA patients	DSR 1061959
1.61 (1.26, 2.02)	Any cancers	German RA patients	DSR 1061959
0.20 (0.12, 0.33)	Breast cancer (incidence for men and women combined)	British RA patients	BSRBR report 2016
0.19	Female breast cancer	Swedish RA patients	ARTIS report 2016

ARTIS = Antirheumatic Therapies in Sweden; BSRBR = British Society of Rheumatology Biologics Registers; DSR = Drug Safety Report; RA= Rheumatoid Arthritis; NMSC = non melanoma skin cancer; PY = patient-years.

To contextualize the risk of malignancy for ocrelizumab, the MAH also evaluated available data from anti-CD20 B cell-depleting therapies. The long-term safety data was largely focused on data generated for rituximab given its substantial clinical development program and duration on the market.

The risk of anti-CD20 B cell depleting agents in impeding the immune system's tumor surveillance, including less common types of breast cancer, lacks a clear mechanistic relationship. Further, clinical evidence from approximately 4.8 million patient exposures with rituximab (to September 2015) provides robust evidence that there is no increased malignancy risk, including breast cancer, associated with anti-CD20 treatment.

An exhaustive assessment on rituximab, including post marketing data in more than 3.8 million patients exposed, was conducted in 2014 and did not show an increased risk of first cancer in non-oncology indications or of second cancer in oncology indications (DSR 1061959).

In this report, there was no finding from a recent analysis of the pooled long-term clinical database in RA; and there was no obvious trend in a malignancy type reported in RA patients in the safety database, therefore a literature review including epidemiology was first performed to guide the analysis of the events reported to the safety database. The literature on RA and rituximab reported that incidence of malignancies with rituximab was within the expected range of the general population, and no increased risk over time or treatment courses was evident.

Since literature on RA (regardless of its treatment) and on granulomatosis polyangiitis/microscopic polyangiitis (GPA/MPA), both indicated an increased risk of NMSC, NMSC was the specific malignancy requiring further investigation regarding rituximab. In the pooled analysis of the clinical program conducted in RA, there was no

evidence of an increased risk of malignancy of any type over time or rituximab treatment courses (including NMSC).

An analysis of the epidemiological data showed that RA patients remain at increased risk of overall malignancy[6], regardless of treatment, compared to the general population. Clinical and epidemiological data on GPA or MPA patients treated with rituximab are sparse, given the orphan disease condition and the recent approval of rituximab in this indication. A detailed review of NMSC cases in the safety database did not reveal any specific pattern, and was consistent with epidemiology and literature publications in non-oncology indications.

In conclusion, this extensive consolidated assessment of literature, epidemiology, clinical and safety data in oncology and non-oncology indications for rituximab did not point to an increased risk related to rituximab as compared to the known risks of malignancies and second malignancies in these populations. The Company's conclusions were endorsed by the Pharmacovigilance Risk Assessment Committee (PRAC) in the context of a rituximab PBRER assessment procedure.

More recently in 2016, a specific assessment of the risk of breast cancer observed in the Swedish RA registry Antirheumatic Therapies in Sweden (ARTIS) and the British RA registry British Society of Rheumatology Biologics Registers (BSRBR) confirmed the results of the exhaustive review conducted in 2014 and no increased risk was seen with rituximab for female breast cancer (ARTIS Report 2016, BSRBR Report 2016).

Frequency with 95% CI:

In the clinical studies with ocrelizumab SC, malignancies were reported in 2 (1.5%, %CI: 0.19, 5.41) of the 131 patients from OCARINA I. One patient experienced basal cell carcinoma and one patient experienced papillary thyroid cancer. In OCARINA II, no malignancies were reported in the 181 patients who received ocrelizumab SC.

The incidence rates of malignancies reported in ocrelizumab IV clinical studies in MS patients (MS All Exposure Population; Pool B) are summarized in Table 49 and RA (RA All Exposure Population; Pool E) in Table 50.

Malignancy was reported in a total of 19 (0.9%) ocrelizumab-treated patients in the MS program (Pool B) and 4 (0.4% patients) patients in the comparator groups (Placebo and IFN) of the RMS and PPMS studies. Consequently, a higher incidence rates of first malignancy was reported in MS patients treated with ocrelizumab (Pool B) (0.43 [95%

[6] In addition, a recent meta-analysis of the epidemiological data by Simon et al. 2015 showed that although RA patients are at a higher risk of malignancy, regardless of treatment, than the general population (pooled standardized incidence ratios [SIR]=1.09 [95% CI: 1.06-1.13]), there is no evidence that the risk of breast cancer in RA patients is increased when compared to the general population (SIR=0.86 [95% CI: 0.73-1.01]) (Simon et al. 2015).

CI: 0.26, 0.66]) relative to comparator (Placebo and IFN, Pool A and PPMS Study WA25046) treatment (0.20 [95% CI: 0.05, 0.50]). The only cluster identified, which drove the imbalance in malignancy, was for female breast cancer. There was no clinical or histological pattern observed with the reported breast cancer cases. Moreover, there is not a clear biologic rationale why an increased risk of breast cancer would occur over that of multiple other solid tumor types.

No cases of malignancy were identified in Pool B by the herpes-virus related malignancies basket.

Incidence rates of malignancies, including breast cancer, in patients treated with ocrelizumab remained within the range of placebo data from clinical trials in MS (0.50 per 100PY [95%CI: 0.36, 0.673]) (Laser Analytica Report 2016) and epidemiological data (0.67 per 100PY [95%: 0.63, 0.71]) (Nielsen et al. 2006).

The incidence rates of malignancy were also standardized to the 2000 U.S. standard population to allow comparison with the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database and restricted to the age range of the clinical studies with ocrelizumab in MS: 15 to 59 years old). When comparing against the standardized incidence rates in SEER database, standardized malignancy rates in the ocrelizumab group (Pool B) were similar:

- all malignancies excluding NMSC: ocrelizumab 0.26 per 100PY (95% CI: 0.13, 1.58) and adjusted SEER[7] 0.24 per 100PY (95% CI: 0.24, 0.24)
- female breast cancer: ocrelizumab 0.19 per 100PY (95% CI: 0.08, 2.48) and SEER[8] 0.12 per 100PY (95% CI: 0.12, 0.12)

No conclusion can be made to date concerning the risk of malignancy because of the low number of events and the limited follow-up period. A multi-source non-interventional PASS BA39730 to assess and characterize the long-term safety data (including malignancies) from the use of ocrelizumab in patients with MS is ongoing. The malignancies monitoring plan has been updated to clarify the ongoing assessment process, including removal of the reference to the biannual DSR on malignancies.

In the RA program, there were no imbalances in the rate of malignancy between placebo (1.11 per 100PY [95% CI: 0.53, 2.04]), ocrelizumab 400 mg (0.90 per 100PY [95% CI: 0.41, 1.70]), and ocrelizumab 1000 mg (1.32 per 100PY [95% CI: 0.68, 2.31]) groups during the controlled treatment period (Pool D).

Across the RA program, malignancy was reported in a total of 94 (3.2%) patients treated with ocrelizumab. The incidence rate of malignancy for all patients exposed to ocrelizumab during the RA development program (Pool E) was 1.31 per 100PY (95% CI:

[7] Assumes 9% lower malignancy risk in MS vs. the general population (Catalá-López et al. 2014).
[8] Adjustment not applicable as breast cancer risk is reported to be similar in MS and general population (Catalá-López et al. 2014)

1.06, 1.60); consistent with previous reports of malignancy in RA patients (1.27 per 100PY [95% CI: 1.21, 1.33] per Mellemkjaer et al. 1996); and 1.30 [95%CI: 1.19, 1.41] per Wolfe et al. 2007).

Table 49 Incidence Rate of Malignancies per 100 Patient-Years – Clinical Studies in Multiple Sclerosis

Malignancy type	Pooled PBO/ IFN Controls	Pool B (MS All Exposure)
	N = 1065 (female N = 668)	OCR (N = 2147)
Any malignancy	0.20 (0.05, 0.50)	0.43 (0.26, 0.66)
Any malignancy excluding NMSC	0.10 (0.01, 0.35)	0.34 (0.19, 0.55)
Female breast cancer	0 (0, 0.29)	0.26 (0.11, 0.54)

IFN = interferon beta-1a; MS = multiple sclerosis; PBO = placebo; NMSC = non-melanoma skin cancer; OCR = ocrelizumab.

Notes: Multiple occurrences of the same AE in one patient will be counted only once. 95% CI is calculated using an exact method based on the Poisson distribution. For patients with malignancies patient-years are calculated from first treatment to onset of first malignancy. Malignancies are identified using adverse events falling into the Standard MedDRA Query 'Malignant tumours (narrow)'. For patients with any malignancy excluding NMSC patient-years are calculated from first treatment to onset of first malignancy excluding NMSC. For any malignancy excluding NMSC the following PTs were excluded: 'basal cell carcinoma', 'Bowen's disease', 'squamous cell carcinoma', and 'squamous cell carcinoma of skin'. For patients with breast cancer patient-years are calculated from first treatment to onset of first breast cancer. Breast cancer is identified using PTs of 'invasive ductal breast carcinoma', 'breast cancer', 'intraductal proliferative breast lesion', 'inflammatory carcinoma of the breast', and 'invasive breast carcinoma'. Only female patients are selected. The clinical cutoff dates are 22 January 2015 for Study WA21493, 2 April 2015 for Study WA21092; 12 May 2015 for Study WA21093; and 24 July 2015 for Study WA25046.

Sources: t_ae_100py_bscmo_MAL_ph3_spa; t_ae_100py_bscm_MAL_spb2; t_ae_100py_bscmo_MAL_EXMSMAL_ph3_spa; t_ae_100py_bscm_MAL_EXMSMAL_spb2, t_ae_100py_bscmo_BC_female_ph3_spa; t_ae_100py_bscm_BC_female_spb2.

Table 50 Incidence Rate of Malignancies per 100 Patient-Years – Clinical Studies in Rheumatoid Arthritis

Malignancy type	Pool E (RA All Exposure)
	OCR (N = 2926)
Any malignancy	1.31 (1.06, 1.60)
Malignancy excluding NMSC	0.90 (0.70, 1.15)
Female breast cancer	0.12 (0.05, 0.25)

OCR = ocrelizumab; NMSC = non-melanoma skin cancer; RA = rheumatoid arthritis.

Notes: Multiple occurrences of the same AE in one patient will be counted only once. For patients with malignancies PYs are calculated from first treatment to onset of first malignancy / breast cancer, and, if no breast cancer then to onset of first malignancy. 95% CI is calculated using an exact method based on the Poisson distribution. Malignancies are identified using adverse events falling into the Standard MedDRA Query 'Malignant tumours (narrow)'. For patients with any malignancy excluding NMSC patient-years are calculated from first treatment to onset of first malignancy excluding NMSC. For any malignancy excluding NMSC the following PTs were excluded: 'basal cell carcinoma', 'Bowen's disease', 'squamous cell carcinoma', and 'squamous cell carcinoma of skin'. Breast cancer is identified using PTs of 'invasive ductal breast carcinoma', 'breast cancer', 'intraductal proliferative breast lesion', 'inflammatory carcinoma of the Breast', and 'invasive breast carcinoma'. Only female patients are selected.

Sources: t_ae_100py_bscm_MAL_spe; t_ae_100py_bscm_BC_female_spe; t_ae_100py_bscm_MALENMSC_spe.

Seriousness/Outcomes:

In the clinical studies with ocrelizumab SC, from OCARINA I study, the event of basal cell carcinoma was reported as non-serious and recovered. The event of papillary thyroid cancer was reported as serious and unresolved at the time of the data cut off. The patient underwent thyroidectomy and was recovering post data cut-off. Both events were assessed as unrelated to the study drug by the Investigator.

The outcomes reported in ocrelizumab IV clinical studies in MS (MS All Exposure Population; Pool B) are summarized in Table 51 and in RA (RA All Exposure Population; Pool E) in Table 52. All malignancies reported in Pool B except basal cell carcinomas were assessed by the Investigators as serious. One of the malignancies in Pool B (metastatic pancreatic carcinoma) led to a fatal outcome. The Investigator assessed the event as unrelated to study drug.

Eight of the malignancies in Pool E (0.3% of patients) led to the fatal outcome Preferred Terms of metastatic gastric cancer, gastrointestinal carcinoma, lung adenocarcinoma, metastatic lung adenocarcinoma, malignant lung neoplasm, breast cancer, B-cell lymphoma, and metastatic rectosigmoid cancer).

Table 51 Malignancies by Outcome – Clinical Studies in Multiple Sclerosis

Outcome	Pool B (MS All Exposure OCR (N=2147)
Fatal	1/21 (4.8%)
Not recovered/Not resolved	7/21 (33.3%)
Recovered/Resolved	7/21 (33.3%)
Recovered/Resolved with sequelae	3/21 (14.3%)
Recovering/Resolving	3/21 (14.3%)

MS = multiple sclerosis; OCR = ocrelizumab.

Notes: Percentages are based on the total number of events. For frequency counts by outcome, multiple occurrences of the same AE in an individual are counted separately. Malignancies are identified using adverse events falling into the Standard MedDRA Query 'Malignant tumours (narrow)'. The clinical cutoff dates are 22 January 2015 for Study WA21493, 2 April 2015 for Study WA21092; 12 May 2015 for Study WA21093; and 24 July 2015 for Study WA25046.

Source: ah_t_ae_out_ev_MAL_spb2

Table 52 Malignancies by Outcome – Clinical Studies in Rheumatoid Arthritis

Outcome	Pool E (RA All Exposure) OCR (N=2926)
Fatal	8/121 (6.6%)
Not recovered/Not resolved	34/121 (28.1%)
Recovered/Resolved	62/121 (51.2%)
Recovered/Resolved with sequelae	7/121 (6.6%)
Recovering/Resolving	0
Missing	10/121 (8.3%)

OCR = ocrelizumab; RA = rheumatoid arthritis.

Notes: Percentages are based on the total number of events. For frequency counts by outcome, multiple occurrences of the same AE in an individual are counted separately. Malignancies are identified using adverse events falling into the Standard MedDRA Query 'Malignant tumours (narrow)'. For frequency counts by outcome, multiple occurrences of the same AE with the same outcome in an individual are counted only once.

Source: ah_t_ae_out_ev_MAL_spe.

Severity and Nature of Risk:

In the clinical studies with ocrelizumab SC, the two malignancies reported in OCARINA I were Grade 2 (1 event of basal cell carcinoma, 0.8%) and Grade 3 (1 event of papillary thyroid cancer, 0.8%).

The intensity grades reported in ocrelizumab IV clinical studies in MS (MS All Exposure Population; Pool B) are summarized in Table 53 and in RA (RA All Exposure Population; Pool E) in Table 54.

The majority of events in Pool B were of Grade 3 intensity. There was one Grade 4 event (invasive ductal breast carcinoma), and one Grade 5 event (metastatic pancreatic carcinoma).

The majority of events in Pool E were of Grade 2 or 3 intensity. There were 17 Grade 4 events, and seven Grade 5 events.

Table 53 Intensity (Grade) of Malignancies– Clinical Studies in Multiple Sclerosis

Intensity (Grade)	Pool B (MS All Exposure) OCR (N=2147)
1	0
2	3 (0.1%)
3	11 (0.5%)
4	1 (<0.1%)
5	1 (<0.1%)

MS = multiple sclerosis; OCR = ocrelizumab.

Notes: Multiple events in one individual are counted only once (AE with most extreme intensity is used). Malignancies are identified using adverse events falling into the Standard MedDRA Query 'Malignant tumours (narrow)'. The clinical cutoff dates are 22 January 2015 for Study WA21493; 2 April 2015 for Study WA21092; 12 May 2015 for Study WA21093; and 24 July 2015 for Study WA25046.

Source: t_ae_int_MAL_spb2.

Table 54 Intensity (Grade) of Malignancies– Clinical Studies in Rheumatoid Arthritis

Intensity (Grade)	Pool E (RA All Exposure) OCR (N=2926)
1	20 (0.7%)
2	17 (0.6%)
3	32 (1.1%)
4	17 (0.6%)
5	7 (0.2%)

OCR = ocrelizumab; RA = rheumatoid arthritis.

Notes: Multiple events in one individual are counted only once (AE with most extreme intensity is used). Malignancies are identified using adverse events falling into the Standard MedDRA Query 'Malignant tumours (narrow)'.

Source: t_ae_int_MAL_spe.

The time of onset from the first administration of ocrelizumab for breast cancer (the most commonly reported malignancy in Pool B; 0.3% of patients) was between 1 and 3 years after the first dose of ocrelizumab.

The time of onset from the first administration of ocrelizumab IV for basal cell carcinoma (the most commonly reported malignancy in Pool E; 0.9% of patients) was between 3 months and 3 years after the first dose of ocrelizumab.

Impact on quality of life:

Most malignancies have a substantial impact on QOL, and may require repeated hospitalization, long-term treatment and may shorten life expectancy.

Risk factors and risk groups:

In nonclinical safety studies with ocrelizumab, no risk factors that are considered predictive of carcinogenic risk (e.g., chronic inflammation, aberrant proliferation, or dysplasia) were identified.

No risk factors for malignancies, including breast cancer, specific to the MS population have been identified in clinical studies with ocrelizumab. There is no evidence that switching from other DMTs increases the risk for malignancy.

Preventability:

There are no options above and beyond standard cancer screening methods for malignant neoplasms.

Impact on the benefit-risk balance of the product:

Malignancy was reported in 0.9% of the ocrelizumab-treated patients in the MS program. The only cluster identified, which drove the imbalance in malignancy, was for female breast cancer. All malignancies except basal cell carcinomas were serious (majority were of Grade 3) and one of the malignancies (metastatic pancreatic carcinoma) led to death.

Compared against the standardized incidence rates in the SEER database, the standardized malignancy rates in the ocrelizumab treated group in the MS studies were similar.

No conclusion can be made to date concerning the risk of malignancy because of the low number of events and the limited follow-up period. The contrasting and often conflicting roles of B cell subsets on the process of tumor surveillance leads to a significant uncertainty regarding the impact of depleting CD20 mAbs on tumor development, progression and overall incidence. The specific biological plausibility of an increased risk of malignancies, including breast cancer, remains unlikely.

The administration of ocrelizumab to patients with an active malignancy is contraindicated in the EU SmPC.

Although malignancies are frequently serious, their rate in the ocrelizumab MS studies was low, and the biological plausibility unclear. Therefore, the impact of malignancies on the benefit-risk balance of ocrelizumab is considered low.

Public health impact:

No public health impact is foreseen. No additional monitoring beyond the recommendations for cancer screening applicable to the general population is necessary.

SVII.3.1.2.2 PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Potential mechanisms:

The precise mechanisms through which ocrelizumab exerts its therapeutic clinical effects in MS are not fully elucidated but involve immunomodulation through the reduction in the number and function of B cells. Since B cells play an important role in maintaining normal immune response by their involvement in humoral defense, Ag presentation, and coordination of T-cell activity, patients may be at an increased risk of infection following administration of ocrelizumab.

Evidence source(s) and strength of evidence:

Clinical studies of ocrelizumab: WA21092, WA21093, WA25046, WA21493, BN29739, MN30035, MA30005, WA20494, WA20495, WA20496, WA20497, WA18230, ACT2847g, GA00931, JA21963, JA22003, WA20499, WA20500, BO18414, WA40404, BA39730, ML29966, MN39158, MN39159, MA30143, CN41144, and CN42097.

Characterization of the risk:

Background Incidence/Prevalence:

Hematological malignancies are currently ranked as the second most frequent underlying condition for progressive multifocal leukoencephalopathy (PML) after human immunodeficiency virus (HIV) infection and studies have reported higher IRs compared with those in autoimmune indications.

Frequency with 95% CI:

No cases of PML were observed in the clinical trials of ocrelizumab in patients with rheumatoid arthritis, SLE, LN or NHL (for exposure, see Part II, Module SIII.2). These clinical development programs have been discontinued.

No cases of PML were identified in the clinical studies with ocrelizumab SC. No cases of PML were identified in the controlled treatment period of the ocrelizumab IV in MS clinical trials (pivotal Phase III studies and the Phase II study; for exposure, see Part II,

Module SIII.2). To date, no cases have been observed in the ongoing OLEs of these studies or in the other ongoing MS clinical trials.

As of 27 March 2023, there have been 13 confirmed cases of PML in approximately 302,000 patients with MS treated with ocrelizumab reported from post-marketing sources. Of these 13 confirmed PML cases, 11 cases are carry-over cases of PML attributed to prior DMT exposure. In the remaining two cases, the patients had not had prior exposure to DMTs known to be causally associated with PML. One case was confounded by advanced age (PPD years) and the presence of pre-existing lymphopenia. In the remaining case, the patient had not been exposed to a confounding immunosuppressant but did have a concomitant immunosuppressive condition of treatment emergent lymphopenia of unknown etiology (maximum severity: Grade 2).

Seriousness/Outcomes:

All 13 confirmed cases (as of 27 March 2023) were reported as serious. Of the 11 confirmed carry-over cases, 2 patients died, in the remaining 9 cases, event outcome was reported as not recovered/not resolved in 4, recovered/resolved in 2, recovering/resolving in 1 and was not reported in 2 cases. In the 2 confirmed non-carry-over cases, both patients died.

Severity and Nature of Risk:

Progressive multifocal leukoencephalopathy is a rare progressive subacute-demyelinating disorder of the CNS usually leading to death or severe disability.

Impact on quality of life:

Progressive multifocal leukoencephalopathy causes gradual, progressive CNS demyelination, multifocal neurological deficit, and may lead to death, usually within 1 year. Hence, the impact on QOL is very substantial.

Risk factors and risk groups:

Primary infection with or reactivation of the JC-Virus , a polyoma virus that resides in latent form in approximately 50% of patients with MS (Gorelik 2010), can lead to PML. PML has been observed very rarely in patients treated with anti-CD20 antibodies, including ocrelizumab, and mostly associated with risk factors (patient population e.g., lymphopenia, advanced age, polytherapy with immunosuppressants). To date, no specific risk factors associated with anti-CD20 mAbs have been identified (e.g., prolonged exposure) beside the known risk factors.

The main risk factor for PML in patients with MS is previous exposure to natalizumab. The risk of PML is lowest among patients negative for anti-JC virus antibodies, and highest in patients positive for anti-JC virus antibodies, who had taken

immunosuppressants before commencing natalizumab treatment, and who had received 25 to 48 months of natalizumab therapy (Piehl 2011; Prosperini 2011; Bloomgren 2012). The risk of PML increases with the number of natalizumab infusions given (Holmen 2011). Natalizumab-treated patients with prior hematopoietic stem cell transplantation may also be at an increased risk (Fernandez 2012). EMA's recommendations to minimize the risk of PML with natalizumab outline that in patients who have not been treated with immunosuppressants before starting natalizumab, the level of anti-JC virus antibodies relates to the level of risk for PML. Patients with a high Ab index who have not used immunosuppressants before natalizumab and have been treated with natalizumab for more than 2 years are considered at higher risk of PML (EMA 2016b). The mechanisms by which natalizumab increases the risk of PML are unknown, but may involve an altered trafficking of lymphoid cells harboring latent JC virus, decreased immune surveillance, or a combination of these processes (Rudick 2006). A PML risk has also been associated with other MS DMTs, including fingolimod and dimethyl fumarate (Berger 2017).

Preventability:

Ocrelizumab administration must be delayed in patients with an active infection until the infection is resolved.

When initiating ocrelizumab after an immunosuppressive therapy or initiating an immunosuppressive therapy after ocrelizumab, the potential for overlapping PD effects should be taken into consideration. The prescriber should exercise caution when prescribing ocrelizumab taking into consideration the pharmacodynamics of other MS DMTs. Ocrelizumab has not been studied in combination with other MS DMTs. A natalizumab wash-out period of approximately 12 weeks following the last dose should be considered balancing the risk of return of MS disease activity with possible additive immunosuppressive effects of each drug (Natalizumab EU SmPC).

The prescriber must monitor patients 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, the prescriber must withhold dosing with ocrelizumab and evaluate, including magnetic resonance imaging (MRI) scan preferably with contrast (compared with pre-treatment MRI), confirmatory CSF testing for JC Viral DNA and repeat neurological assessments, should be considered. If PML is confirmed, treatment must be discontinued permanently.

Impact on the benefit-risk balance of the product:

Physicians are instructed to be vigilant for early signs and symptoms of PML and if PML is suspected, dosing with ocrelizumab must be withheld and evaluations including MRI scan, CSF testing for JC Viral DNA and repeat neurological assessments performed and if PML is confirmed, treatment must be discontinued permanently.

PML may have a fatal or disabling outcome. To date, the available evidence for a causal association between ocrelizumab and PML, according to the Segec methodology, is assessed as weak and corresponds to a potential (not identified) risk. The reporting rate for PML in the post-marketing setting is very low. Therefore, the impact of PML on the benefit-risk balance of ocrelizumab is considered low.

Public health impact:

Minimal public health impact is foreseen due to the rarity of this event.

SVII.3.1.3 Presentation of the Missing Information

SVII.3.1.3.1 Safety in pregnancy and lactation

Evidence source:

There is a limited amount of data from the use of ocrelizumab in pregnant women. No B cell count data have been collected in infants exposed to ocrelizumab and the potential duration of B-cell depletion in infants is unknown (see section 4.4 of EU SmPC).

Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. 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-cell levels have recovered; therefore, measuring CD19-positive B-cell level, in neonates and infants, prior to vaccination is recommended.

In an embryo-fetal development study in cynomolgus monkeys, there was no evidence of maternal toxicity, teratogenicity, or embryotoxicity following ocrelizumab treatment at 75/100 mg/kg (loading dose/study dose). Flow cytometric analyses demonstrated reductions in B cells (the anticipated pharmacological effect) in maternal and fetal peripheral blood (see Section SII.1.3).

Pregnant patients are excluded from clinical trials. Pregnant patients and in utero to ocrelizumab exposed fetuses, embryo, neonates and infants as well as neonates and infants exposed to ocrelizumab via the breastfeeding mother are vulnerable patient populations. The safety profile is expected to be different from that in the general patient population with MS, because both pregnant women as well as newborn babies have an altered immune system due to physiological mechanisms, which may lead to an

increased risk of infections or altered immune response to vaccinations. These patient populations are in need of further characterization. The MAH is conducting Study BA39732 (MELODIC), a Multisource Surveillance Study of Pregnancy and Infant Outcomes in Ocrelizumab-exposed Women with Multiple Sclerosis to assess pregnancy-related safety data from women with MS exposed to ocrelizumab. The MAH is also conducting a prospective observational pregnancy registry study WA40063 designed to assess and characterize frequency of maternal, fetal, and infant outcomes among women with MS exposed to ocrelizumab. In addition, an ongoing Phase IV open-label placental study (MN42988/MINORE) will evaluate B cell levels in infants potentially exposed to ocrelizumab during pregnancy. Study MN42989 (SOPRANINO), is also an ongoing Phase IV multicenter, open-label study evaluating B-cell levels in infants of lactating women with clinically isolated syndrome or MS receiving ocrelizumab. The MAH will continue to monitor these events as part of routine signal detection activities and is collecting data of maternal, fetal and infant outcomes via enhanced pregnancy follow up process and Studies WA40063 and BA39732 (MELODIC).

SVII.3.1.3.2 Long-term safety of ocrelizumab treatment

Evidence source:

Patients with MS have been treated in clinical trials over a limited amount of time. As can be seen from Table 19, in Pool B of the pivotal trials (patients with RMS or PPMS), of the 2147 patients in the ocrelizumab treated group (4484.5 PYs in total), 1340 patients (62.4%) received at least 4 ocrelizumab doses, which corresponds to 796.6 PYs. Only one patient received 11 doses. Ocrelizumab use over the long-term is considered missing information because normal use is expected to be for a long period and clinical trials were conducted for a set period. The long-term safety of ocrelizumab has to be further characterized. A multi-source non-interventional PASS BA39730 to assess and characterize the long-term safety data from the use of ocrelizumab in patients with MS is ongoing.

In addition, the MAH is conducting Study WA40404 (OHAND): “A Phase IIIb Multicenter, Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Ocrelizumab in Adults with Primary Progressive Multiple Sclerosis” and Study MN39158 (LIBERTO): ‘A single arm, open-label multicenter extension Study to evaluate effectiveness and safety of ocrelizumab in patients with multiple sclerosis previously enrolled in a Hoffmann-La-Roche sponsored ocrelizumab Phase IIIb/IV clinical trial.

SVII.3.1.3.3 Safety in pediatric population

Evidence Source:

The safety and efficacy of ocrelizumab in children and adolescents has been studied in the ongoing Phase II open-label study of ocrelizumab in children and adolescents with RRMS (WA39085/OPERETTA 1). The objective of the study is to evaluate the safety,

tolerability, pharmacokinetics, and pharmacodynamic effects of ocrelizumab in the pediatric population aged 10-17 years old.

The MAH recently initiated a Phase III study (WN42086/OPERETTA 2) with the first patient enrolled in May 2022. This study will evaluate the safety and efficacy of ocrelizumab in comparison with fingolimod in children and adolescents with RRMS.

At the DLP (27 March 2023) of the most recent PBRER RDR 1122140 (reporting interval 28 March 2022 to 27 March 2023) cumulative and new information received from the Global Safety Database (cases of patients with age <18 years), cases of drug exposure in utero or via breastfeeding, and the published literature was reviewed and evaluated.

Based on the data analyses in this PBRER, the pattern of AEs reported and the use of ocrelizumab in pediatric population was in line when compared to the cumulative data. Upon review of the cases, no safety concern specific to the pediatric population has been identified with ocrelizumab.

The safety in pediatric patients remains to be under missing information and needs to be further characterized.

The MAH will continue to monitor pediatric patients treated off-label with ocrelizumab through routine PV activities.

The results of the ocrelizumab non-clinical immunotoxicity Study 15-3109 conducted in juvenile cynomolgus monkeys are summarized in Section SII.1.3.1.

PART II: MODULE SVIII— SUMMARY OF THE SAFETY CONCERNS

Table 55 Summary of safety concerns

Summary of safety concerns	
Important identified risks	Infusion-related reactions (observed with the IV formulation) and injection reactions (observed with the SC formulation) Infections
Important potential risks	Malignancies including breast cancer Progressive multifocal leukoencephalopathy
Missing information	Safety in pregnancy and lactation Long-term safety of ocrelizumab treatment Safety in pediatric population

IV = intravenous; SC = subcutaneous

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES ROUTINE PHARMACOVIGILANCE ACTIVITIES BEYOND ADVERSE REACTIONS REPORTING AND SIGNAL DETECTION

Specific adverse reaction follow-up questionnaire for progressive multifocal leukoencephalopathy

The purpose of these follow-up questionnaires is to ensure an adequate follow-up and acquisition of all appropriate information for all suspected PML cases reported from any source.

Specific pregnancy and infant health guided questionnaire for safety in pregnancy and lactation

Ocrelizumab specific the ‘1st Year of Infants Life Guided Questionnaire’ has been designed to collect and solicit follow-up information on the first year of life of all infants born to women who have been exposed to ocrelizumab at any time during pregnancy or within six months prior to conception, respectively, as part of routine PV. Outcomes in infants exposed to ocrelizumab via breastfeeding are also in scope. The reason for the infant’s first year of life questionnaire is to collect additional information on the health of the infant during the first year of life to better assess and describe potential adverse infant outcomes (e.g., infections and impaired vaccination response) among women treated with ocrelizumab during pregnancy or within six months prior to conception or of breastfeeding women. This infant’s first year of life follow-up questionnaire has been implemented for worldwide use for pregnancies where the pregnancy outcome was reported as live birth and the pregnant mother had been exposed to ocrelizumab during pregnancy and/or during the six months prior to conception, or where the infant was exposed to ocrelizumab via breastfeeding (which is defined as partial or complete

breastfeeding of an infant whose mother received an ocrelizumab infusion during the past 6 months).

Other forms of routine pharmacovigilance activities for pregnancy and/or breastfeeding

The Roche standard pregnancy follow-up process was implemented for all products to request additional information on the medication history of the exposed parent, relevant medical history for the mother and father, previous obstetric history, the current pregnancy, fetal and infant conditions, and results of tests and investigations for any pregnancy complication or congenital abnormality during pregnancy or within the first year of the infant's life.

Cumulative data will be presented in Periodic Safety Update Reports (PSURs)/PBRERs.

Refer to Annex 4 for questionnaires.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Safety concern: Infections

Table 56 BA39730- PASS

Study/activity short name and title: A Long-Term Surveillance of Ocrelizumab-Treated Patients with Multiple Sclerosis
Study Objectives: The primary objective is: To estimate (overall and by MS type) the event rates of SAEs, including malignancy and serious infections, following ocrelizumab treatment in patients with MS. The secondary objective is: To compare the incidence of each serious safety event between ocrelizumab-exposed patients with RMS and patients with RMS exposed to other approved disease modifying therapies (DMTs: overall, and by individual DMTs if possible), within the same data source. If sufficient data are available, an exploratory objective of this study is to compare the safety profile of patients with PPMS exposed to ocrelizumab to the safety profile of patients with PPMS not exposed to any DMTs.
Study design: A multi-source, non-interventional post authorization safety study
Study populations: Multiple sclerosis patients exposed to ocrelizumab and MS patients treated with other approved DMTs.
Milestones: Start date of study: 2019 End of study 2028 Cumulative reports submitted with PBRER Interim report 1 (Comparative safety report): 2022 Interim report 2 (Comparative safety report): 2024 Interim report 3 (Comparative safety report): 2026 Final report of study results: 2029

DMT = disease modifying therapies, MS = Multiple sclerosis, SAE = Serious adverse event, RMS = relapsing forms of multiple sclerosis; PASS = post authorization safety study; PBRER = Periodic Benefit Risk Evaluation Report; PPMS = primary progressive multiple sclerosis.

Table 57 WA40404–Efficacy and safety of ocrelizumab in adults with PPMS later in their disease course

Study/activity short name and title: A Phase IIIb Multicenter, Randomised, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of ocrelizumab in Adults with Primary Progressive Multiple Sclerosis
Rationale and Study Objectives: To evaluate the safety and efficacy of ocrelizumab (Ocrevus®) compared with placebo in patients EDSS 3 to 8 using 9-Hole Peg Test as the primary efficacy outcome, and 12 week confirmed disability progression as a key secondary endpoint. Baseline assessment of features characteristic of imaging inflammatory activity (T1 Gd enhancing MRI lesions and/or new/enlarging T2 lesions) will be undertaken to explore treatment effect in subgroups with different inflammatory profiles
Study design: Multicenter, randomized, double-blind, placebo controlled
Study populations: Adults patients with primary progressive multiple sclerosis
Milestones Final report: June 2028

EDSS = Expanded Disability Status Scale; MRI = Magnetic resonance imaging; PPMS = primary progressive multiple sclerosis.

Safety concern: Malignancies including breast cancer

Study BA39730 is described in Table 56 above and study WA40404 is described in Table 57 above.

Safety concern: Progressive multifocal leukoencephalopathy

Study BA39730 is described in Table 56 above.

Safety concern: Safety in pregnancy and lactation

Table 58 BA39732- Non-interventional PASS

Study/activity short name and title: A multi-source surveillance study of pregnancy and infant outcomes in ocrelizumab-exposed women with multiple sclerosis
Rationale and Study Objectives: The objectives are as follows: To estimate the frequency of selected adverse pregnancy outcomes in women with MS exposed to ocrelizumab during the defined exposure window (i.e., spontaneous abortions, fetal death /stillbirths, elective abortions, preterm births, C-sections, and urinary and other infections in pregnancy). To estimate the frequency of selected adverse fetal/neonatal/infant outcomes at birth and up to the first year of life of infants from pregnancies in women with MS exposed to ocrelizumab—i.e., major congenital malformations, small for gestational age, adverse effects on immune system development (e.g., severe infectious disease in the first year of life). To compare the frequency of each safety event of interest between ocrelizumab-exposed pregnant women with MS and two comparison cohorts: (1) primary comparison cohort —pregnancies in women with MS who have not been exposed to ocrelizumab (overall and in two strata—pregnancies exposed to any non-ocrelizumab DMTs approved for the treatment of MS or any new DMT approved during the study period [subcohort 1a], and pregnancies not exposed to these DMTs [subcohort 1b]), and (2) secondary comparison cohort —pregnancies in women without MS who have not been exposed to ocrelizumab.
Study design: An observational study using multiple sources of secondary data, with validation of selected outcomes
Study populations: Ocrelizumab-exposed women with multiple sclerosis
Milestones Protocol submission: November 2019 Start of study dataset creation: 2018 Study finish: June 2029 Final report: June 2030

DMT = disease-modifying treatment; MS = multiple sclerosis; PASS = post authorization safety study.

Safety concern: Long-term safety of ocrelizumab treatment - PASS

Study BA39730 is described in Table 56 above and study WA40404 is described in Table 57 above.

Safety concern: Safety in Pediatric Population

On 2 August 2017, the Sponsor received a partial clinical hold from FDA indicating that the studies in pediatric patients may not be initiated until the investigation related to the premature deaths in juvenile animal toxicology study has been concluded and a

monitoring strategy in pediatric patients has been identified. On 29 March 2019, the Sponsor submitted a response package to FDA to address the partial clinical hold in pediatric studies, including the final juvenile toxicity report for Study 15-3109. Upon review of the response package, the FDA indicated on 26 April 2019 that the partial clinical hold was removed and that the Sponsor may proceed with the proposed pediatric study WA39085 (OPERETTA 1), which is currently ongoing. The MAH recently initiated a Phase III study (WN42086/OPERETTA 2) with the first patient enrolled in May 2022. This study will evaluate the safety and efficacy of ocrelizumab in comparison with fingolimod in children and adolescents with RRMS.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 59 On-going and planned additional pharmacovigilance activities

Study/ Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
NA	NA	NA	NA	NA
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
NA	NA	NA	NA	NA
Category 3 - Required additional pharmacovigilance activities				
BA39730- A Long-Term Surveillance of Ocrelizumab-Treated Patients with Multiple Sclerosis Ongoing	The primary objective is: • To estimate (overall and by MS type) the event rates of SAEs, including malignancy and serious infections, following ocrelizumab treatment in patients with MS. The secondary objective is: • To compare the incidence of each serious safety event between ocrelizumab-exposed patients with RMS and patients with RMS exposed to other approved disease modifying therapies (DMTs: overall, and by individual DMTs if possible), within the same data source. If sufficient data are available, an exploratory objective of this study is to compare the safety profile of patients	Malignancies including breast cancer Progressive multi focal leukoencephalopathy Long-term safety of ocrelizumab treatment Infections	Start date of study End of study Semi-annual safety reports Interim report 1 Interim report 2 Interim report 3 Final report of study results	2019 2028 Cumulative reports submitted with PBRER 2022 2024 2026 2029

Study/ Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
	with PPMS exposed to ocrelizumab to the safety profile of patients with PPMS not exposed to any DMTs.			
BA39732- A multi-source surveillance study of pregnancy and infant outcomes in ocrelizumab-exposed women with multiple sclerosis (MS) Ongoing	• To estimate the frequency of selected adverse pregnancy outcomes in women with MS exposed to ocrelizumab during the defined exposure window (i.e., spontaneous abortions, fetal death/stillbirths, elective abortions, preterm births, C-sections, and urinary and other infections in pregnancy) • To estimate the frequency of selected adverse fetal/neonatal/infant outcomes at birth and up to the first year of life of infants from pregnancies in women with MS exposed to ocrelizumab—i.e., major congenital malformations, small for gestational age, adverse effects on immune system development (e.g., severe infectious disease in the first year of life) • To compare the frequency of each safety event of interest between ocrelizumab-exposed pregnant women with MS and two comparison cohorts: (1) primary comparison cohort —pregnancies in women with MS who have not been exposed to ocrelizumab (overall and	Safety in pregnancy and lactation	Protocol Submission: Start of study dataset creation: Study finish Final report	November 2019 2018 June 2029 June 2030

Study/ Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
	in two strata—pregnancies exposed to any non-ocrelizumab DMTs approved for the treatment of MS or any new DMT approved during the study period [subcohort 1a], and pregnancies not exposed to these DMTs [subcohort 1b]) and (2) secondary comparison cohort — pregnancies in women without MS who have not been exposed to ocrelizumab.			
Study WA40404- A Phase IIIb Multicenter, Randomised, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Ocrelizumab in Adults with Primary Progressive Multiple Sclerosis Ongoing	To evaluate the safety and efficacy of ocrelizumab (Ocrevus®) compared with placebo in patients EDSS 3 to 8 using 9HPT as the primary efficacy outcome, and 12 week confirmed disability progression as a key secondary endpoint. Baseline assessment of features characteristic of imaging inflammatory activity (T1 Gd enhancing MRI lesions and/or new/enlarging T2 lesions) will be undertaken to explore treatment effect in subgroups with different inflammatory profiles	Infection Malignancies including breast cancer Long-term safety of ocrelizumab treatment	Final report	June 2028

9HPT = 9-Hole Peg Test; DMT = disease-modifying therapies; EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging; MS = multiple sclerosis; NA = not applicable; PBRER = Periodic Benefit-Risk Evaluation Report; PPMS = primary progressive multiple sclerosis; RMS = relapsing forms of multiple sclerosis; SAE = serious adverse events.

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing post-authorization efficacy studies with ocrelizumab.

PART V: RISK-MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK-MINIMIZATION ACTIVITIES)

RISK MINIMIZATION PLAN
V.1 ROUTINE RISK MINIMIZATION MEASURES
Table 60 Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk minimization activities
Infusion-related reactions (observed with the IV formulation) and injection reactions (observed with the SC formulation)	**Routine risk communication:** Section 4.2 of the EU SmPC-Posology and method of administration Section 4.4 of the EU SmPC- Special warnings and precautions for use Section 4.8 of the EU SmPC-Undesirable effects Sections 2, 3, and 4 of the EU Package Leaflet **Routine risk minimization activities recommending specific clinical measures to address the risk:** **Injection reactions (observed with SC formulation)** • Physicians should alert patients that injection reactions can occur within 24 hours of injection. • Patients should be observed for at least one hour after the initial dose of the medicinal product for any symptom of severe injection reactions. • Appropriate resources for the management of severe reactions of severe injection reactions, hypersensitivity reactions and/or anaphylactic reactions should be available for the initial dose of the medicinal product. • Shortly before injection, patients should receive premedication to reduce the potential for occurrence of injection reactions. Refer to Section 4.2 of the EU SmPC for ocrelizumab SC-(Posology and method of

Safety concern	Routine risk minimization activities
	administration) and to Section 4.4 (Special warnings and precautions for use) for detailed information. • **Infusion-related reactions (observed with the IV formulation)** Withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each ocrelizumab infusion. • Premedication for infusion-related reactions is required. • Appropriate resources for the management of severe reactions such as serious IRR, hypersensitivity reactions and/or anaphylactic reactions should be available. • Patients should be observed for at least one hour after the completion of the ocrelizumab infusion for any symptom of IRR. Physicians should alert patients that an IRR can occur within 24 hours of infusion. Refer to Section 4.2 of the EU SmPC for ocrelizumab IV-(Posology and method of administration) and to Section 4.4 (Special warnings and precautions for use) for detailed information. **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** Ocrelizumab is a medicinal product subject to restricted medical prescription: Section 4.2 of the EU SmPC states: **SC formulation**: Treatment should be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions. **IV formulation:** Treatment should be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions and who have access to appropriate medical support to manage severe reactions such as serious infusion related reactions (IRRs).

Safety concern	Routine risk minimization activities
Infections	**Routine risk communication:** Section 4.3 of the EU SmPC-Contraindications Section 4.4 of the EU SmPC- Special warnings and precautions for use Section 4.8 of the EU SmPC-Undesirable effects Section 2 and 4 of the EU Package Leaflet **Routine risk minimization activities recommending specific clinical measures to address the risk:** • An active infection must be excluded prior to ocrelizumab administration, because the infusion must be delayed in patients with an active infection until the infection is resolved. • It is recommended to verify the patient's immune status before dosing since severely immunocompromised patients should not be treated. • Physicians should take prompt action for patients presenting with pneumonia because there may be an increased risk of aspiration pneumonia and severe pneumonia in patients treated with ocrelizumab. • HBV screening should be performed before initiation of treatment with ocrelizumab as per local guidelines because patients with active HBV infection should not be treated with ocrelizumab. Patients with positive serology; carriers of HBV should be referred to a liver disease expert before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation. • For PML, see under respective risk. Refer to Section 4.3 of the EU SmPC-(Contraindications) and to Section 4.4 (Special warnings and precautions for use) for detailed information. **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** Ocrelizumab is a medicinal product subject to restricted medical prescription.

Safety concern	Routine risk minimization activities
Malignancies including breast cancer	**Routine risk communication:** Section 4.3 of the EU SmPC- Contraindications Section 4.4 of the EU SmPC- Special warnings and precautions for use Section 5.3 of the EU SmPC- Preclinical safety data Section 2 of the EU Package Leaflet **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Patients should be asked whether they have an active malignancy, are actively being monitored for a malignancy, or have known risk factor for malignancy, because patients with a known active malignancy should not be treated with ocrelizumab, and individual benefit risk should be considered in patients with known risk factors for malignancies and in patients who are being actively monitored for recurrence of malignancy. Patients should be instructed to follow standard breast cancer screening per local guidelines. Refer to Section 4.3 of the EU SmPC- (Contraindications) and to Section 4.4 (Special warnings and precautions for use) for detailed information. **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** Ocrelizumab is a medicinal product subject to restricted medical prescription.
Progressive multifocal leukoencephalopathy	**Routine risk communication:** Section 4.4 of the EU SmPC- Special warnings and precautions for use Section 2 of the EU Package Leaflet **Routine risk minimization activities recommending specific clinical measures to address the risk:** Physicians should be vigilant for the early signs and symptoms of PML, which can include any new onset, or worsening of neurological signs or symptoms. If PML is suspected, dosing with ocrelizumab must be withheld. Evaluation including MRI scan

Safety concern	Routine risk minimization activities
	preferably with contrast (compared with pre-treatment MRI), confirmatory CSF testing for JC Viral Deoxyribonucleic acid and repeat neurological assessments, should be considered. If PML is confirmed treatment must be discontinued permanently. As for any other active infection, current PML is a contraindication for treatment with ocrelizumab. Refer to Section 4.3 of the EU SmPC- (Contraindications) and to Section 4.4 (Special warnings and precautions for use) for detailed information. **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** Ocrelizumab is a medicinal product subject to restricted medical prescription.
Safety in pregnancy and lactation	**Routine risk communication:** Section 4.4 of the EU SmPC- Special warnings and precautions for use Section 4.6 of the EU SmPC- Section 4.6 Fertility, pregnancy and lactation Section 5.3 of the EU SmPC-Preclinical safety data Section 2 of the EU Package Leaflet. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Women of childbearing potential should be instructed that they should use contraception while receiving ocrelizumab and for 12 months after the last infusion of ocrelizumab. • For activities required in case that an infant is exposed in utero to ocrelizumab, please refer to the risk of impaired immunisation response. • Human IgGs are known to be excreted in breast milk during the first few days after birth (colostrum period), which decrease to low concentrations soon afterwards.

Safety concern	Routine risk minimization activities
	If clinically needed, ocrelizumab can be used during breastfeeding starting a few days after birth. Refer to Section 4.4 (Special warnings and precautions for use) and Section 4.6 (Fertility, pregnancy and lactation) for detailed information. **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** Ocrelizumab is a medicinal product subject to restricted medical prescription.
Long-term safety of ocrelizumab treatment	**Routine risk communication:** Section 3 of the EU Package Leaflet **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** Ocrelizumab is a medicinal product subject to restricted medical prescription.
Safety in pediatric population	**Routine risk communication:** Section 4.2 of the EU SmPC "Posology and method of administration" Section 2 of the EU Package Leaflet **Routine risk minimization activities recommending specific clinical measures to address the risk:** None. **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** Ocrelizumab is a medicinal product subject to restricted medical prescription.

CSF= Cerebrospinal fluid, EU = European Union; HBV= hepatitis B virus, IRR= infusion related reactions, IV = intravenous, PML= Progressive multifocal leukoencephalopathy, MRI = Magnetic resonance imaging, SC = subcutaneous, SmPC= Summaries of product characteristic.

V.2. ADDITIONAL RISK MINIMIZATION MEASURES

Routine risk minimization activities as described in Part V.1 are considered sufficient to manage the safety concerns of the medicinal products.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 61 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Infusion-related reactions (observed with the IV formulation) and injection reactions (observed with the SC formulation)	**Routine risk communication:** Section 4.2 of the EU SmPC-Posology and method of administration Section 4.4 of the EU SmPC- Special warnings and precautions for use Section 4.8 of the EU SmPC-Undesirable effects Sections 2, 3, and 4 of the EU Package Leaflet **Routine risk minimization activities recommending specific clinical measures to address the risk:** **Injection reactions (observed with SC formulation)** • Physicians should alert patients that injection reactions can within 24 hours of injection. • Patients should be observed for at least one hour after the initial dose of the medicinal product for any symptom of severe injection reactions. • Appropriate resources for the management of severe reactions of severe injection reactions, hypersensitivity reactions and/or anaphylactic reactions should be available for the initial dose of the medicinal product. • Shortly before injection, patients should receive premedication to reduce the potential for occurrence of injection reactions. Refer to Section 4.2 of the EU SmPC for ocrelizumab SC-(Posology and method of administration) and to Section 4.4 (Special warnings and precautions for use) for detailed information. **Infusion-related reactions (observed with the IV formulation)**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• Withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each ocrelizumab infusion. • Premedication for infusion-related reactions is required. • Appropriate resources for the management of severe reactions such as serious IRR, hypersensitivity reactions and/or anaphylactic reactions should be available. • Patients should be observed for at least one hour after the completion of the ocrelizumab infusion for any symptom of IRR. Physicians should alert patients that an IRR can occur within 24 hours of infusion. Refer to Section 4.2 of the EU SmPC- Posology and method of administration) and to Section 4.4 (Special warnings and precautions for use) for detailed information. **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** Ocrelizumab is a medicinal product subject to restricted medical prescription: Section 4.2 of the EU SmPC states: **SC formulation**: Treatment should be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions. **IV formulations**: Treatment should be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions and who have access to appropriate medical support to manage severe reactions such as serious infusion related reactions (IRRs). **Additional risk minimization measures:** None	

Safety concern	Risk minimization measures	Pharmacovigilance activities
Infections	**Routine risk communication:** Section 4.3 of the EU SmPC- Contraindications Section 4.4 of the EU SmPC- Special warnings and precautions for use Section 4.8 of the EU SmPC-Undesirable effects Section 2 and 4 of the EU Package Leaflet **Routine risk minimization activities recommending specific clinical measures to address the risk:** • An active infection must be excluded prior to ocrelizumab administration because the infusion must be delayed in patients with an active infection until the infection is resolved. • It is recommended to verify the patient's immune status before dosing since severely immunocompromised patients should not be treated. • Physicians should take prompt action for patients presenting with pneumonia because there may be an increased risk of aspiration pneumonia and severe pneumonia in patients treated with ocrelizumab. • HBV screening should be performed before initiation of treatment with ocrelizumab as per local guidelines because patients with active HBV infection should not be treated with ocrelizumab. Patients with positive serology; carriers of HBV should be referred to a liver disease expert before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation. • For PML, see under respective risk. Refer to Section 4.3 of the EU SmPC- (Contraindications) and to Section 4.4 (Special warnings and precautions for use) for detailed information.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study BA39730 Study WA40404

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Other risk minimization measures beyond the Product Information: ***Medicine's legal status*:** Ocrelizumab is a medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None	
Malignancies including breast cancer	**Routine risk communication:** Section 4.3 of the EU SmPC- Contraindications Section 4.4 of the EU SmPC- Special warnings and precautions for use Section 5.3 of the EU SmPC- Preclinical safety data Section 2 of the EU Package Leaflet **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Patients should be asked whether they have an active malignancy, are actively being monitored for a malignancy, or have known risk factor for malignancy, because patients with a known active malignancy should not be treated with ocrelizumab, and individual benefit risk should be considered in patients with known risk factors for malignancies and in patients who are being actively monitored for recurrence of malignancy. Patients should be instructed to follow standard breast cancer screening per local guidelines. Refer to Section 4.3 of the EU SmPC- (Contraindications) and to Section 4.4 (Special warnings and precautions for use) for detailed information. **Other risk minimization measures beyond the Product Information:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study BA39730 Study WA40404

Safety concern	Risk minimization measures	Pharmacovigilance activities
	***Medicine's legal status*:** Ocrelizumab is a medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None	
Progressive multifocal leukoencephalopathy	**Routine risk communication:** Section 4.4 of the EU SmPC- Special warnings and precautions for use Section 2 of the EU Package Leaflet **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Physicians should be vigilant for the early signs and symptoms of PML, which can include any new onset, or worsening of neurological signs or symptoms. If PML is suspected, dosing with ocrelizumab must be withheld. Evaluation including MRI scan preferably with contrast (compared with pre-treatment MRI), confirmatory CSF testing for JC Viral Deoxyribonucleic acid and repeat neurological assessments, should be considered. If PML is confirmed treatment must be discontinued permanently. As for any other active infection, current PML is a contraindication for treatment with ocrelizumab. Refer to Section 4.3 of the EU SmPC- (Contraindications) and to Section 4.4 (Special warnings and precautions for use) for detailed information. **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** Ocrelizumab is a medicinal product subject to restricted medical prescription.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Follow-up questionnaire **Additional pharmacovigilance activities:** Study BA39730

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: None	
Safety in pregnancy and lactation	**Routine risk communication:** Section 4.4 of the EU SmPC- Special warnings and precautions for use Section 4.6 of the EU SmPC- Section 4.6 Fertility, pregnancy and lactation Section 5.3 of the EU SmPC-Preclinical safety data Section 2 of the EU Package Leaflet. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Women of childbearing potential should be instructed that they should use contraception while receiving ocrelizumab and for 12 months after the last infusion of ocrelizumab. • For activities required in case that an infant is exposed in utero to ocrelizumab, please refer to the risk of impaired immunisation response. • Human IgGs are known to be excreted in breast milk during the first few days after birth (colostrum period), which decrease to low concentrations soon afterwards. If clinically needed, ocrelizumab can be used during breastfeeding starting a few days after birth. Refer to Section 4.4 (Special warnings and precautions for use) and Section 4.6 (Fertility, pregnancy and lactation) for detailed information. **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire **Additional pharmacovigilance activities:** Study BA39732

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Ocrelizumab is a medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None	
Long-term safety of ocrelizumab treatment	**Routine risk communication:** Section 3 of the EU Package Leaflet. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** Ocrelizumab is a medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study BA39730 Study WA40404
Safety in pediatric population	**Routine risk communication:** Section 4.2 of the EU SmPC "Posology and method of administration" Section 2 of the EU Package Leaflet. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** Ocrelizumab is a medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

CSF= Cerebrospinal fluid, EU = European Union; HBV= hepatitis B virus, IRR= infusion related reactions, IV = intravenous, PML= Progressive multifocal leukoencephalopathy, MRI = Magnetic resonance imaging, SC = subcutaneous, SmPC= Summaries of product characteristic.

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PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR OCREVUS (OCRELIZUMAB)

This is a summary of the risk management plan for ocrelizumab. The risk management plan details important risks of ocrelizumab, how these risks can be minimized, and how more information will be obtained about ocrelizumab risks and uncertainties (missing information).

Ocrelizumab summary of product characteristics and its package leaflet give essential information to healthcare professionals and patients on how ocrelizumab should be used.

This summary of the risk management plan for ocrelizumab should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report.

Important new concerns or changes to the current ones will be included in updates of the ocrelizumab risk management plan.

I. THE MEDICINE AND WHAT IT IS USED FOR

Ocrelizumab is authorized for the treatment of relapsing and primary progressive forms of multiple sclerosis (see EU Summary of Product Characteristics for the full indication). It contains ocrelizumab as the active substance and it is given by intravenous or subcutaneous route.

Further information about the evaluation of ocrelizumab benefits can be found in ocrelizumab European Public Assessment Report, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage.

https://www.ema.europa.eu/en/medicines/human/EPAR/ocrevus

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of ocrelizumab, together with measures to minimize such risks and the proposed studies for learning more about ocrelizumab risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and summary of product characteristics addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of ocrelizumab is not yet available, it is listed under 'missing Information' below.

II.A List of Important Risks and Missing Information

Important risks of ocrelizumab are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of ocrelizumab. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Infusion-related reactions (observed with the IV formulation) and injection reactions (observed with the SC formulation) • Infections
Important potential risks	• Malignancies including breast cancer • Progressive multifocal leukoencephalopathy
Missing information	• Safety in pregnancy and lactation • Long-term safety of ocrelizumab treatment • Safety in pediatric population

IV = intravenous; SC = subcutaneous.

II.B Summary of Important Risks

Important identified risk: Infusion-related reactions (observed with the IV formulation) and injection reactions (observed with the SC formulation)	
Evidence for linking the risk to the medicine	Clinical studies of ocrelizumab: WA21092, WA21093, WA25046, WA21493, BN29739, MN30035, MA30005, WA20494, WA20495, WA20496, WA20497, WA18230, ACT2847g, GA00931, JA21963, JA22003, WA20499, WA20500, BO18414, MA30143 substudy, CN41144, and CN42097.
Risk factors and risk groups	Symptoms of injection reactions have been more frequently reported with the first injection. Reactions related to infusion of ocrelizumab occur most often at the first infusion in patients who have not had this type of infusion before. In patients who receive ocrelizumab, the risk of infusion-related reactions was reduced by 2-fold or more when both oral antihistamine and methylprednisolone were administered before the infusion, compared with methylprednisolone alone (with the exception of Dose 1, infusion 2). Adding analgesics/antipyretics to oral histamines did not appear to have additional benefit. Dosing intervals other than every 6 months have not been systematically studied in multiple sclerosis patients and it is not known whether delaying dosing beyond the 6-month dosing schedule would be associated with an increased likelihood of infusion-related reactions beyond what was observed with the first infusion. The low number of patients with treatment-induced anti-drug antibodies did not allow for an evaluation of the impact of anti-drug antibodies on rate and intensity of infusion-related reactions.
Risk minimization measures	**Routine risk communication:** Section 4.2 of the European Union Summary of Product Characteristics - Posology and method of administration Section 4.4 of the European Union Summary of Product Characteristics - Special warnings and precautions for use Section 4.8 of the European Union Summary of Product Characteristics - Undesirable effects Sections 2, 3, and 4 of the European Union Package Leaflet **Routine risk minimization activities recommending specific clinical measures to address the risk:** **Injection reactions (observed with SC formulation)** • Physicians should alert patients that injection reactions can occur within 24 hours of injection. • Patients should be observed for at least one hour after the initial dose of the medicinal product for any symptom of severe injection reactions.

Important identified risk: Infusion-related reactions (observed with the IV formulation) and injection reactions (observed with the SC formulation)	
	• Appropriate resources for the management of severe reactions of severe injection reactions, hypersensitivity reactions and/or anaphylactic reactions should be available for the initial dose of the medicinal product. • Shortly before injection, patients should receive premedication to reduce the potential for occurrence of injection reactions. Refer to Section 4.2 of the European Union Summary of Product Characteristics for ocrelizumab SC (Posology and method of administration) and to Section 4.4 (Special warnings and precautions for use) for detailed information. **Infusion-related reactions (observed with the IV formulation** • Withholding of medicines for high blood pressure should be considered for 12 hours prior to and throughout each ocrelizumab infusion. • Treatment with other medicines such as corticosteroid and antihistamine to prevent or reduce possible side effects such as infusion-related reactions are required before each infusion; you may also receive medicines used to reduce fever. • Appropriate resources should be available for the management of severe reactions such as serious infusion-related reactions, or allergic reactions to ocrelizumab or any of the other ingredients of this medicine. • Patients should be observed for at least one hour after the completion of the ocrelizumab infusion for any symptom of infusion-related reaction. Physicians should alert patients that an infusion-related reaction can occur within 24 hours of infusion. Section 4.2 of the European Union Summary of Product Characteristics - Posology and method of administration) and Section 4.4 (Special warnings and precautions for use) includes more detailed information. **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** Ocrelizumab is a medicinal product subject to restricted medical prescription. **SC formulation**: Treatment with ocrelizumab should be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions. **IV formulation**: Treatment with ocrelizumab should be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions and who have

Important identified risk: Infusion-related reactions (observed with the IV formulation) and injection reactions (observed with the SC formulation)	
	access to appropriate medical support to manage severe reactions such as serious infusion-related reactions. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

IV = intravenous; SC = subcutaneous.

Important identified risk: Infections	
Evidence for linking the risk to the medicine	Clinical studies of ocrelizumab: WA21092, WA21093, WA25046, WA21493, BN29739, MN30035, MA30005, WA20494, WA20495, WA20496, WA20497, WA18230, ACT2847g, GA00931, JA21963, JA22003, WA20499, WA20500, BO18414, WA40404, BA39730, ML29966, MN39158, MA30143, CN41144, and CN42097.
Risk factors and risk groups	Previous or concomitant medicines that affect the immune system such as chemotherapy, immunosuppressants or other medicines used to treat multiple sclerosis can be important contributing factors. Exploratory analyses were carried out in order to identify prognostic and treatment-emergent risk factors for infections and serious infections. Risk factors for serious infections were only explored for rheumatoid arthritis because event numbers were too low in the multiple sclerosis studies. Data from the rheumatoid arthritis cohort indicated that ocrelizumab treatment might increase the risk of serious infections for patients from Asia on long term steroid treatment, notably on the ocrelizumab 1000 mg dose. However, these observations do not reach statistical significance and are confounded with Asian region, which cannot be correlated with Asian ethnicity, lower body weight, as well as increased treatment with the drug. In the multiple sclerosis population, where patients were treated with ocrelizumab as monotherapy, there was no imbalance in serious infections observed. Of note, in the multiple sclerosis clinical program, the population only received intermittently corticosteroids for symptomatic treatment of relapse, and included a very low number of Asian patients, with no clinical sites in Asia. In the multiple sclerosis studies, mean and median levels of neutrophils (a type of white blood cell) did not change during treatment with ocrelizumab. Most events were of Grade 1 (mild) and 2 (moderate) neutropenia (low numbers of neutrophils) without any temporal pattern associated with infections. Anti-CD20 antibody therapy may trigger Hepatitis B virus reactivation in patients with a history of Hepatitis B virus infection. However, no such reports in multiple sclerosis patients treated with ocrelizumab were reported. Similarly, immunomodulatory

Important identified risk: Infections	
	therapy may trigger reactivation of hidden herpes virus in patients who had a herpes infection in the past.
Risk minimization measures	**Routine risk communication:** Section 4.3 of the European Union Summary of Product Characteristics – Contraindications Section 4.4 of the European Union Summary of Product Characteristics – Special warnings and precautions for use Section 4.8 of the European Union Summary of Product Characteristics –Undesirable effects Section 2 and 4 of the European Union Package Leaflet **Routine risk minimization activities recommending specific clinical measures to address the risk:** • An active infection must be excluded prior to ocrelizumab administration because the infusion must be delayed in patients with an active infection until the infection is resolved. • It is recommended to verify the patient's immune status before dosing since patients with a severely weakened immune system should not be treated. • Physicians should take prompt action for patients presenting with pneumonia (lung infection) because there may be an increased risk of aspiration pneumonia (a type of lung inflammation that is due to material from the stomach or mouth entering the lungs) and severe pneumonia in patients treated with ocrelizumab. • Hepatitis B virus screening should be performed before initiation of treatment with ocrelizumab as per local guidelines because patients with active Hepatitis B virus infection should not be treated with ocrelizumab. Patients with positive serology (blood serum diagnostic); carriers of Hepatitis B virus should be referred to a liver disease expert before start of treatment and should be monitored and managed following local medical standards to prevent Hepatitis B reactivation. • For progressive multifocal leukoencephalopathy (a rare and life-threatening brain infection), see under respective risk. Section 4.3 of the European Union Summary of Product Characteristics – (Contraindications) and Section 4.4 (Special warnings and precautions for use) includes more detailed information. **Other risk minimization measures beyond the Product**

Important identified risk: Infections	
	Information: ***Medicine's legal status*:** Ocrelizumab is a medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study BA39730, Study WA40404 See section II.C of this summary for an overview of the post-authorization development plan.

Important potential risk: Malignancies including breast cancer	
Evidence for linking the risk to the medicine	Clinical studies of ocrelizumab: WA21092, WA21093, WA25046, WA21493, BN29739, MN30035, MA30005, WA20494, WA20495, WA20496, WA20497, WA18230, ACT2847g, GA00931, JA21963, JA22003, WA20499, WA20500, BO18414, WA40404, BA39730, MA30143, MN39158, MN39159, ML29966, CN41144, and CN42097.
Risk factors and risk groups	In nonclinical safety studies (animal studies) with ocrelizumab, no risk factors that are considered predictive of cancer (e.g., chronic inflammation, unusual cell proliferation, or dysplasia) were identified. No risk factors for cancers, including breast cancer, specific to the multiple sclerosis population have been identified in clinical studies with ocrelizumab. There is no evidence that switching from other disease-modifying therapies increases the risk for cancer.
Risk minimization measures	**Routine risk communication:** Section 4.3 of the European Union Summary of Product Characteristics – Contraindications Section 4.4 of the European Union Summary of Product Characteristics – Special warnings and precautions for use Section 5.3 of the European Union Summary of Product Characteristics – Preclinical safety data Section 2 of the European Union Package Leaflet **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Patients should be asked whether they have an active cancer, are actively being monitored for a cancer, or have known risk factor for cancer, because patients with a known active cancer should not be treated with ocrelizumab, and individual benefit risk should be considered in patients with known risk factors for cancers and in patients who are being actively monitored for recurrence of cancer. Patients should be instructed to follow standard breast cancer screening per local guidelines.

Important potential risk: Malignancies including breast cancer	
	Section 4.3 of the European Union Summary of Product Characteristics – (Contraindications) and Section 4.4 (Special warnings and precautions for use) includes more detailed information. **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** Ocrelizumab is a medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study BA39730, Study WA40404 See section II. C of this summary for an overview of the post-authorization development plan.

Important potential risk: Progressive multifocal leukoencephalopathy	
Evidence for linking the risk to the medicine	Clinical studies of ocrelizumab: WA21092, WA21093, WA25046, WA21493, BN29739, MN30035, MA30005, WA20494, WA20495, WA20496, WA20497, WA18230, ACT2847g, GA00931, JA21963, JA22003, WA20499, WA20500, BO18414, WA40404, BA39730, ML29966, MN39158, MN39159, MA30143, CN41144, and CN42097.

Important potential risk: Progressive multifocal leukoencephalopathy	
Risk factors and risk groups	Primary infection with or reactivation of the JC-Virus, a polyoma virus that resides in hidden form in approximately 50% of patients with multiple sclerosis, can lead to a rare and life-threatening viral brain infection called progressive multifocal leukoencephalopathy (PML). PML has been observed very rarely in patients treated with anti-CD20 antibodies, including ocrelizumab, and has mostly been associated with the presence of risk factors (patient population e.g., lymphopenia, advanced age or polytherapy with immunosuppressants). To date, no specific risk factors associated with anti-CD20 monoclonal antibodies have been identified (e.g., prolonged exposure) beside the known risk factors. The main risk factor for PML in patients with multiple sclerosis is previous exposure to natalizumab. The risk of PML is lowest among patients negative for anti-JC-Virus antibodies, and highest in patients positive for anti-JC-Virus antibodies, who had taken immunosuppressants before commencing natalizumab treatment, and who had received 25 to 48 months of natalizumab therapy. The risk of PML increases with the number of natalizumab infusions given. Natalizumab-treated patients with prior hematopoietic stem cell transplantation (a procedure in which a person receives blood-forming stem cells [cells from which all blood cells develop] from a genetically similar, but not identical, donor) may also be at an increased risk. The European Medicines Agency recommendations to minimize the risk of PML with natalizumab outline that in patients who have not been treated with immunosuppressants before starting natalizumab, the level of anti-JC virus antibodies relates to the level of risk for PML. The patients with a high antibody level who have not used immunosuppressants before natalizumab and have been treated with natalizumab for more than 2 years are considered at higher risk of PML. The mechanisms by which natalizumab increases the risk of PML are unknown but may involve an altered trafficking of lymphoid cells harboring latent JC-Virus, decreased immune surveillance, or a combination of these processes. A PML risk has also been associated with other multiple sclerosis disease-modifying therapies, including fingolimod and dimethyl fumarate.
Risk minimization measures	**Routine risk communication**: Section 4.4 of the European Union Summary of Product Characteristics – Special warnings and precautions for use Section 2 of the European Union Package Leaflet **Routine risk minimization activities recommending specific clinical measures to address the risk**: • Physicians should be alert for the early signs and symptoms of PML (a rare and life-threatening viral brain infection) which can include any new onset, or worsening of neurological signs or symptoms (such as memory lapses, trouble thinking, difficulty walking, sight loss, changes in the way of talking). If PML is suspected, dosing with ocrelizumab must be withheld. Evaluation including magnetic resonance

Important potential risk: Progressive multifocal leukoencephalopathy	
	imaging (MRI) scan preferably with contrast (compared with pre-treatment MRI), confirmatory cerebrospinal fluid testing for JC Viral Deoxyribonucleic acid presence, and repeat neurological assessments, should be considered. If PML is confirmed, treatment must be discontinued permanently. As for any other active infection, current PML is a contraindication for treatment with ocrelizumab. Section 4.3 of the European Union Summary of Product Characteristics – (Contraindications) and Section 4.4 (Special warnings and precautions for use) includes more detailed information. **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status***: Ocrelizumab is a medicinal product subject to restricted medical prescription. **Additional risk minimization measures**: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study BA39730 See section II.C of this summary for an overview of the post-authorization development plan.

CD20 = cluster of differentiation 20; MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy.

Missing information: Safety in pregnancy and lactation	
Risk minimization measures	**Routine risk communication:** Section 4.4 of the European Union Summary of Product Characteristics - Special warnings and precautions for use Section 4.6 of the European Union Summary of Product Characteristics - Section 4.6 Fertility, pregnancy and lactation Section 5.3 of the European Union Summary of Product Characteristics -Preclinical safety data Section 2 of the European Union Package Leaflet. **Routine risk minimization activities recommending specific clinical measures to address the risk**: • Women of childbearing potential should be instructed that they should use contraception while receiving ocrelizumab and for 12 months after the last infusion of ocrelizumab. • For activities required in case that an infant is exposed in utero to ocrelizumab, please refer to the risk of impaired immunisation response. • Human IgGs are known to be excreted in breast milk during the first few days after birth (colostrum period), which decrease to low concentrations soon afterwards.

Missing information: Safety in pregnancy and lactation	
	If clinically needed, ocrelizumab can be used during breastfeeding starting a few days after birth. Section 4.4 of the European Union Summary of Product Characteristics (Special warnings and precautions for use) and Section 4.6 (Fertility, pregnancy and lactation) includes more detailed information. **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status***: Ocrelizumab is a medicinal product subject to restricted medical prescription. **Additional risk minimization measures**: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study BA39732 See section II. C of this summary for an overview of the post-authorization development plan.

Missing information: Long-term safety of ocrelizumab treatment	
Risk minimization measures	**Routine risk communication:** Section 3 of the European Union Package Leaflet **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Ocrelizumab is a medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study BA39730, Study WA40404 See section II.C of this summary for an overview of the post-authorization development plan.

Missing information: Safety in pediatric population	
Risk minimization measures	**Routine risk communication:** Section 4.2 of the European Union Summary of Product Characteristics Posology and method of administration Section 2 of the European Union Package Leaflet

Missing information: Safety in pediatric population	
	Routine risk minimization activities recommending specific clinical measures to address the risk: None **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** Ocrelizumab is a medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of ocrelizumab.

II.C.2 Other studies in post-authorization development plan

Study short name: BA39730- A long-term surveillance of ocrelizumab-treated patients with multiple sclerosis

Purpose of the study:

The primary objective is:

- To estimate (overall and by multiple sclerosis [MS] type) the event rates of serious adverse events, including malignancy and serious infections, following ocrelizumab treatment in patients with MS.

The secondary objective is:

- To compare the incidence of each serious safety event between ocrelizumab-exposed patients with relapsing forms of multiple sclerosis (RMS) and patients with RMS exposed to other approved disease modifying therapies (DMTs: overall, and by individual DMTs if possible), within the same data source.

If sufficient data are available, an exploratory objective of this study is to compare the safety profile of patients with primary progressive multiple sclerosis (PPMS) exposed to ocrelizumab to the safety profile of patients with PPMS not exposed to any DMTs.

Study short name: BA39732 - A multi-source surveillance study of pregnancy and infant outcomes in ocrelizumab-exposed women with multiple sclerosis.

Purpose of the study:

The objectives are as follows:

- To estimate the frequency of selected adverse pregnancy outcomes in women with MS exposed to ocrelizumab during the defined exposure window (i.e., spontaneous abortions, fetal death/stillbirths, elective abortions, preterm births, C-sections, and urinary and other infections in pregnancy)
- To estimate the frequency of selected adverse fetal/neonatal/infant outcomes at birth and up to the first year of life of infants from pregnancies in women with MS exposed to ocrelizumab—i.e., major congenital malformations, small for gestational age, adverse effects on immune system development (e.g., severe infectious disease in the first year of life)
- To compare the frequency of each safety event of interest between ocrelizumab-exposed pregnant women with MS and two comparison cohorts:

– (1) primary comparison cohort—pregnancies in women with MS who have not been exposed to ocrelizumab (overall and in two strata—pregnancies exposed to any non-ocrelizumab DMTs approved for the treatment of MS or any new DMT approved during the study period [subcohort 1a], and pregnancies not exposed to these DMTs [subcohort 1b])

– (2) secondary comparison cohort—pregnancies in women without MS who have not been exposed to ocrelizumab.

Study short name: WA40404 A Phase IIIb multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of ocrelizumab in adults with primary progressive multiple sclerosis.

Purpose of the study:

To evaluate the safety and efficacy of ocrelizumab compared with placebo in patients (with Expanded Disability Status Scale score 3 to 8) using the 9-Hole Peg Test as the primary efficacy outcome, and 12 week confirmed disability progression as a key secondary endpoint.

Baseline assessment of features characteristic of imaging inflammatory activity (T1 Gadolinium-enhancing magnetic resonance imaging lesions and/or new/enlarging T2 lesions) will be undertaken to explore treatment effect in subgroups with different inflammatory profiles.

ANNEX 1:

EUDRAVIGILANCE INTERFACE

(NOT APPLICABLE)

ANNEX 2:

TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME

ANNEX 2

TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAM

Table 1 Planned and Ongoing Studies

Study	Summary of Objectives	Safety Concerns Addressed	Protocol Link Milestones
BA39730 - A long-term surveillance of ocrelizumab-treated patients with multiple sclerosis Ongoing Category 3	The primary objective is: • To estimate (overall and by MS type) the event rates of SAEs, including malignancy and serious infections, following ocrelizumab treatment in patients with MS. The secondary objective is: • To compare the incidence of each serious safety event between ocrelizumab-exposed patients with RMS and patients with RMS exposed to other approved disease modifying therapies (DMTs: overall, and by individual DMTs if possible), within the same data source. If sufficient data are available, an exploratory objective of this study is to compare the safety profile of patients with PPMS exposed to ocrelizumab to the safety profile of patients with PPMS not exposed to any DMTs.	Infections Malignancies including breast cancer Progressive multifocal leukoencephalopathy Long-term safety of ocrelizumab treatment	Start date of study: 2019 End of study: 2028 Semi-annual safety reports: Cumulative reports submitted with PBRER Interim report 1: 2022 Interim report 2: 2024 Interim report 3: 2026 Final report of study results: 2029

Study	Summary of Objectives	Safety Concerns Addressed	Protocol Link Milestones
BA39732 - A multi-source surveillance study of pregnancy and infant outcomes in ocrelizumab-exposed women with multiple sclerosis Ongoing Category 3	The objectives are as follows: • To estimate the frequency of selected adverse pregnancy outcomes in women with MS exposed to ocrelizumab during the defined exposure window (i.e., spontaneous abortions, fetal death/stillbirths, elective abortions, preterm births, C-sections, and urinary and other infections in pregnancy) • To estimate the frequency of selected adverse fetal/neonatal/infant outcomes at birth and up to the first year of life of infants from pregnancies in women with MS exposed to ocrelizumab—i.e., major congenital malformations, small for gestational age, adverse effects on immune system development (e.g., severe infectious disease in the first year of life) • To compare the frequency of each safety event of interest between ocrelizumab-exposed pregnant women with MS and two comparison cohorts: (1) primary comparison cohort—pregnancies in women with MS who have not been exposed to ocrelizumab (overall and in two strata—pregnancies exposed to any non-ocrelizumab DMTs approved for the treatment of MS or any new DMT approved during the study period [subcohort 1a], and pregnancies not exposed to these DMTs [subcohort 1b]) and (2) secondary	Safety in pregnancy and lactation	Protocol submission: November 2019 Start of study dataset creation: 2018 Study finish: June 2029 Final report: June 2030

Study	Summary of Objectives	Safety Concerns Addressed	Protocol Link Milestones
	comparison cohort—pregnancies in women without MS who have not been exposed to ocrelizumab.		
Study WA40404 A Phase IIIb multicenter, randomised, double-blind, placebo controlled study to evaluate the efficacy and safety of ocrelizumab in adults with primary progressive multiple sclerosis Ongoing Category 3	To evaluate the safety and efficacy of ocrelizumab (Ocrevus®) compared with placebo in patients EDSS 3 to 8 using 9HPT as the primary efficacy outcome, and 12 week confirmed disability progression as a key secondary endpoint. Baseline assessment of features characteristic of imaging inflammatory activity (T1 Gd-enhancing MRI lesions and/or new/enlarging T2 lesions) will be undertaken to explore treatment effect in subgroups with different inflammatory profiles.	Long-term safety of ocrelizumab treatment Infection Malignancies including breast cancer	Final report: June 2028

9HPT = 9-Hole Peg Test; DMT = disease-modifying therapies; EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging; MS = multiple sclerosis; PBRER = Periodic Benefit-Risk Evaluation Report; PPMS = primary progressive multiple sclerosis; RMS = relapsing forms of multiple sclerosis; SAE = serious adverse events.

Table 2 Completed Studies

Study	Summary of Objectives	Safety concerns addressed	Date of Final Study Report Submission Link to Report
Monkey Study 17-1133 - Non-clinical expanded pre- and postnatal development study in cynomolgus monkeys to assess the immunization status of babies born to mothers treated with ocrelizumab. Complete Category 3	To assess immunization status of babies born to mothers treated with ocrelizumab in cynomolgus monkeys.	Safety in pregnancy and lactation	Final report: 26 June 2020
Study BN29739: A Phase IIIb, multicentre, randomized, parallel-group, open-label study to evaluate the effects of ocrelizumab on immune responses in patients with relapsing forms multiple sclerosis. Complete Category 3	The primary efficacy objective for this study is as follows: • To characterize the humoral immune response (IgG) to tetanus toxoid adsorbed vaccine in patients with RMS who are treated with ocrelizumab (ocrelizumab; Group A), compared with that of patients with RMS who are not treated with ocrelizumab (Group B). The secondary efficacy objectives for this study are as follows: 1. To characterize the humoral immune response (IgG and IgM) to the 23-PPV in Group A patients (Groups A1 and A2) compared with Group B patients.	Impaired immunization response	Final CSR Report No. 1111938. CSR sign off date: 21 April 2022

Study	Summary of Objectives	Safety concerns addressed	Date of Final Study Report Submission Link to Report
	2. To characterize the humoral immune response (IgG and IgM) in ocrelizumab-treated patients to 23-PPV boosted by a subsequent 13-PCV vaccine booster (Group A1) compared with unboosted 23-PPV (Group A2). 3. To characterize the humoral immune response (IgG and IgM) to keyhole limpet hemocyanin in Group A patients compared with Group B patients. 4. To characterize the humoral immune response (hemagglutination inhibition titers) to influenza vaccine in ocrelizumab-treated patients (Group A2) patients compared with patients not treated with ocrelizumab (Group B). 5. To evaluate the long-term effects of ocrelizumab on MRI parameters of disease activity and progression during the Optional Ocrelizumab Extension Period of the study.		

13-PCV = 13-valent pneumococcal conjugate; 23-PPV = 23-valent pneumococcal polysaccharide vaccine; CSR = clinical study report; Ig = immunoglobulin; MRI = magnetic resonance imaging; RMS = relapsing forms of multiple sclerosis.

ANNEX 3:

PROTOCOLS FOR PROPOSED, ONGOING AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

PROTOCOLS FOR PROPOSED, ONGOING AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

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1. PART A: REQUESTED PROTOCOLS OF STUDIES IN THE PHARMACOVIGILANCE PLAN, SUBMITTED FOR REGULATORY REVIEW WITH THIS UPDATED VERSION OF THE RMP

Not applicable.

2. PART B: REQUESTED AMENDMENTS OF PREVIOUSLY APPROVED PROTOCOLS OF STUDIES IN THE PHARMACOVIGILANCE PLAN, SUBMITTED FOR REGULATORY REVIEW WITH THIS UPDATED VERSION OF THE RMP

Not applicable.

3. PART C: PREVIOUSLY AGREED PROTOCOLS FOR ON-GOING STUDIES AND FINAL PROTOCOLS NOT REVIEWED BY THE COMPETENT AUTHORITY

Approved Protocols

Study	Protocol Title	Protocol Number / Version	Protocol Date	Procedure Number and Date of Outcome
BA39730	A long-term surveillance of ocrelizumab-treated patients with multiple sclerosis	v1.0	31 October 2018	EMA/CHMP/PRAC/905044/2019 final assessment report dated 31 January 2019
BA39732	A multi-source surveillance study of pregnancy and infant outcomes in ocrelizumab-exposed women with multiple sclerosis	v4.0	14 March 2023	Not applicable
WA40404	A Phase IIIb multicenter, randomised, double-blind, placebo controlled study to evaluate the efficacy and safety of ocrelizumab in adults with primary progressive multiple sclerosis	v5.0	13 October 2022	Not applicable

Final Protocols Not Reviewed or Not Approved:

Not applicable.

TITLE:	**LONG-TERM SURVEILLANCE OF OCRELIZUMAB-TREATED PATIENTS WITH MULTIPLE SCLEROSIS (MANUSCRIPT STUDY)**
PROTOCOL NUMBER:	BA39730
VERSION NUMBER:	1.0
AUTHOR:	David Wormser, Ph.D. F. Hoffmann-La Roche Ltd 4070 Basel Switzerland
DATE FINAL:	See electronic date stamp below
EU PAS REGISTER NUMBER:	EUPAS28619
ACTIVE SUBSTANCE:	L04AA36 (ocrelizumab)
STUDIED MEDICINAL PRODUCT:	OCREVUS®
PRODUCT REFERENCE NUMBER:	RO4964913
PROCEDURE NUMBER:	EMEA/H/C/004043
JOINT PASS	No
RESEARCH QUESTION AND OBJECTIVES:	The research question is to assess and characterize the long-term safety data from the use of ocrelizumab in patients with multiple sclerosis (MS) overall and by MS type (e.g., relapsing forms of multiple sclerosis [RMS], primary progressive multiple sclerosis

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
Fontoura, Paulo (fontourp)	Company Signatory	31-Oct-2018 14:02:34
Angst-Wu, Leanne (angstwul)	Deputy QPPV	31-Oct-2018 09:38:33

	[PPMS], other). The primary objective is to estimate (overall and by MS type) the event rates of serious adverse events (SAEs), including malignancy and serious infections, following ocrelizumab treatment in patients with MS. The secondary objective is to compare the incidence of each serious safety event between ocrelizumab-exposed patients with RMS and patients with RMS exposed to other approved disease modifying therapies (DMTs; overall, and by individual DMTs if possible), within the same data source. If sufficient data are available, an exploratory objective of this study is to compare the safety profile of patients with PPMS exposed to ocrelizumab to the safety profile of patients with PPMS not exposed to any DMTs.
COUNTRIES OF STUDY POPULATION:	Denmark, France, Germany, Italy, Sweden, and countries determined to be contributing safety data to MSBase
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration GmbH Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen Germany
MAH CONTACT PERSON:	Joanna Evershed Roche Products Ltd 6 Falcon Way Welwyn Garden City AL7 1TW United Kingdom

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ARTIS	Anti-Rheumatic Therapies in Sweden
BMSD	Big MS Data
BSRBR	British Society for Rheumatology Biologics Register
CI	confidence interval
CNS	central nervous system
CRO	contract research organization
DMT	disease modifying therapy
eCRF	electronic case report form
EC	Ethics Committee
EDC	electronic data capture
EDMUS	European Database for Multiple Sclerosis
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
E.U.	European Union
FDA	(United States) Food and Drug Administration
GPP	Good Pharmacoepidemiology Practice
HR	hazard ratio
IgG1	immunoglobulin G1
IRB	Institutional Review Board
ISPE	International Society of Pharmacoepidemiology
JCV	John Cunningham virus
MAH	marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSDN	(Italian) Multiple Sclerosis Database Network
MSDS3D	Multiple Sclerosis Documentation System 3D
NI-PASS	non-interventional post-authorization safety study
NMSC	non-melanoma skin cancer
OFSEP	Observatoire Français de la Sclérose en Plaques
PASS	post-authorization safety study
PBRER	periodic benefit-risk evaluation report

Abbreviation	Definition
PML	progressive multifocal leukoencephalopathy
PPMS	primary progressive multiple sclerosis
PRAC	Pharmacovigilance Risk Assessment Committee
PS	propensity score
RMS	relapsing forms of multiple sclerosis
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SPMS	secondary progressive multiple sclerosis
U.K.	United Kingdom
U.S.	United States

3. RESPONSIBLE PARTIES

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4. ABSTRACT

TITLE:	**LONG-TERM SURVEILLANCE OF OCRELIZUMAB-TREATED PATIENTS WITH MULTIPLE SCLEROSIS (MANUSCRIPT STUDY)**
PROTOCOL NUMBER:	BA39730
VERSION NUMBER:	1.0
DATE OF SYNOPSIS:	See electronic date stamp on the cover page

Rationale and Background

Ocrelizumab, a recombinant, humanized monoclonal immunoglobulin G1 (IgG1) antibody that selectively targets CD20-expressing B cells, received European Medicines Agency (EMA) approval in January 2018 for the treatment of relapsing forms of multiple sclerosis (RMS) or primary progressive multiple sclerosis (PPMS) (OCREVUS® Summary of Product Characteristics).

Ocrelizumab has demonstrated superior efficacy in a double-blind, randomized Phase II trial (Study WA21493) compared with placebo in relapsing-remitting multiple sclerosis (RRMS) (Kappos et al. 2011); in a double-blind, randomized, placebo-controlled Phase III trial in PPMS (ORATORIO [Study WA25046]) (Montalban et al. 2017); and in two double-blind, randomized Phase III trials compared with interferon β-1a in RMS (OPERA I [Study WA21092] and OPERA II [Study WA21093]) (Hauser et al. 2017). Frequencies of adverse events (AEs) and serious adverse events (SAEs) in the ocrelizumab group were similar to interferon β-1a or placebo (OPERA studies and ORATORIO study, respectively). Pooled trial data indicated an imbalance in malignancies in the ocrelizumab treatment group versus pooled interferon β-1a and placebo. The only cluster of events that could be identified was for female breast cancer; incidences remained within the range of placebo data from clinical trials in multiple sclerosis (MS) and epidemiological data. Thus, no firm conclusion could be made concerning malignancy risk, due to the low number of events and limited follow-up.

This longitudinal observational study is part of the European Union (E.U.) risk management plan and is designed to further assess the long-term safety profile of ocrelizumab in the real world setting. The study will provide safety data for a 10 year period after ocrelizumab launch, specifically targeting the rate of SAEs, including serious infections and malignancies.

Research Question and Objectives

The research question is to assess and characterize the long-term safety data from the use of ocrelizumab in patients with MS (overall and by MS type [e.g, RMS, PPMS, other])

The primary objective for this study is:

- to estimate (overall and by MS type) the event rates of SAEs, including malignancy and serious infections, following ocrelizumab treatment in patients with MS.

The secondary objective for this study is:

- to compare the incidence of each serious safety event between ocrelizumab-exposed patients with RMS and patients with RMS exposed to other approved disease

modifying therapies (DMTs: overall, and by individual DMTs if possible), within the same data source.

If sufficient data are available, an exploratory objective of this study is to compare the safety profile of patients with PPMS exposed to ocrelizumab to the safety profile of patients with PPMS not exposed to any DMTs.

Study Design

This post-authorisation safety study (PASS) is a multi-source, multi-country, non-interventional, longitudinal cohort study based on secondary use of data captured for patients with MS who have newly initiated treatment with ocrelizumab or another DMT after the marketing authorization date of ocrelizumab in the target country. Patients on ocrelizumab or another DMT will be followed for up to a maximum of 10 years following their first exposure to the DMT.

Comparisons of the incidence of SAEs including malignancies and infections will be made between patients with MS initiating ocrelizumab treatment and those initiating treatment with other approved DMTs. As there are no approved DMTs for certain forms of MS (e.g., PPMS), the comparison will also involve patients with MS not treated with any DMTs, if feasible.

Population

This study will include patients with MS who have initiated treatment with ocrelizumab or another DMT during the study period, or patients with MS not on DMT therapy in routine clinical practice.

Patients must meet the following criteria for inclusion in the study:

- A diagnosis of MS
- Aged 18 years or older
- Ocrelizumab group:
  - Patient must be newly treated with ocrelizumab during the study observational period
- DMT comparator group:
  - Patient who has never received treatment with ocrelizumab (at any time in the complete available history) and must be newly treated with an approved DMT other than ocrelizumab during the study observational period
- Non-DMT comparator group:
  - Patient who has never received ocrelizumab or any other DMT within the complete history recorded within available medical records and during individual follow-up in the study observational period

Patients who meet the following criterion will be excluded from study participation:

- Patient who has received ocrelizumab in the context of a previous clinical trial or Compassionate Use program, if information is available

Variables

Primary Safety Variables

- Serious adverse events, including death (date of onset and detail)
- Non-melanoma skin cancer (NMSC)

Secondary Variables

- Patient-specific information (date of birth, date of death, sex, country of residence)

- Disease-specific information (date of MS onset, MS type, Expanded Disability Status Scale [EDSS], relapses, John Cunningham virus [JCV] antibody status and, if available, index)
- MS treatment information (all previous and current DMTs)
- If available in data source:
    - Patient-specific information (employment status, smoking status, weight, height, ethnicity)
    - Disease-specific information (date of MS diagnosis, MS diagnostic criteria used, MRI information, lab test results, comorbid diseases, past major disease, family history of malignancies)
    - Treatment information (MS symptomatic medications and any other medications)
    - Pregnancy (Y/N)

Data Sources

This PASS will use data from the following MS-specific registry sources:

- Multiple Sclerosis Documentation System 3D (MSDS3D) in Germany
- Big MS Data (BMSD) Group, a collaboration of MS registries from Denmark, France, Italy, Sweden, and the international registry MSBase

Study Size

The target study size for this study will be approximately 5000 patients with MS exposed to ocrelizumab and 3500 patients with MS treated with other DMTs across all data sources. Assuming ocrelizumab does not increase the risk of malignancy excluding NMSC (true hazard ratio [HR] = 1.0, incidence rate of 3.7 per 1000 patient-years), an overall study duration of 10 years with a 2 year patient selection period and a follow-up period of at least 8 years, a drop-out rate of 5% per year in each arm, and a one-sided type-I error of 0.025, the study (expecting 278 malignancies) could rule out a HR ≥1.43 with 80% power.

For female breast cancer and serious infections, the outcome and HR (incidence rate per 1000 person years, expected number of events) expected to be ruled out are as follows: breast cancer, 1.79 (2.1,111); progressive multifocal leukoencephalopathy (PML), 10 (0.04, not estimable); herpes-related infection, 2.6 (0.4, 47); candida-related infections, 1.59 (2.1, 171); respiratory infections, 1.20 (16.6, 1052); and urinary tract infections, 1.16 (26.6, 1582).

Data Analysis

For semi-annual safety reports, data will be analyzed every 6 months. These reports will have aggregated data from each observational source on safety events occurring in each treatment group, which includes analysis of the primary objective.

- The total number of safety events (incident and recurrent) and unadjusted rates per 100 patient-years with 95% confidence intervals (CIs) will be provided for each treatment group, ocrelizumab and other DMTs (all DMTs combined and individual DMTs). Information on other DMTs will be provided only from registries which allow sharing of such data.
- For analyses of malignancy and PML, an ever-exposed model will be applied that includes all person-time observed since the first drug dose in the study until censorship. For all other SAEs, the analysis will be based on a time-on-drug approach. For analyses of death, both approaches will be used.
- First, event rates (i.e., accounting for multiple events) will be estimated based on the Poisson distribution and presented over the cumulative follow-up period and

stratified into one-year periods. Then, incidence rates (i.e., accounting for first event only) will be estimated.

Interim and final comparative safety reports addressing the secondary objective will be prepared 4, 6, 8, and 10 years after the study start.

- Within each data source, the ocrelizumab group will be compared to each DMT comparator group using propensity score (PS) based methods (inverse probability of treatment weighting or PS adjustment) using variables likely to include, but not limited to: age, sex, calendar time, disease duration prior to treatment initiation, proportion of disease duration spent treated with DMT, EDSS, comorbidities, prior DMT exposure, concomitant drugs (e.g., other concomitant immunomodulators/ suppressants), pre-baseline relapse activity, and (if appropriate) country.
- Unadjusted and adjusted HRs will be presented from Cox proportional hazard models or appropriate causal inference methods.
- Meta-analyses of results across the data sources will be conducted using aggregated data from each source.

Milestones

Start Date of Study

The study start date will be the date of the study dataset creation at the first data source. The planned start date is in 2018, following the launch of ocrelizumab in the E.U. in January 2018.

End of Study

The end of the study will be the date from which analysis of data required to fulfil study objectives is complete. The planned end of study date is in 2028. The final report will be provided in 2029.

Length of Study

This study will last approximately 10 years.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Study milestones are given in Table 1. All study reports will be submitted to the Health Authorities through scheduled periodic benefit-risk evaluation reports (PBRERs).

Table 1 Study Milestones

Milestone	Planned Date
Registration of protocol in the E.U. PAS register	After approval of protocol
Start date of study	2018
End of study	2028
Semi-annual safety reports	Scheduled regulatory safety reporting every 6 months
Interim report 1 (Comparative safety report)	2022
Interim report 2 (Comparative safety report)	2024
Interim report 3 (Comparative safety report)	2026
Final report of study results	2029
Registration of the results in the E.U. PAS register	After approval of final study report

E.U. = European Union; PAS = post-authorization study.

Data will be extracted from the selected data sources biannually for semi-annual safety reports on new and cumulative safety events. For registries using linkage to other national registers to collect information, the linkage may not be performed for every semi-annual safety report. However, all information will be included in the interim and final reports. The interim and final comparative safety reports will be prepared 4, 6, 8, and 10 years after the study start.

The reporting periods for the study will differ by data source due to differences in launch date in each country, as seen in Table 2.

Table 2 Reporting Periods by Data Source and Country for Comparative Safety Interim Reports and Final Report

Data source	Country	Expected Launch Date Ocrelizumab	Interim Report 1 2022	Interim Report 2 2024	Interim Report 3 2026	Final Report 2029
MSDS3D	Germany	January 2018	Up to 4 years after launch date	Up to 6 years after launch date	Up to 8 years after launch date	Up to 10 years after launch date
MSBase[a]	Several European countries[b], Australia, Canada, and U.S.	Varies by country				
OFSEP[a]	France	Q2 2019				
Danish MS Registry[a]	Denmark	January 2018				
Swedish MS Registry[a]	Sweden	Q3 2018				
Italian MS Registry[a]	Italy	Q3 2018				

MSDS3D = Multiple Sclerosis Documentation System 3D; OFSEP = Observatoire Français de la Sclérose en Plaques; MS = multiple sclerosis.

[a] A member of the Big MS Data Group of registries (see Section 9.4.2)

[b] Including Czech Republic, Netherlands, Spain, UK

7. RATIONALE AND BACKGROUND

7.1 RATIONALE

Multiple sclerosis (MS) is a chronic, inflammatory, and demyelinating disease of the central nervous system (CNS) that affects approximately 2.3 million people worldwide (MSIF 2013). While MS is a global disease, the prevalence of MS is highest in North America and Europe (140 and 108 per 100,000 respectively) (MSIF 2013). MS is commonly diagnosed between 20 to 40 years of age (Tullman 2013). Overall, women are affected approximately twice as often as men, except in individuals with the primary progressive form of the disease, where there is no gender difference in prevalence (MSIF 2013; Tullman 2013). The reasons for these observed differences are unclear.

In approximately 85% of patients, MS begins as a relapsing, episodic disorder with gradual complete or incomplete recovery (relapsing-remitting MS [RRMS]). If left untreated, the majority of these patients will transition to a progressive form, characterized by worsening neurologic disability either with or without occasional superimposed relapses (relapsing or non-relapsing secondary progressive MS [SPMS]). Patients accumulate disability as a result of incomplete recovery from acute relapses and/or gradual disease progression (Tullman 2013). Primary progressive MS (PPMS) is a less common form of MS, accounting for approximately 10% of all cases. It is characterized by a progressive course from disease onset, with infrequent superimposed discrete clinical attacks or relapses (Lublin 2014).

Evidence suggests that inflammation is present in the CNS throughout all MS clinical courses, from RRMS to SPMS and in PPMS (Frischer et al. 2009). Differences between disease phenotypes are due to the differential contribution of each of the inflammatory and neurodegenerative processes to the pathophysiology of CNS damage over time (Frischer et al. 2009; Frischer et al. 2015).

OCREVUS® (ocrelizumab) was approved by the European Medicines Agency (EMA) on January 12, 2018 for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease and for the treatment of adult patients with early PPMS in terms of disease duration and level of disability (see the OCREVUS® Summary of Product Characteristics for further details). In the United States (U.S.), OCREVUS® was approved by the U.S. Food and Drug Administration (FDA) on March 28, 2017 for the treatment of adult patients with RMS or PPMS (OCREVUS® U.S. Prescribing Information).

Ocrelizumab is a recombinant, humanized monoclonal immunoglobulin G1 (IgG1) antibody that selectively targets CD20-expressing B cells. Ocrelizumab has demonstrated superior efficacy in a double-blind, randomized Phase II trial (Study WA21493) compared with placebo in RRMS (Kappos et al. 2011); in two identical, randomized, active-controlled Phase III trials (OPERA I [Study WA21092] and OPERA II [Study WA21093]) compared with interferon β-1a in RMS (Hauser et al. 2017); and in another double-blind randomized,

placebo-controlled Phase III trial (ORATORIO [Study WA25046]) versus placebo in PPMS (Montalban et al. 2017). Results of these studies show that depletion of CD20+ B cells leads to a significant impact on a broad range of clinical measures of the disease, including disability progression, in addition to an impact on magnetic resonance imaging (MRI) outcomes related to disease progression and reflective of neural tissue loss.

This longitudinal observational study is part of the risk management plan and designed to further assess the long-term safety profile of ocrelizumab in the real world setting. The study will provide safety data for a 10 year period after ocrelizumab launch in Europe by assessing rates of serious adverse events.

7.2 BACKGROUND

Ocrelizumab has demonstrated a favorable safety profile in RMS and patients with PPMS (Hauser et al. 2017; Montalban et al. 2017). The proportion of patients with adverse events (AEs) was similar in ocrelizumab-treated patients compared with interferon β-1a (both 83.3%) or placebo-treated patients (95.1% [ocrelizumab] vs. 90.0% [placebo]). The most common AEs were infusion-related reactions, nasopharyngitis, and urinary tract infections. Patients treated with ocrelizumab (versus interferon β-1a or placebo) reported more herpes virus-associated infections than patients who received interferon β-1a or placebo (RMS trials: 5.9% vs. 3.4%; PPMS trial: 4.7% vs. 3.3%), infusion-related reactions (RMS trials: 34.3% vs. 9.7%; PPMS trial: 39.9% vs. 25.5%), and upper respiratory tract infections (RMS trials: 15.2% vs 10.5%; PPMS trial: 10.9% vs. 5.9%). The overall percentage of patients reporting a serious infection was lower in ocrelizumab-treated patients in the RMS trials compared to interferon β-1a-treated patients (1.3% vs. 2.9%), and similar in the PPMS trial (6.2% [ocrelizumab] and 5.9% [placebo]) (Hauser et al. 2017; Montalban et al. 2017).

Eight deaths occurred during the controlled treatment periods of the pivotal Phase III ocrelizumab trials (RMS trials: 2 interferon β-1a-treated patients [suicide and mechanical ileus] and 1 ocrelizumab-treated patient [suicide]; PPMS trial: 1 placebo patient [road traffic accident] and 4 ocrelizumab-treated patients [pulmonary embolism, pneumonia, pancreatic carcinoma, and pneumonia aspiration]) (Hauser et al. 2017; Montalban et al. 2017). Although the proportion of patients experiencing serious adverse events (SAEs) was similar between ocrelizumab and the comparator groups (RMS trials: 6.9% [ocrelizumab] and 8.7% [interferon β-1a]; PPMS trial: 20.4% [ocrelizumab] and 22.2% [placebo]), data are needed to confirm the safety and efficacy of ocrelizumab over a long treatment duration and, importantly, in a clinical practice setting.

In controlled studies, the pooled overall incidence of a first neoplasm among patients with MS who were treated with ocrelizumab (Phase II study, OPERA I and II, and ORATORIO) was 0.40 per 100 patient-years of exposure (6467 patient-years of exposure), as compared with 0.20 per 100 patient-years for pooled comparator groups (interferon β-1a or placebo, 2053 patient-years of exposure) (Montalban et al. 2017).

In Phase II trials, two neoplasms were reported in patients with RRMS treated with ocrelizumab; none in patients receiving placebo (Kappos et al. 2011; Genentech, Inc. 2017). In RMS trials (OPERA I and II), neoplasms occurred in 4 patients (0.5%, n=4/825) treated with ocrelizumab (including 2 patients with invasive ductal breast carcinoma) during the controlled treatment period, and 2 patients (0.2%, n=2/826) treated with interferon β-1a (Hauser et al. 2017). In the controlled treatment period of the PPMS trial (ORATORIO), neoplasms occurred in 2.3% of patients (n=11/486) who received ocrelizumab (including two events of invasive ductal breast carcinoma and one event each of breast cancer and invasive breast carcinoma), and 0.8% of patients (n=2/239) who received placebo (Montalban et al. 2017).

Pooled data from the Phase II study, OPERA I and II, and ORATORIO indicated an imbalance in malignancies in the ocrelizumab treatment group versus pooled interferon β-1a and placebo. The only cluster that could be identified was for female breast cancer, and although cancer incidences remained within the range of placebo data from clinical trials in MS and epidemiological data, no firm conclusion could be made concerning the risk due to the low number of events and the limited follow-up period.

For updated safety information refer to the current ocrelizumab Investigator's Brochure.

8. RESEARCH QUESTION AND OBJECTIVES

8.1 RESEARCH QUESTION

The research question is to assess and characterize the long-term safety data from the use of ocrelizumab in patients with MS overall and by MS type (e.g., RMS, PPMS, other).

8.2 OBJECTIVES

The primary objective is:

- to estimate (overall and by MS type) the event rates of SAEs, including malignancy and serious infections, following ocrelizumab treatment in patients with MS.

The secondary objective is:

- to compare the incidence of each serious safety event between ocrelizumab-exposed patients with RMS and patients with RMS exposed to other approved disease modifying therapies (DMTs: overall, and by individual DMTs if possible), within the same data source.

If sufficient data are available, an exploratory objective of this study is to compare the safety profile of patients with PPMS exposed to ocrelizumab to the safety profile of patients with PPMS not exposed to any DMTs.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This post-authorisation safety study (PASS) is a multi-source, multi-country, non-interventional, longitudinal cohort study based on secondary use of data captured for patients with MS in existing disease registries.

Approximately 5000 patients who have initiated treatment with ocrelizumab and 3500 patients exposed to other DMTs will be followed up to a maximum of 10 years following their first exposure to the DMT of interest, until censoring, until lost to follow-up, or until death, whichever comes first. Follow-up is planned regardless of whether patients discontinue treatment with DMT (ocrelizumab or another DMT).

Newly treated by ocrelizumab or other DMT is defined as those patients who initiate treatment with ocrelizumab or another DMT after the marketing authorization date of ocrelizumab in the target country. All available information on previous and current DMT treatment will be extracted for all patients. Within each dataset, a specific DMT comparator cohort will be compared using propensity score (PS) methods (inverse probability of treatment weighting and/or adjusting for the PS as a model covariate) to the ocrelizumab cohort in order to provide an internal comparator. The PS model will utilize baseline characteristics, and the populations will be restricted so that the necessary assumptions (i.e., positivity) of the PS-based methods are satisfied. Baseline characteristics' measurement periods will vary according to the nature of the variable and will be defined in the analysis plan. The non-treatment cohort will be matched to the ocrelizumab cohort with derived index dates.

Data on SAEs, including malignancies and infections, will be analysed to meet the primary and secondary study objectives.

Comparisons will be made between patients with MS initiating ocrelizumab and those initiating other DMTs. As there are no approved DMTs for certain forms of MS (e.g., PPMS), the comparison will also involve patients with MS not treated with any DMTs, if feasible.

This PASS will include data from the following sources (for details see Section 9.4):

- Multiple Sclerosis Documentation System 3D (MSDS3D) in Germany
- The Big MS Data (BMSD) Group, a collaboration of MS registries from Denmark, France, Italy, Sweden and the international registry MSBase

Data sources selected for this PASS have combined access to over 100,000 patients with MS, which is expected to be sufficient to provide the required sample size (see Section 9.5 for details). However, if one of the listed data sources fails to contribute a sufficient number of patients for the study, additional data sources may be added or substituted.

9.2 SETTING

9.2.1 Study population

This study will include patients with MS who have initiated treatment with ocrelizumab or another DMT during the study period, or patients with MS not on DMT therapy in routine clinical practice.

The study population covers a broad range of countries including Denmark, France, Germany, Italy, Sweden, and countries determined to be contributing safety data to MSBase such as Netherlands, Spain, U.K., Australia, Canada, and U.S.

Selection criteria

Patients who fulfill the following selection criteria will be included:

- A diagnosis of MS
- Aged 18 years or older
- Ocrelizumab group:
    - Patient must be newly treated with ocrelizumab during the study observational period
- DMT comparator group:
    - Patient who has never received treatment with ocrelizumab (at any time in the complete available history) and must be newly treated with an approved DMT other than ocrelizumab during the study observational period
- Non-DMT comparator group:
    - Patients who has never received ocrelizumab or any other DMT within the complete history recorded within available medical records and during individual follow-up in the study observational period

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

- Received ocrelizumab in the context of a previous clinical trial or Compassionate Use program, if information is available

Patients with prior or concomitant conditions relevant to serious infections or malignancies (e.g., concomitant disease or prior malignancy) will not be excluded from the study. Medically relevant prior and/or concomitant diseases will be considered at the analysis stage.

Patients with MS who switch treatments during the follow-up will not be excluded from the study. These patients will be followed until the end of the study, until lost to follow-up, or until death. Patients included in the DMT comparator group who then receive ocrelizumab can be included in the ever-exposed analysis for both ocrelizumab and the comparator groups and will also be included in the time-on-drug analysis of the ocrelizumab group.

The study population will include patients with MS who are treatment naïve to DMTs (ocrelizumab or other DMTs) and patients with MS already treated with DMTs other than ocrelizumab before switching to ocrelizumab or to another DMT (prevalent patients). Data on previous treatments will be extracted to assess exposure 'overlap' periods.

The ocrelizumab-exposed RMS patient group is expected to have differential MS severity compared to patients with RMS exposed to other DMTs. The label indication for ocrelizumab treated patients with RMS requires evidence of disease activity within the previous 24 months prior to treatment, while the label indication varies for other DMT comparators (e.g., alemtuzumab is indicated only in patients with active RRMS, while the label for interferon β-1a does not restrict to patients with active RRMS). Failure to adequately control for group differences in disease activity could lead to differential apparent AE rates for ocrelizumab as the rates for various AEs are associated with disease severity. Such AEs include infections, cardiovascular events, or metabolic events, and the latter two could manifest as study outcomes as deaths or other SAEs. A channeling effect is a similar concern when comparing PPMS ocrelizumab patients to the non-DMT comparator, as PPMS patients treated with ocrelizumab may have differential MS severity compared with those undergoing other treatments or no treatment. Note that the comparator for PPMS patients is the non-DMT group as no DMTs other than ocrelizumab are approved to treat patients with PPMS. See Section 9.7 for details on the analysis and Section 9.9 for further comments on limitations of the research method.

Only patients who have either previously given informed consent for secondary data use or reside in a country with national regulations allowing secondary use of data for research purposes will be included in the study population.

9.2.2 Study period

The overall observation period of the study is 10 years and will cover the period from Q1 2018 (launch of ocrelizumab in the E.U.) up to Q1 2028 to allow a maximum patient follow-up of 10 years. However, ocrelizumab-treated patients with MS in MSBase countries in which ocrelizumab was launched before Q1 2018 (e.g., Australia, Canada) may also be considered for the study. Patients with an MS diagnosis will be followed from the first treatment with ocrelizumab or with another approved DMT until the end of the follow-up period, until death, or until lost to follow-up, whichever comes first.

Due to different market launch dates for ocrelizumab in different European countries, the start of follow-up will vary across participating registries and countries. Estimates of local launch dates are provided in Table 2. Within each country, the maximum possible follow-up time for ocrelizumab exposed patients depends on the first patient treated with ocrelizumab being recorded in the registry after market launch.

The reporting periods for the study will differ by data source due to differences in launch date in each country, as seen in Table 2.

9.2.3 Follow-up (exposure periods)

Index date: For both the ocrelizumab group and the DMT comparator group, the index date is defined as the first dose of the medication and denotes the start of the follow-up observation period. If patients start multiple DMTs, each DMT initiation is a potential index date. For the untreated group, the index dates will be derived from that of the respective ocrelizumab patients being used for the comparison.

For ocrelizumab and each DMT, there will be two types of exposure follow-up periods. The exposure period used will depend on the outcome that is analyzed (see Section 9.7.1; Llung et al. 2014; Kearsley-Fleet et al. 2016):

- **Ever-exposed follow-up period:** total patient-years observed (irrespective of treatment received) will be calculated from the index date until either the event (when analyzing first events), death, lost to follow-up, or the end of the study, whichever occurs first. Because different outcome events are being evaluated, ever-exposed follow-up period may vary for each analysis because date of event may vary. There will be no adjustment for competing risks.
- **Time-on-drug follow-up period:** total patient-years exposed from first drug dose of index drug up to a risk window after the last administration of the index drug. Risk windows will depend on the DMT and will be based on the half-life as well as the mechanism of action, including lymphocyte count recovery, as described in the Summary of Product Characteristics and the literature. Sensitivity analyses will vary the risk window to assess the robustness of findings, including but not limited to 1) 364 days for ocrelizumab and a proportionate increase for other DMTs (see Table 3), and 2) up until the date of switch to another DMT. The half-life and risk window for each DMT are listed in Table 3 below. Time-on-drug exposure periods will only be created for the index drug in a group.

Table 3 Half-Life and Risk Windows for DMTs

MS DMT	Half-life	Primary Risk Window (days)	Larger Risk Window (days) for Sensitivity Analysis
Ocrelizumab[a]	26 days	182	364
Interferon β-1b[b]	5 hrs	91	182
Interferon β-1a[c]	50-60 hrs	91	182
Glatiramer acetate[d]	<24 hrs	91	182
Natalizumab[e]	16 +/- 4 days	91	182
Fingolimod[f]	6-9 days	91	182
Teriflunomide[g]	19 days	121	242
Alemtuzumab[h]	4-5 days	364	1820
Dimethyl fumarate[i]	1 hr	91	182
Cladribine[j]	1 day	364	1456
Mitoxantrone[k]	23-215 hrs	91	182

DMT = disease modifying therapy; hrs = hours
[a] OCREVUS® (ocrelizumab) Summary of Product Characteristics
[b] EXTAVIA® (interferon β-1b) Summary of Product Characteristics
[c] Rebif® (interferon β-1a) Summary of Product Characteristics
[d] Medicines and Healthcare Products Regulatory Agency product details (glatiramer acetate)
[e] Tysabri® (natalizumab) Summary of Product Characteristics
[f] GILENYA® (fingolimod) Summary of Product Characteristics
[g] AUBAGIO® (teriflunomide) Summary of Product Characteristics
[h] LEMTRADA® (alemtuzumab) Summary of Product Characteristics
[i] Tecfidera® (dimethyl fumarate) Summary of Product Characteristics
[j] MAVENCLAD® (cladribine) Summary of Product Characteristics; Protocol MS 700568-0002
[k] Scott and Figgitt 2004

9.3 VARIABLES

9.3.1 Primary Safety Variables

Outcome variables will be described according to Medical Dictionary for Regulatory Activities (MedDRA) classification or another standard coding system along with the date of each outcome event:

- SAEs, including:
    - Malignancy (overall and categorized by subtype, including breast cancer)
    - Serious infections (overall and categorized by subtype, including progressive multifocal leukoencephalopathy [PML], herpetic infections, candida infections, urinary tract infection, respiratory tract infections, etc.)
    - Any other SAEs, including death (categorised by major type)
- Non-melanoma skin cancer (NMSC)

9.3.2 Secondary Variables

Data elements which are key to conduct this PASS and will be extracted from all data sources are:

- Patient-specific information
    - Date of birth
    - Date of death, if applicable
    - Primary and underlying causes of death, if applicable
    - Sex
    - Country of residence
- Disease-specific information
    - Date of MS onset (first clinical manifestation)
    - MS type
        - RMS
            - Relapsing remitting
            - Secondary progressive
        - PPMS
        - Other
    - Expanded Disability Status Scale (EDSS) scores (including dates of assessment) or a proxy measure (e.g., Patient Determined Disease Steps) if EDSS is not available
        - For up to 2 years prior to index date
        - During study follow-up
    - Relapses (including dates of onset), including glucocorticoid treatment (yes/no)
        - For up to 2 years prior to index date
        - During study follow-up
    - John Cunningham virus (JCV) antibody status (Pos/Neg with index) (including date of sample), if available
- MS treatment information
    - All previous and current DMTs, including all known immunosuppressants for the treatment of MS
        - Drug name
        - Start date
        - Stop date (e.g., date of last administration) (for medications ceased)

        - Major reason for discontinuation/switch (if available) (for medications ceased)

Data elements considered important but not mandatory for conduct of this PASS will be extracted if collected by a data source:

- Patient-specific information
    - Employment status
    - Smoking status (never, former, current)
    - Weight, height, ethnicity
- Disease-specific information
    - Date of MS diagnosis
    - MS diagnostic criteria used
    - Brain MRI information (including date of assessment)
    - Lab test results (e.g., lymphocyte counts, liver enzymes), including date of test. Classification can be provided as normal and value if abnormal.
    - Current comorbid disease (e.g., none, cardiovascular, respiratory, gastrointestinal, psychiatric, metabolic, malignancies, musculo-skeletal, other auto-immune conditions, other)
    - Past major disease (e.g., malignancies)
    - Family history of malignancies
    - Any available personal or family genetic testing for malignancy risk factors (e.g., BRCA1 and 2)
- Treatment information (non-MS disease modifying and immunotherapy)
    - MS symptomatic therapy
        - Drug name
        - Start date
        - Stop date and reason of discontinuation (for medications ceased)
        - Dose, schedule
    - Other therapies
        - Drug name
        - Indication
        - Start and stop dates
        - Dose, route, schedule
- Pregnancy (Y/N)
    - If yes, date of last menstrual period or other estimated date of start of pregnancy

9.4 DATA SOURCES

European healthcare registries have been previously used to assess the long-term safety in post-marketing commitments requested by the FDA and EMA (Neovius et al. 2011; Xue and Ma 2013). Furthermore, EMA began a patient registry initiative in 2015 to facilitate the use of registry data for informing regulatory decisions. In July 2017, EMA hosted the MS registries workshop and released a set of recommendations (Report on Multiple Sclerosis Registries). Subsequently, the BMSD Group, industry partners, and EMA had a follow-up meeting in February 2018 to discuss the implementation of the recommendations, including development of a safety core protocol (Section 9.4.2).

As such, data received in this study will be obtained through the BMSD Group, a collaboration of MS registries from Denmark, France, Italy, Sweden, and the international registry MSBase, as well as through MSDS3D in Germany. Both the BMSD Group and MSDS3D are led by academic institutions that prospectively collect high quality data allowing for the safety monitoring of ocrelizumab over the long-term.

Post-marketing safety studies can have greater efficiency and faster data generation when based on established high-quality data sources. Advantages over site-based prospective data collection include:

- Less potential for selection bias and greater generalizability of findings because many registries are population-based (e.g., Nordic registries)
- Greater credibility of study findings because registries complement prospective non-interventional studies from industry. Furthermore, Nordic registries have the ability to collect additional data through linkage with their other population-based registries (e.g., cancer registry and death registry) and, therefore, allow for malignancy follow-up, even in the event a patient stops treatment with the product of interest and/or has been lost to follow-up in the disease-specific registry. It has been argued that disease registries, rather than specific product registries, are more likely to be successful in systematically collecting interpretable long-term safety data, thereby allowing comparisons, to the extent possible, across types and generations of drugs (Gliklich et al. 2014)
- 'Automatic' generation of comparator data within the same data source, thus same source population, in order to contextualize a product's safety profile (for those data sources from which comparator data will be drawn)

The next sections provide details on the different registries considered for this study.

9.4.1 Multiple Sclerosis Documentation System 3D (MSDS3D)

MSDS3D is an internet-based patient management and documentation system in Germany which allows the management of patient visit schedules and documentation of diagnostic, clinical, and safety data via different modules. It was reengineered in 2010 based on a previous MS documentation system (Ziemssen et al. 2013).

Data can be entered into MSDS3D software through an internet or computer-based electronic case report form (eCRF) / electronic data capture (EDC) system and uploaded into a central database. Anonymized data exports can be provided on an ad-hoc basis. Adverse events are captured through a custom safety module that uses MedDRA and WHO-DD coding systems and that has been used in previous studies (Ziemssen et al. 2015; Haase 2018).

Data collected in MSDS3D for a longitudinal, observational study in patients with MS exposed to ocrelizumab and other DMTs will be used as secondary data for the objectives of this PASS. This study will start data collection in 2018 and is expected to enroll 3000 ocrelizumab-treated patients and 1500 patients exposed to approved MS DMTs other than ocrelizumab (Roche Study ML39632) from approximately 250 sites across Germany.

9.4.2 Big MS Data (BMSD) Group

The BMSD Group is following up on guidance recommendations from the EMA Initiative for Patient Registries MS Workshop (Report on Multiple Sclerosis Registries) and collaborating to develop standards for registry safety data collection and reporting. This protocol BA39730 is aligned with a core study protocol "*A prospective observational long-term safety surveillance study in the Big MS Data (BMSD) Group network*," developed jointly by industry partners and the BMSD Group.

9.4.2.1 MSBase

MSBase is a longitudinal, observational registry that collects clinical, therapeutic, imaging, and safety data from routine clinical practice for patients with MS. MSBase was started with an overall objective to facilitate the collection of epidemiological information through its unique web interface and to use the collected information to answer epidemiological questions that aim to improve the quality of care of patients with MS (Butzkueven et al. 2006; MSBase 2017).

MSBase was started in 2003 and contains data on >50,000 patients from 115 centers across over 72 countries. In Europe, the largest contributors are Italy, Spain, and Netherlands with approximately 10,000, 4,000 and 3,000 patients respectively. To avoid patient duplication, patient data from clinics who contribute to both MSBase and a country-specific registry in Section 9.4.2.2 – 9.4.2.5 will only be extracted from one data source.

Data is imported into the MSBase registry from a number of sources: MSBase web-based data entry system, iMed software application, or through local registry integration. Safety data will be collected through an MSBase-specific safety module using a MedDRA coding system (Haartsen et al. 2015).

9.4.2.2 Observatoire Français de la Sclérose en Plaques (OFSEP)

OFSEP is a longitudinal observational registry that collects clinical, therapeutic, imaging, and safety data as well as biological samples from routine clinical practice for patients with MS or related diseases in France. OFSEP is based on European Database for Multiple

Sclerosis (EDMUS) software and was started to promote research that aims to improve the diagnosis and treatment of people with MS and to advance the understanding of the causes and mechanisms of the disease (OFSEP 2016).

OFSEP was started in 2011 and contains data on >50,000 patients and 23,000 active patients (with consultation in the last two years) from 35 centers (hospital and hospital outpatient departments) across France. Approximately 57% of total patients have the relapse remitting form of MS and 11% have PPMS. Of the patients with RRMS, 23% are currently on no DMT, 41% are on first-line treatment and 32% are on second-line treatment. Median length of follow-up for patients is over 12 years and as of December 2016, 35% of patients had a consultation within the last year.

Data is collected via the EDMUS data collection system and reported on a biannual basis. Adverse events are collected through a safety module.

9.4.2.3 Danish MS Registry

The Danish MS Registry is a population-level registry that collects clinical, therapeutic, and safety data via different modules (Brønnum-Hansen et al. 2011; Koch-Henriksen et al. 2015). The Danish MS Registry started with a nationwide population-based MS prevalence survey and continues as a means of promoting research on high-quality real-world data in MS.

The registry contains data at a near population level (26,300 patients of which 16,000 were alive at end of 2017). Of the 16,000 active patients, approximately 59% currently receive DMT. As reporting of all patients on DMTs is mandatory (Koch-Henriksen and Sørensen 2000; Koch-Henriksen et al. 2015), data completeness is estimated at above 90% and lifetime follow-up can be expected for all patients, as long as they remain in the country.

The Danish MS Registry uses the COMPOS® online data collection system. Data can be exported on an ad-hoc basis as required by study timelines. Safety events can also be captured by linkage to other Danish national registries using the personal identification number (CPR-number) which is used by all national registers.

9.4.2.4 Swedish MS Registry

The Swedish MS Registry is a near population-level registry (>80% coverage) that has been active since 2001 with a primary objective to collect data to assess the long-term effectiveness of disease-modifying treatments (Hillert and Stawiarz, 2015).

The Swedish MS Registry contains data on approximately 15,000 patients since 2001. All serious adverse reactions as defined by the Swedish Health Authorities will be reported to the registry. Lifetime follow-up in national patient registers can be expected due to a unique personal identification number, as long as the patient remains in the country.

The Swedish MS Registry uses the COMPOS® online data collection system. Data can be exported on an ad-hoc basis as required by study timelines. Safety events can also be captured by linkage to other Swedish national registries using the personal identification number (CPR-number) which is used by all national registers.

9.4.2.5 Italian MS Registry

The Italian Registry is active since 2000. From 2000 to 2015, the registry was in the framework of the Italian Multiple Sclerosis Database Network (MSDN). Since 2015, the framework has been altered to a near population-level registry promoted and founded by the Italian Multiple Sclerosis Society and its Italian Multiple Sclerosis Foundation in collaboration with the University of Bari, with continuity in the existing MSDN-iMed© software's database collection.

The Italian MS Registry currently contains data (clinical, therapeutic, imaging, lab and safety data) on approximately 50,000 patients from 72 MS Italian centers. About 50% of patients have a follow-up period longer than 5 years, and 30% longer than 10 years. About 70% of the population is represented by DMT-treated patients.

A data collection web-site is currently available at https://registroitalianosm.it/, where each center can enter data through a personalized password. It is possible to check the presence of a unique valid code identifier, through the patient encrypted fiscal code, in order to overcome duplications. Several quality controls have been implemented in order to increase the quality and generalizability of data collected. Safety data will be collected through a specific safety module using the MedDRA coding system.

9.5 STUDY SIZE

The target for this study will be approximately 5000 patients with MS exposed to ocrelizumab and 3500 patients with MS treated with other DMTs. Within each data source, the number of patients included in the comparator group is assumed to be at least half of the number of patients exposed to ocrelizumab.

Power calculations are presented to provide the expected precision of hazard ratio (HR) estimates for important SAEs, including malignancy (excluding NMSC) and serious infections. No formal hypothesis testing will be performed.

For malignancy excluding NMSC, an incidence rate of 3.7 per 1000 patient-years in the reference group is assumed, based on the real-world data from British Columbia, Canada (Kingwell et al. 2012). Assuming that ocrelizumab does not increase the risk of malignancy (true HR = 1.0), an overall study duration of 10 years with a 2 year patient selection period and a follow-up period of at least 8 years, a drop-out rate of 5% per year in each arm, a one-sided type-I error of 0.025 and with a sample size of 5000 patients recruited in the ocrelizumab group and 3500 patients in the non-ocrelizumab group across all data sources, the study could rule out a HR ≥1.43 with 80% power, based on expecting 278

malignancies.

For female breast cancer and serious infections, given the same assumptions of the parameters, the HRs expected to be ruled out with 80% power are listed in Table 4, which includes incidence rates and expected number of events.

Note that this power is only realized in the ideal case of unbiased treatment effect estimates across all data sources.

Table 4 Effect Size to be Ruled Out with 80% Power and Sample Size Consisting of 5000 Ocrelizumab-Treated Patients with MS and 3500 Patients with MS Treated with Approved DMTs Other Than Ocrelizumab

Outcome	Incident Rate per 1000 PY in the Reference Group	Expected Number of Events	HR Expected to be Ruled Out
Malignancy			
Malignancy (excl NMSC)[a]	3.7	278	1.43
Breast cancer (female)[b]	2.1	111	1.79
Infections[c]			
PML	0.04	not estimable	10
Herpes-related infections	0.4	47	2.6
Candida-related infections	2.1	171	1.59
Respiratory infections	16.6	1052	1.20
Urinary tract infections	26.6	1582	1.16

DMT = disease modifying therapy; HR = hazard ratio; MS = multiple sclerosis; NMSC = non-melanoma skin cancer; PML = progressive multifocal leukoencephalopathy; PY = patient-years.
Note: Assumptions underlying these calculations:
- No difference in risk between the exposed and unexposed (i.e., hazard ratio = 1)
- Proportion of females = 60%

[a] Kingwell et al. 2012, British Columbia (Canada), BC MS database linked to BC cancer registry
[b] Nielsen et al. 2006, Denmark MS Registry
[c] Swedish MS registry linked to Swedish Patient registry (unpublished)

9.6 DATA MANAGEMENT

Overall, this study will follow the relevant chapters of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

The processes for data management differ by country and data source. Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except selected study staff. Appropriate data storage and archiving procedures will be followed, with periodic backup of files. Standard procedures will be in place to restore files in the event of a hardware or software failure.

MS registries

Data at BMSD registries will be extracted and analysed for this study locally by each registry holder. Extraction of data and data management will be done according to registry-specific procedures. Routine procedures pre-specified and approved by each disease registry will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality-control checks of all programs. The datasets and analytic programs relevant for the execution of this PASS will be stored according to the registries' procedures to allow future analysis if needed. Statistical Analysis System (SAS) software version 9.2 or later, or other appropriate statistical software, including R, version 3.2 or later, will be utilized for access to the raw data, to manage the analytic datasets, and to conduct data analysis. Aggregated results in tables will be transferred electronically to IQVIA.

Data collected via MSDS3D, including quality checking of the data, is done by a contract research organization (CRO) responsible for Roche Study ML39632. Data extracts of patient-level data for secondary use will be transferred electronically to IQVIA for analysis and meta-analysis.

IQVIA

IQVIA will receive patient-level data extracts from MSDS3D and aggregated data from the other data sources for all semi-annual and interim reports as well as the final report. Furthermore, IQVIA will conduct the meta-analyses using aggregated data from each source for the interim and final reports. Data extracts and analysis programs will be stored to allow any necessary future analysis. All analyses done by IQVIA will be performed using SAS software version 9.2 or later, or other appropriate statistical software, including R, version 3.2 or later.

9.7 DATA ANALYSIS

9.7.1 Safety Analyses

Data will be analyzed every 6 months over a study duration of 10 years. Variables (e.g., age, sex, EDSS, type and duration of prior DMTs, etc) will be summarized using mean, median, standard deviation, and range for continuous data and counts and percentages for categorical data. Missing values will be counted and presented for each variable.

Patients will be selected over a period of time and the study will end on a specific calendar date (10 years from the start of the study). Thus, patients who enroll later will be followed for a shorter period than patients who enroll early owing to administrative censoring. Other patients may be lost to follow-up in the data sources. Therefore, methods accounting for right-censored data will be used.

Two main analytical approaches will be used depending on the outcome of interest, as

described in methods used by Anti-Rheumatic Therapies in Sweden (ARTIS) and the British Society for Rheumatology Biologics Register (BSRBR) (Llung et al. 2014; Kearsley-Fleet et al. 2016). For analyses of risk of malignancy and of PML, an ever-exposed model will be applied that includes all person-time observed since the first drug dose in the study until study end. For all other SAEs, the analysis will be based on a time-on-drug approach that uses person-time as exposed from first drug dose in the study up to a risk window after the last administration of ocrelizumab or other DMT (see Section 9.2.3). Time on ocrelizumab or other DMT will be summarized, and rates of treatment cessation and switching will be calculated. An outcome of interest occurring during the defined risk window period will be allocated to the preceding treatment. The risk windows will be varied in sensitivity analyses to assess the robustness of findings, including but not limited to 72 weeks after last administration of the index drug and up until the date of switch to another DMT. For analyses of risk of death, both analytical approaches will be used − an ever-exposed and an on-drug model.

9.7.1.1 Semi-annual safety reports

Semi-annual cumulative safety study reports will be prepared, with aggregated data from all observational sources on safety events occurring in each treatment group. In these semi-annual safety reports, the total number of safety events (incident and recurrent) and unadjusted rates per 100 patient-years with 95% confidence intervals (CIs) will be provided.

Incidence rates (involving first events only) and event rates (including all reoccurring events during the risk window) will be calculated for all events. Incidence rates (involving time to first events only) and event rates (including all reoccurring events during the risk window) will be calculated for all outcome variables.

All rates will be reported stratified by MS type (overall, RMS, PPMS, other) and sex (overall, male, female).

These reports will be based on a common reporting template used by all participating registries to relay ongoing information with regards to safety within these registries. Meta-analyses will not be conducted for biannual reports.

9.7.1.2 Interim and Final Comparative Safety Reports

In addition to the semi-annual safety reports, interim and final comparative safety reports addressing the secondary objectives will be prepared 4, 6, 8, and 10 years after the study start, respectively.

To compare incidence rates between ocrelizumab-treated and comparator patients within registries, unadjusted and adjusted HRs will be presented. The HRs comparing patients with MS exposed to ocrelizumab with patients with MS exposed to any other approved DMT (or to individual DMTs if possible) with associated CIs will be estimated using survival analysis including Cox proportional-hazard models. Additional comparative

analyses may involve comparator groups defined by line of treatments/number of switches (e.g., by number of prior DMT starts). The assumptions of the models will be tested.

Analyses will be conducted within each data source separately using ocrelizumab and DMT comparator groups. PS adjustment will be used to adjust for measured confounders. Standard regression-based covariate adjustments and/or appropriate causal inference methods (Hernán and Robins 2017) may also be applied. Potential confounders are likely to include, but will not be limited to, age, sex, calendar time, disease duration prior to treatment initiation, proportion of disease duration spent treated with DMT, EDSS, comorbidities, prior drug exposure, concomitant drugs (e.g., other concomitant immunomodulators/suppressants), pre-baseline relapse activity, and (if appropriate) country. For each registry, variables associated with ocrelizumab and other DMT use at a significance level of P<.10 will be used to generate individual propensity scores for each patient. Baseline variables will be reported for these groups. The propensity score models will be checked by examining the expected bias, which is the likely bias in the treatment estimate due to each confounder.

Further analyses involve subgroup analyses of absolute and relative risks by patient-level characteristics including age, sex, MS subtype, disease duration, EDSS, comorbidities, prior drug exposure, and concomitant drugs, if possible. If PML cases are observed in this study, descriptive analyses will be conducted taking into account duration of exposure to ocrelizumab, and type and duration of prior exposure to immunosuppressive/ immunomodulatory drugs, as well as information on JCV antibody titre, if available.

Meta-analysis of results across the data sources will be conducted using aggregated data from each source. The overall treatment effect (expressed as a HR and CI) will be estimated using a random effects model and the Hartung-Knapp estimator (Hartung 1999; Hartung and Knapp 2001a; Hartung and Knapp 2001b). Heterogeneity will be assessed using Cochran's Q and the I2 statistic. As a sensitivity analysis, the heterogeneity parameter $\tau 2$ will be estimated, and an additional sensitivity analysis will estimate the overall treatment effect and CI using a fixed effect model with the Mantel-Haenszel estimator (Wiksten, et al 2016). Results will be graphically displayed using forest plots.

Since data will be used for on-going risk characterization, results will not be adjusted for multiplicity analysis of multiple endpoints or at multiple time points.

These interim and final comparative reports may also include analysis of an exploratory objective, to compare the safety profile of patients with PPMS exposed to ocrelizumab to the safety profile of patients with PPMS never exposed to any DMTs. If sufficient data is available, the methods used for the secondary analyses would be applied to the exploratory analysis. The ocrelizumab group will be compared to the non-DMT comparator group using a similar methodology, with any visit on or after diagnosis in the non-DMT comparator group as a potential entry date. Since prior use of any DMTs is a confounding

variable, only patients with PPMS with no DMT treatment prior to starting treatment with ocrelizumab will be compared. If patient numbers are low, a descriptive analysis will be conducted.

All analyses will be performed based on a common core protocol and reporting template. MSDS3D will contribute patient-level data for analysis. The other registries will submit aggregated-level data. All results will then be collated and meta-analyzed in a single report for submission to Health Authorities. Pooled analyses stratified by registries comparing ocrelizumab to all DMTs combined and individual DMTs, if possible, will be presented.

Full details of planned statistical methodology, including handling of missing and censored data and sensitivity analyses to quantify the potential effect of unmeasured confounding, will be specified in the Statistical Analysis Plan (SAP) which will be developed after approval of the study protocol.

9.8 DATA QUALITY ASSURANCE AND QUALITY CONTROL

Marketing Authorization Holder

The Marketing Authorization Holder (MAH) 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 (if applicable), and documentation of Institutional Review Board (IRB)/Ethics Committee (EC) and governmental approval/notification (if required).

The MAH shall ensure that the datasets and statistical programs used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.

Registries

The registries' standard operating procedures, internal policies and process guidance, and/or routine practice will be used for the conduct of this PASS. These procedures may include, among others, rules for data storage, methods to maintain and archive project and study documents, quality-control procedures for programming, standards for writing analysis plans, and review of analysis programs and study documents by senior staff and internal audits.

IQVIA

All aspects of the study from protocol development to the reporting of the results are conducted within the work-frame of the IQVIA Quality Management System and in accordance to IQVIA policies and procedures, including quality control on the study methodology, statistical analysis plan, programming, data management and analysis, study results, conclusions, and study reports.

Retention of Records

Records and documents pertaining to the conduct of this study must be retained for at least 15 years after completion 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 MAH. Written notification should be provided to the MAH prior to transferring any records to another party or moving them to another location.

All data sources will comply with F. Hoffmann-La Roche Ltd procedures regarding archiving and record management.

9.9 LIMITATIONS OF THE RESEARCH METHOD

This study aims to evaluate the long-term safety of ocrelizumab and other available DMTs in patients with MS in a real-world setting. The following sections address the potential limitations:

- Sample size: Uptake of new medications such as ocrelizumab is unpredictable and has the potential to impact the feasibility of reaching the sample size over all selected data sources for this PASS. However, continuous check of patient numbers per data source will allow strategies to be employed in response to any such challenges and to reduce or eliminate the potential impact of these factors. These include potential inclusion of additional data sources (e.g., another MS registry) and/or expansion of the patient inclusion period.

  Channeling effect: Factors associated with treatment choice and also with any of the study outcomes of interest will be evaluated at baseline (index date), and will be accounted for in multivariate analyses using PS adjustment . However, if the populations being compared are too different, the PS in the ocrelizumab and comparator cohorts may have areas of non-overlap. Patients with such propensity scores would be excluded, leading to lower power than expected. If this is observed, the previously described strategies to increase the sample size will be employed to recover the lost power. Specifically, the non-DMT exposed patient group is expected to differ systematically from the DMT-exposed group with regards to MS severity and other variables that could also be associated with the outcomes of interest.

- Residual confounding between the study population and comparators: The planned analysis of baseline characteristics will examine the distributions of key variables that could cause confounding (e.g., age, sex, comorbidities), and will be accounted for using PS adjustment. However, residual confounding due to unknown and imprecisely measured confounders may still remain. Sensitivity analyses will be conducted to quantify the potential effect of unmeasured confounding, but such analyses will not be able to assess the actual amount of bias (if any) in the study results.
- There is a risk that due to switching of treatments, the DMT that caused a condition might not be the DMT in use when the condition is diagnosed. This risk is higher for diseases with long latency periods such as malignancy. For this reason, malignancy and PML are only analyzed using "ever-exposed" periods in the analysis. For other outcomes, sensitivity analyses will vary the size of the risk window used to define the "time-on-drug" exposure periods. This will allow for an assessment of the robustness of the conclusions to the risk window used. This is the reason why a pre-index observation period in the registry of up to 2 years is desired in order to allow capture of previous DMTs.

9.10 OTHER ASPECTS

None.

10. PROTECTION OF HUMAN PATIENTS

10.1 INFORMED CONSENT

Whenever possible, the MAH shall ensure that patients at the occasion of the primary data collection have explicitly agreed to any secondary use of their data if they provide patient-level data to the MAH. In case it is not possible/practical to obtain or retrieve informed consent for use of secondary data in a non-interventional study, certain other precautions must be taken, including:

- Ensuring data are anonymised / pseudonymised
- Ensuring final analysis data are anonymised / pseudonymised
- Ensuring possibility of linkage back to individual identified patients is impossible or tightly controlled
- Obtaining ethical committee approval for use of data as proposed (e.g., the review of and extraction of information from individual medical charts) ahead of study initiation

In the unusual circumstance that individual patients can be identified directly from their data received, then approval to use that data should be sought where possible.

10.2 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the Guidelines for Good Pharmacoepidemiology Practice (GPP) published by the International Society of Pharmacoepidemiology (ISPE) and the laws and regulations of the country in which the research is conducted.

The study will comply with national and European Union (E.U.) requirements for ensuring the well-being and rights of participants in a non-interventional post-authorization safety study (NI-PASS).

10.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

As the study will be operating using secondary data extracted from a number of sources, additional ethical approvals are typically not required. If required by local regulations, each data source will submit this protocol and relevant supporting information to the relevant IRB/EC for review and approval before the study is initiated.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This is an NI-PASS involving the use of secondary data and the reporting of adverse reactions in the form of Individual Case Safety Reports is not required.

12. PLANS FOR DISSEMINATION AND COMMUNICATION OF STUDY RESULTS

Regardless of the outcome of the study, the MAH is dedicated to openly providing information on the study to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The MAH will comply with all requirements for publication of study results.

Semi-annual safety reports will be prepared over the entire 10-year study period and submitted with PBRERs.

The first interim report will be submitted 4 years after study start. The estimated year is 2022. Further interim reports will be submitted every 2 years until 2026. These reports will add cumulative data from the launch date until the end of the respective reporting period (see Table 2).

The final report will be submitted in 2029.

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Appendix 1
List of Stand-Alone Documents Not Included in the Protocol

None.

Appendix 2
ENCePP Checklist for Study Protocols (Revision 4)

Doc.Ref. EMA/540136/2009

Adopted by the ENCePP Steering Group on 15/10/2018

Study title:
LONG-TERM SURVEILLANCE OF OCRELIZUMAB-TREATED PATIENTS WITH MULTIPLE SCLEROSIS (MANUSCRIPT STUDY)

EU PAS Register® number: Study not registered
Study reference number (if applicable): BA39730

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	8.1
2.1.2 The objective(s) of the study?	☒	☐	☐	8.2
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	8.2

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7.1
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7.1
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2; 9.4
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2.2
4.2.2 Age and sex	☒	☐	☐	9.2.1
4.2.3 Country of origin	☒	☐	☐	9.2.1
4.2.4 Disease/indication	☒	☐	☐	9.2.1
4.2.5 Duration of follow-up	☒	☐	☐	9.2.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.2.3

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.2.3; 9.7
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.2.3
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.2.1

Comments:

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.1
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.1
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.7
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.2; 9.4; 9.7
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.7

Comments:

This study uses data from established MS registries routinely used for research.

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.1
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4.2

Comments:

Coding of covariates, if applicable, will be described in the SAP which will be developed after approval of the study protocol.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.2.3; 9.7

Comments:

Missing values will be counted and presented for each variable. Full methodological methods for handling missing data in the analysis will be elaborated in the statistical analysis plan.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8

Comments:

Quality control includes independent review of study results by senior staff.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☒	☐	
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.9

Comments:

Avoidance of selection bias was considered during the selection of patient population and data sources

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.3
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.1

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: David Wormser, Ph.D.

Date: 29/10/2018

Signature: D. Wormser

Appendix 3
Description of Data Sources

Table A3-1 Description of data sources and information available

	MSDS3D	MSBase	OFSEP	Danish MS Registry	Swedish MS Registry	Italian MS Registry
Database information						
Principal Investigator	Tjalf Ziemmsen	Helmut Butzkueven	Sandra Vukusic	Melinda Magyari	Tomas Olsson & Jan Hilllert	Maria Trojano
Type of database	MS registry	MS registry	MS registry	MS registry	MS registry	MS registry
Geographic coverage	Germany	72 countries worldwide, including Netherlands, Spain, U.K., Australia, Canada, and U.S.	France	Denmark	Sweden	Italy
Start of data collection	2001	2003	2011	2015	2004	2000 as MSDN, transition to current format in 2015
Number of prevalent patients with MS	4500 (3000 OCR / 1500comparator)	55,000	>50,000	>20,000	14,500	50,000
Median follow-up duration (years)	~8	4.05 (IQR: 0.88-8.81)	15.2 (mean)	Lifelong	Lifelong	50% of patients have >5 years of data
Inclusion of untreated patients with MS	Yes	Yes	Yes	No	Yes	TBD
Can patients be linked to additional data sources?	No	No	No	Yes	Yes	No
If yes, what linkages are possible?	Not applicable	Not applicable	Not applicable	Linkable to the National Patient Register, Causes of Death Registry, Nationa Prescription Registry, Cancer Registry, etc.	Linkable to the National Patient Register, Causes of Death Registry, National Prescription Registry, Cancer Registry, etc.	Not applicable

Table A3-1 Continued

	MSDS3D	MSBase	OFSEP	Danish MS Registry	Swedish MS Registry	Italian MS Registry
Frequency data refresh	Real time	TBD	Monthly	Ad-hoc	TBD	TBD
Comparator data available?	Yes	Yes	Yes	Yes	Yes	Yes
Comparisons to drug-specific groups feasible?	Yes	Yes	Yes	TBD	No	Yes
Patient-specific data						
Year of birth	Yes	Yes	Yes	Yes	Yes	Yes
Gender	Yes	Yes	Yes	Yes	Yes	Yes
Comorbidity	Yes	Not minimum dataset, but spontaneous reporting	Yes, history of cancer, family history of MS	Available through linkage to other registries	Available through linkage to other registries	TBD
MS-related information						
Date of onset of MS symptoms	Yes	Yes	Yes	Yes	Yes	Yes
Date of first MS diagnosis	Yes	Yes	Yes	Yes	Yes	TBD
MS type	Yes	Yes	Yes	Yes	Yes	Yes
EDSS score	Yes	Yes	Yes	Yes	Yes	Yes
MS relapse	Yes	Yes	Yes	Yes	Yes	Yes
JCV antibody status	Yes	Yes	Yes	Yes	Blood samples available	Yes
MS treatment						
DMT used	Yes	Yes	Yes	Yes	Yes	Yes
Date of first administration of each DMT	Yes	Yes	Yes	Yes	Yes	Yes

Table A3-1 Continued

	MSDS3D	MSBase	OFSEP	Danish MS Registry	Swedish MS Registry	Italian MS Registry
Date of last administration of each DMT	Yes	Yes	Yes	Yes	Yes	Yes
Type DMTs prior OCR	Yes	Yes	Yes	Yes	Yes	Yes
Duration of DMTs used prior to OCR	Yes	Yes	Yes	Yes	Yes	Yes
Adverse events						
Serious adverse events	Yes	Yes[a]	Yes[b]	Available through linkage to other quality registries[c]	Available through linkage to other quality registries[d]	Yes
Malignancy	Yes	Yes[a]	Yes[b]	Yes	Yes	Yes
Infections	Yes	Yes[a]	Yes[b]	Yes	Yes	Yes
Other SAEs	Yes	Yes[a]	Yes[b]	Yes	Yes	Yes
Reimbursement						
Expected launch date	January 2018	Varies by country	Q2 2019	January 2018	Q3 2018	Q3 2018

DMT = disease modifying therapy; EDSS = Expanded Disability Status Scale; JCV = John Cunningham virus; MS = multiple sclerosis; MSDS3D = Multiple Sclerosis Documentation System 3D; OCR = ocrelizumab; OFSEP = Observatoire Français de la Sclérose en Plaques; SAEs = serious adverse events.

[a] Full list of SAEs collected in OFSEP can be found at http://www.ofsep.org/images/CLINIQUE/FicheMinimaleOFSEP_EIG_2016-04-05.pdf.

[b] Serious adverse drug reactions, as defined by the Swedish Health Authorities are also collected in the Swedish National MS registry

TITLE:	**MULTISOURCE SURVEILLANCE STUDY OF PREGNANCY AND INFANT OUTCOMES IN OCRELIZUMAB-EXPOSED WOMEN WITH MULTIPLE SCLEROSIS**
PROTOCOL NUMBER:	BA39732
VERSION NUMBER:	4.0
AUTHOR:	Erwan Muros-Le Rouzic F. Hoffman-La Roche Ltd. 4070 Basel, Switzerland
DATE FINAL:	See electronic date stamp below
DATE(S) AMENDED:	V4 See electronic date stamp below V3 16 June 2021 V2 14 December 2020 V1 27 January 2020
EU PAS REGISTER NUMBER:	EUPAS33879
ACTIVE SUBSTANCE:	L04AA36 (ocrelizumab)
STUDIED MEDICINAL PRODUCT:	OCREVUS®
PRODUCT REFERENCE NUMBER(S):	RO4964913
PROCEDURE NUMBER(S):	EMEA/H/C/004043; IND 100,593 BLA 761053
JOINT PASS:	No
RESEARCH QUESTION AND OBJECTIVES:	To assess and characterize pregnancy and infant outcomes of women with multiple sclerosis exposed to ocrelizumab during the 6 months before the estimated first day of the last menstrual period or at any time during pregnancy

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
14-Mar-2023 10:32:49	Company Signatory	Muros, Erwan (muroslee)

COUNTRIES OF STUDY POPULATION:	United States, Denmark
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration GmbH Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen Germany

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ATC	Anatomical therapeutic chemical
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence interval
CNS	Central nervous system
CSR	Clinical study report
DAPI	Dynamic Assessment of Pregnancies and Infants
DDD	Defined daily dose
DMSR	Danish Multiple Sclerosis Registry
DMT	Disease-modifying therapy
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU PAS Register	European Union electronic Register of Post-Authorisation Studies
EUROCAT	European Surveillance of Congenital Anomalies program
FDA	Food and Drug Administration
FSS	Functional Systems Score
GPP	Guidelines for Good Pharmacoepidemiology Practices
GVP	Guideline on Good Pharmacovigilance Practices
HIPAA	Health Insurance Portability and Accountability Act
HIRD®	Healthcare Integrated Research Database
ICD-9	International Classification of Diseases, 9th Revision
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
ICD-10-CA	International Classification of Diseases, 10th Revision, Canadian Modification
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IgG1	Immunoglobulin G1
IM	Intramuscular
IRB	Institutional review board
ISPE	International Society for Pharmacoepidemiology

Abbreviation	Definition
IV	Intravenous
LMP	First day of the last menstrual period
MarketScan	IBM MarketScan Commercial Claims and Encounters Database
MCM	Major congenital malformation
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSIF	Multiple Sclerosis International Federation
NA	Not applicable
NDI	National Death Index
NMSS	National Multiple Sclerosis Society
NPV	Negative predictive value
PADER	Periodic adverse drug experience report
PAS	Postauthorization study
PASS	Postauthorization safety study
PBRER	Periodic benefit-risk evaluation report
PHI	Protected health information
PMR	Postmarketing requirement
PPMS	Primary progressive multiple sclerosis
PPV	Positive predictive value
Qn yyyy	Quarter of the calendar year
RMS	Relapsing forms of multiple sclerosis
RRMS	Relapsing-remitting multiple sclerosis
RTI-HS	RTI Health Solutions
SAP	Statistical analysis plan
SC	Subcutaneous
SGA	Small for gestational age
STORK	Systematic Tracking of Real Kids
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TORCH	Toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19, Zika virus), rubella, cytomegalovirus (CMV), and herpes
US	United States
USPI	US prescribing information
WHO	World Health Organization

3. RESPONSIBLE PARTIES

Each research partner under contract with Roche, as detailed further below, will share responsibility for the study design and conduct of the study and carry out all aspects of study implementation, including but not limited to:

- Obtaining local institutional review board and ethics approvals, as required;
- Interacting with other registries to achieve linkage with required data sets;
- Contributing to the development of the monitoring plan, statistical analysis plan (SAP), and study data validation plan;
- Managing raw data files;
- Obtaining ocrelizumab uptake monitoring data; and
- Preparing the analytical data sets following the protocol, the ocrelizumab uptake monitoring plan, the SAP, and any activities relating to validation of the study endpoints.

In addition to the responsibilities listed above for research partners, RTI Health Solutions serves as the coordinating center, with responsibilities including:

- Facilitating communication among all research partners, Roche, and the independent scientific advisors;
- Drafting and coordinating the development of common documents (e.g., the protocol, SAP, and reports); and
- Conducting the meta-analysis of aggregated results from individual data sources.

The investigators at RTI Health Solutions are responsible for conducting analyses in the IBM MarketScan Commercial Claims and Encounters Database. The investigators at Carelon Research (formerly HealthCore) are responsible for conducting analyses in the Healthcare Integrated Research Database (HIRD®); investigators at Optum are responsible for conducting analyses in the Optum Dynamic Assessment of Pregnancies and Infants™ (DAPI); and investigators at Aarhus University in Denmark are responsible for conducting analyses in the Danish National Health Databases and The Danish Multiple Sclerosis Registry.

Independent scientific advisors, listed below, will provide scientific and technical advice and recommendations throughout the project.

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4. ABSTRACT/SYNOPSIS

TITLE:	**MULTISOURCE SURVEILLANCE STUDY OF PREGNANCY AND INFANT OUTCOMES IN OCRELIZUMAB-EXPOSED WOMEN WITH MULTIPLE SCLEROSIS**
PROTOCOL NUMBER:	BA39732
VERSION NUMBER:	4.0
DATE OF PROTOCOL AMENDMENT:	See electronic date stamp on the cover page

Rationale and Background

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system, thought to be a complex interaction of genetic susceptibility and environmental factors. Its prevalence is highest in North America and Europe. Multiple sclerosis is more frequent in women than men, with an overall sex ratio of 2 to 3 women for every 1 man, except in patients with primary progressive MS, where the frequency is similar in both sexes. Multiple sclerosis is commonly diagnosed during reproductive years. About 85% of people with MS have relapsing-remitting MS, a form of MS with exacerbations or relapses during which new symptoms appear or previous symptoms worsen and periods of partial or complete remission. If left untreated, most patients who are diagnosed with relapsing-remitting MS will eventually progress to a chronic form characterized by progressive worsening of neurologic function over time with occasional relapses, which is categorized as secondary progressive MS. Approximately 15% of people with MS are diagnosed with primary progressive MS (PPMS), a form of MS with steadily worsening neurologic symptoms from the onset of disease and no clear relapses.

OCREVUS® (ocrelizumab) was approved by the United States (US) Food and Drug Administration (FDA) on 28 March 2017, for the treatment of adult patients with relapsing forms of MS (RMS) and PPMS. Subsequently, OCREVUS® was approved in the EU, Switzerland, Australia, Canada, and other countries. In 2019, the RMS indication was expanded to include “clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease” (OCREVUS® PI 2022).

Ocrelizumab is a recombinant humanized monoclonal immunoglobulin G1 (IgG1) antibody that selectively targets CD20-expressing (CD20+) B cells. Two identical, randomized, active-controlled studies (OPERA I [Study WA21092] and OPERA II [Study WA21093]) have demonstrated superior efficacy outcomes versus interferon beta-1a in RMS; one randomized, placebo-controlled study (ORATORIO [Study WA25046]) demonstrated superior efficacy in PPMS versus placebo. Results of these studies show that depletion of CD20+ B cells leads to a significant impact on a broad range of clinical measures of disease, including disability progression, in addition to an impact on magnetic resonance

imaging (MRI) outcomes related to disease progression and reflective of neural tissue loss, thus further supporting the hypothesis that B cells are central to the pathogenesis of both relapsing and primary progressive MS. Ocrelizumab has demonstrated a favorable safety profile in patients with RMS or PPMS. The proportion of patients with adverse events was similar in patients treated with ocrelizumab and patients treated with interferon beta-1a (both 83.3%) or placebo (95.1% vs. 90.0%). The proportion of patients experiencing a serious adverse event was similar between ocrelizumab and the comparator groups—in RMS: 6.9%, ocrelizumab, and 8.7%, interferon beta-1a; in PPMS: 20.4%, ocrelizumab, and 22.2%, placebo.

Ocrelizumab is a humanized monoclonal antibody of an immunoglobulin G1 subtype, and immunoglobulins are known to cross the placental barrier. B-cell levels in human neonates following maternal exposure to ocrelizumab have not been studied in clinical studies. 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 can affect pregnancy outcomes or infant outcomes in humans.

Roche proposes a non-interventional multidatabase postmarketing safety study to assess pregnancy-related safety data from women with MS exposed to ocrelizumab. This study will be conducted to fulfill part of the FDA postmarketing requirements (PMR 3194-4) for approval of ocrelizumab in the US. The study is listed as an additional pharmacovigilance activity to address the missing information on drug use during pregnancy and lactation in the proposed European Union Risk Management Plan.

Research Question and Objectives

To assess and characterize pregnancy and infant outcomes of women with MS exposed to ocrelizumab during the 6 months before the estimated first day of the last menstrual period (LMP) or at any time during pregnancy.

Specifically, the objectives are as follows:

- To estimate the frequency of selected adverse pregnancy outcomes in women with MS exposed to ocrelizumab during the defined exposure window; i.e., spontaneous abortions, stillbirths, elective abortions, preterm births, C-sections, and urinary and other infections in pregnancy.
- To estimate the frequency of selected adverse fetal/neonatal/infant outcomes at birth and up to the first year of life in infants from pregnancies in women with MS exposed to ocrelizumab; i.e., major congenital malformations (primary study outcome), small for gestational age, adverse effects on immune system development (e.g., severe infectious disease in the first year of life)
- To compare the frequency of each safety event of interest, including major congenital malformations (primary study outcome), between ocrelizumab-exposed pregnancies in women with MS and two comparison cohorts: (1) primary comparison cohort:

pregnancies in women with MS who have not been exposed to ocrelizumab (overall and in two strata—pregnancies exposed to any approved non-ocrelizumab disease-modifying therapies [DMTs] for the treatment of MS or that may be approved during the study period [subcohort 1a] and pregnancies not exposed to approved DMTs [subcohort 1b]) and (2) secondary comparison cohort: pregnancies in women without MS who have not been exposed to ocrelizumab

Study Design

This will be an observational cohort study of ocrelizumab-exposed pregnancies and two matched comparison cohorts using multiple sources of prospectively collected secondary data. The study will be conducted in existing population-based health care databases and registries. The proposed data sources include health care claims from the US and country-level registries from Denmark. Analyses will follow a common protocol and statistical analysis plan (SAP); results will be integrated via meta-analysis. Drug uptake will be monitored annually to determine when the main analysis should start, i.e., when a sufficient number of exposed pregnancies has accumulated (see Study Size). Annual monitoring reports from 2024 onward will also include the comparison cohorts, cohort characterization, and outcome counts. The earliest LMPs in the study data are expected to be in 2017. The study period will start with the first ocrelizumab prescription in each database (expected in 2017 in the US) and will end at the latest date for which data are available for the study from each data source (expected in Q2 2028).

The following cohorts will be assembled: ocrelizumab-exposed pregnancies in women with MS (exposed cohort), pregnancies not exposed to ocrelizumab in women with MS, and pregnancies not exposed to ocrelizumab in women without MS.

Population

Eligibility: The study population will include women from the three study cohorts and their children born during the study period. In each data source, study eligibility for mothers will require continuous enrollment with both medical and pharmacy benefits in the 6 months before the estimated beginning of pregnancy and throughout pregnancy. For children, eligibility criteria are inclusion of their mother in one of the three study cohorts (i.e., successful mother-child linkage is required) and continuous enrollment covering outpatient care and hospitalizations during follow-up (disenrollment will trigger end of follow-up).

For pregnancy outcomes, linkage to an infant is not required (i.e., pregnancies not linked to infants will be retained). For infant outcomes, linkage between the mother and infant is required.

Follow-up: Follow-up of women will start at the estimated beginning of pregnancy and will finish at the end of pregnancy; follow-up of infants will start at birth and finish at 1 year of age. For mothers and infants, follow-up will finish at the earliest of death, disenrollment from the data source, or end of the study period. In addition, for each outcome of interest that

can occur multiple times, follow-up for that outcome will stop at its first occurrence (e.g., urinary tract infections in pregnancy, infections requiring hospitalization in pregnancy).

Variables

Information may vary in the level of detail across data sources.

Exposure

The exposure of interest is ocrelizumab. The exposure window for ocrelizumab will be from 6 months (to take into account the product's half-life and the US prescribing information at the time of approval, March 2017) and 5 times the DMT-specific half-lives for each of the other MS DMTs before LMP to the end of pregnancy (1) to the end of the first trimester for analyses on congenital malformations; (2) to the end of the first trimester or the end of pregnancy if before end of first trimester, for analyses on spontaneous abortions and elective terminations; or (3) to the date of outcome(s) that may occur before the end of pregnancy (e.g., infections during pregnancy).

The sources for ascertainment of medication use will be pharmacy dispensing claims in claim databases and treatment information recorded in the MS Registry (possibly supplemented with data on dispensed prescriptions) in Denmark. The timing of medication use relative to the beginning of pregnancy will be determined or estimated from available data in the data sources.

Primary Study Outcome

- Major congenital malformations in the infants

Other Outcomes

- Spontaneous abortion (pregnancy loss at <20 completed weeks)
- Fetal death/stillbirth (≥20 completed weeks)
- Elective termination: the reason for termination (e.g., therapeutic abortion, abnormal findings in fetus in prenatal tests, ectopic pregnancy) will be ascertained to the extent to which data are available
- Preterm delivery (live birth at <37 completed weeks)
- C-section
- Urinary tract infection in pregnancy
- Infections requiring hospitalization during pregnancy
- Minor congenital malformations in the infants to the extent available, including a category for unspecified cardiac defects
- Small for gestational age
- Adverse effects on the immune system of the infants in the first year, comprising hospitalizations due to infectious diseases, cancer, and vaccine-preventable diseases and vaccine-associated poliomyelitis
- Infant growth and development to the extent available

Covariates

These variables were selected to provide a general description of the health and characteristics of the study cohorts and to explore potential confounding.

- Maternal characteristics at LMP: age, education, race and ethnicity (as available), obesity, medical history (including MS subtype [in Denmark] and other available information), history of smoking, and alcohol intake (information will be limited)
- Maternal obstetric history, including gravidity, parity, previous preterm deliveries, previous spontaneous abortions, or elective terminations, as available
- Medical conditions in pregnancy: such as course of MS; hypertension; diabetes; heart, thyroid, liver, kidney, and respiratory conditions (incl. asthma); and TORCH [toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19, Zika virus), rubella, cytomegalovirus, and herpes] infections, as available
- Medications from 6 months before LMP through delivery, including other MS treatments during the study period; vaccinations; medications to treat diabetes, hypertension, and other diseases; teratogenic medications, and fertility treatment associated with this pregnancy
- Measures of health care services utilization in the 6 months before pregnancy: medications not related to the treatment of MS, health care encounters
- Sex of the infant

Data Sources

The data sources planned for this study are health care claims databases in the US and in the national health care registries in Denmark:

United States

- Healthcare Integrated Research Database (HIRD®)
- Optum Dynamic Assessment of Pregnancies and Infants™ (DAPI) (formerly Systematic Tracking of Real Kids [STORK])
- IBM MarketScan Commercial Claims and Encounters Database (formerly Truven MarketScan Commercial Claims and Encounters Database; hereafter, “MarketScan”)

Denmark

- Nationwide population-based health registries and databases, including the Danish MS Registry

Study Size

The target for this study will be approximately 1,005 pregnancies exposed to ocrelizumab (to identify 405 live births with records linked to maternal records) and 3,015 pregnancies in each of the two comparator cohorts, including women from the 4 proposed data sources (to identify 1,215 live births with records linked to maternal records). This size, assuming that

62% of pregnancies end in a live birth and that 65% of pregnancies ending in live births are successfully linked to infants, will allow exclusion of a relative risk of 2.5 or greater, if the true relative risk is 1, for major malformations combined, which have a baseline prevalence of approximately 3% of live births. Should the actual proportion of live births exceed 62%, fewer pregnant women would be necessary to achieve the target number of linked live births.

Data Analysis

Comparisons will involve ocrelizumab-exposed pregnant women and two comparator cohorts: (1) primary comparison cohort—pregnancies in women with MS who have not been exposed to ocrelizumab (overall and in two strata—pregnancies exposed to non-ocrelizumab DMTs approved for the treatment of MS [subcohort 1a] and pregnancies not exposed to these DMTs [subcohort 1b]) and (2) secondary comparison cohort—pregnancies in women without MS who have not been exposed to ocrelizumab.

To control for confounding and channeling effect, using propensity scores, exposed subjects will be matched in a variable 1:3 ratio (up to 1:3) with subjects from subcohort 1a, with subjects from subcohort 1b, and with subjects from the secondary comparison cohort (separately).

Characteristics of the unmatched and matched cohorts, including the frequency of the outcomes, will be shown in tabular format. Balance in matching will be assessed by examining the distribution of variables in the cohorts and estimating standardized differences for each variable between the ocrelizumab-exposed and comparator cohorts. No statistical tests are planned for this comparison, but variables with standardized differences above 0.1 will be further evaluated and may lead to a re-evaluation of the propensity score estimation.

Unadjusted measures of outcome frequency will be estimated within the matched cohorts.

Measures of association will vary across outcomes and include hazard ratios and relative risks. No adjustment is planned beyond matching.

Subgroup analyses will include strata of maternal age, calendar year, and others (depending on counts and data availability).

Sensitivity analyses will include modifications of the exposure window to start 26, 90, and 130 days before pregnancy (1, 3.5, and 5 mean half-lives of ocrelizumab, respectively), by trimester of pregnancy, around matching and other key analytical factors.

Results will be presented separately for each data source. Overall association results (e.g., relative risks for major congenital malformations) will be summarized across data sources using meta-analytic techniques with random effects. A sensitivity analysis will

remove potential data overlap between HIRD or DAPI and MarketScan by excluding MarketScan results from pooled analyses.

Milestones

Start of Study Observation

The study start date is the date when ocrelizumab is first available in one of the participating US data sources. The planned start date is Q2 2017, coinciding with the availability of ocrelizumab in the US.

End of Study Observation

The end of study observation is the date of the last observation included. The planned end-of-study-observation date is expected within the period Q2 2028-Q1 2029, depending on data availability within each data source.

5. AMENDMENTS AND UPDATES

Substantial protocol amendments/updates so far: Amendments and updates to the study protocol are listed below.

Amendment/ Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
Amendment 3, Protocol BA39732, Version 4.0	See cover page	Throughout	Conception was replaced with LMP as the clinical concept underlying start of pregnancy for this study	This study uses LMP since SAP version 1.0; however, the protocol had not been updated. It has been updated now, in response to FDA Comments on the Annual Interim Report submitted on 29-Jun-2022 for Study BA39732 (PMR 3194-4), received on 8-Dec-2022
Amendment 3, Protocol BA39732, Version 4.0	See cover page	Throughout	Due to an institutional change, HealthCore is now called Carelon Research; HealthCore Integrated Research Database is now called Healthcare Integrated Research Database	To reflect current institutional names.
Amendment 3, Protocol BA39732, Version 4.0	See cover page	4, Abstract 6, Milestones	The description of the content of the monitoring reports has been updated to include covariates and outcome counts	In response to FDA Comments on the Annual Interim Report submitted on 29-Jun-2022 for Study BA39732 (PMR 3194-4), received on 8-Dec-2022

Amendment/ Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
Amendment 3, Protocol BA39732, Version 4.0	See cover page	9.1, Study Design; 9.2.1, Eligibility Criteria; 9.3.1, Exposure; 9.7.1, Study Cohorts; 9.7.6, Statistical Analysis	To modify the definition of the exposure window for non-ocrelizumab medications approved for MS treatment based on 5 times the half-life for the respective therapy	In response to FDA Comments on the Annual Interim Report submitted on 29-Jun-2022 for Study BA39732 (PMR 3194-4), received on 8-Dec-2022
Amendment 3, Protocol BA39732, Version 4.0	See cover page	9.2.1, Eligibility Criteria	An age-related inclusion criterion was added	In response to FDA Comments on the Annual Monitoring Report for Study BA39732 Pregnancy Outcomes Study (PMR 3194-4), received on 8-Dec-2022
Amendment 3, Protocol BA39732, Version 4.0	See cover page	9.3.2, Study Outcomes; Appendix 3	Changes to the clinical and operational definitions have been implemented	To homogenize definitions in this study with those determined as the most appropriate for implementation and in agreement with SAP version 4.0.
Amendment 3, Protocol BA39732, Version 4.0	See cover page	9.3.3, Covariates; 9.9, Limitations of the Research Methods	Added race and ethnicity variable	In response to FDA Comments on the Annual Interim Report submitted on 29-Jun-2022 for Study BA39732 (PMR 3194-4), received on 8-Dec-2022
Amendment 3, Protocol BA39732, Version 4.0	See cover page	4, Abstract 9.3.3, Covariates	Added Zika virus to TORCH infections	For completeness
Amendment 3, Protocol BA39732, Version 4.0	See cover page	9.5, Study Size	The count of ocrelizumab-exposed pregnancies observed in 2022 was added	For completeness

Amendment/ Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
Amendment 3, Protocol BA39732, Version 4.0	See cover page	9.7.9, Sensitivity Analyses; 9.9, Limitations of the Research Methods	Analyses added: pooling of data from Carelon Research, Optum, and Denmark (but not MarketScan)	To avoid any overlap between data from Carelon Research or Optum and data from MarketScan, in response to FDA Comments on the Annual Monitoring Report for Study BA39732 Pregnancy Outcomes Study (PMR 3194-4), received on 8-Dec-2022
Amendment 3, Protocol BA39732, Version 4.0	See cover page	9.7.9, Sensitivity Analyses	Analyses added: stop accrual of pregnant women well before the end of the data availability	To give pregnancies the opportunity to reach term
Amendment 3, Protocol BA39732, Version 4.0	See cover page	10. Protection of Human Subjects	IRB review results have been updated	For completeness
Amendment 3, Protocol BA39732, Version 4.0	See cover page	12, Plans for Disseminating and Communi-cating Study Results	The reference for a conference presentation was added	For completeness
Amendment 3, Protocol BA39732, Version 4.0	See cover page	Appendices	The checklist for reporting in perinatal pharmacoepidemiology has been added	To denote that key methods elements are explicitly included in the protocol or statistical analysis plan for this PASS.
Amendment 2, Protocol BA39732, Version 3.0	21-Jun-2021	9.3.1, Exposure	Drug and code lists were updated to include currently available treatments	For completeness
Amendment 2, Protocol BA39732, Version 3.0	21-Jun-2021	9.4.1, HealthCore Integrated Research Database	Description was updated	For alignment with current information
Amendment 2, Protocol BA39732, Version 3.0	21-Jun-2021	9.5, Study Size	Table 5 column headings were modified to specify whether the study sizes for various outcomes require linkage of mother and infant records	In response to FDA Comments on SAP for Study BA39732 Pregnancy Outcomes Study (PMR 3194-4) received on 23-Mar-2021

Amendment/ Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
Amendment 2, Protocol BA39732, Version 3.0	21-Jun-2021	9.7.6	Exposure is no longer described as varying by time	In response to FDA Comments on SAP for Study BA39732 Pregnancy Outcomes Study (PMR 3194-4) received on 23-Mar-2021
Amendment 1, Protocol BA39732, Version 2.0	14-Dec-2020	4, Abstract/ Synopsis	“Major congenital malformations” is denoted as the primary study outcome	In response to FDA Comments on SAP for Study BA39732 Pregnancy Outcomes Study (PMR 3194-4) received on 17-Nov-2020
Amendment 1, Protocol BA39732, Version 2.0	14-Dec-2020	4, Abstract/ Synopsis	Propensity score estimation and matching will be implemented for comparisons between the ocrelizumab-exposed cohort and subcohorts 1a and 1b instead of with the primary comparison cohort	In response to FDA Comments on SAP for Study BA39732 Pregnancy Outcomes Study (PMR 3194-4) received on 17-Nov-2020
Amendment 1, Protocol BA39732, Version 2.0	14-Dec-2020	4, Abstract/ Synopsis	Measures of association will include relative risks instead of odds ratios	In response to FDA Comments on SAP for Study BA39732 Pregnancy Outcomes Study (PMR 3194-4) received on 17-Nov-2020
Amendment 1, Protocol BA39732, Version 2.0	14-Dec-2020	4, Abstract/ Synopsis	Added sensitivity analyses around matching	In response to FDA Comments on SAP for Study BA39732 Pregnancy Outcomes Study (PMR 3194-4) received on 17-Nov-2020
Amendment 1, Protocol BA39732, Version 2.0	14-Dec-2020	6, Milestones	Updated to reflect current milestones per FDA’s document, Acknowledge Revised Postmarketing Requirement Milestones and Communicate Good Cause and Sufficient Justification for Anticipated Delay, dated 15 January 2020	In response to FDA Comments on SAP for Study BA39732 Pregnancy Outcomes Study (PMR 3194-4) received on 17-Nov-2020

Amendment/ Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
Amendment 1, Protocol BA39732, Version 2.0	14-Dec-2020	8, Research question and objectives	"Major congenital malformations" is denoted as the primary study outcome	In response to FDA Comments on SAP for Study BA39732 Pregnancy Outcomes Study (PMR 3194-4) received on 17-Nov-2020
Amendment 1, Protocol BA39732, Version 2.0	14-Dec-2020	9.3.2, Outcomes	"Major congenital malformations" is denoted as the primary study outcome	In response to FDA Comments on SAP for Study BA39732 Pregnancy Outcomes Study (PMR 3194-4) received on 17-Nov-2020
Amendment 1, Protocol BA39732, Version 2.0	14-Dec-2020	9.5, Study Size	Relative risk is denoted for calculation of study size Propensity score estimation and matching will occur between the ocrelizumab-exposed cohort and subcohorts 1a and 1b instead of with the primary comparison cohort Study size calculations for relative risks ranging from 2 to 5 were added for various study outcomes Study size calculations based on monitoring counts from 2020 were added	In response to FDA Comments on SAP for Study BA39732 Pregnancy Outcomes Study (PMR 3194-4) received on 17-Nov-2020
Amendment 1, Protocol BA39732, Version 2.0	14-Dec-2020	9.7.4, Measures of Association	Propensity score estimation and matching will be implemented for comparisons between the ocrelizumab-exposed cohort and subcohorts 1a and 1b instead of with the primary comparison cohort	In response to FDA Comments on SAP for Study BA39732 Pregnancy Outcomes Study (PMR 3194-4) received on 17-Nov-2020
Amendment 1, Protocol BA39732, Version 2.0	14-Dec-2020	9.7.6, Statistical Analysis	Measures of frequency will include cumulative incidence instead of cumulative risk Measures of association will include relative risks instead of odds ratios and will be estimated using log-binomial regression	In response to FDA Comments on SAP for Study BA39732 Pregnancy Outcomes Study (PMR 3194-4) received on 17-Nov-2020

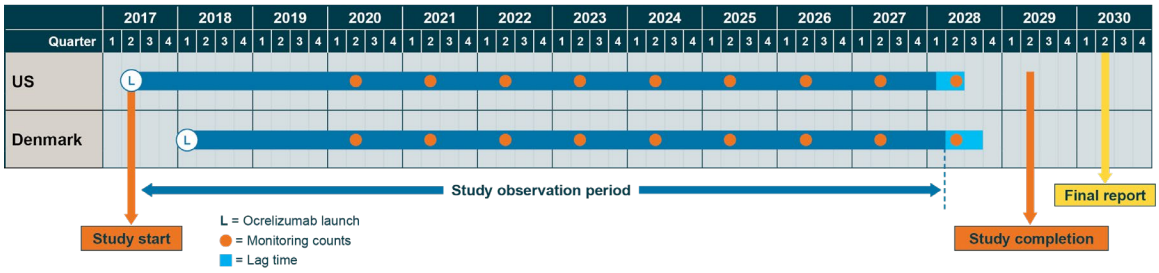
Amendment/ Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
			Analyses will account for matching by weighting; conditional logistic regression models have been removed	
Amendment 1, Protocol BA39732, Version 2.0	14-Dec-2020	9.7.6, Statistical Analysis	Analyses for spontaneous abortions will include the estimation of an incidence rate and a hazard ratio	For consistency with the statistical analysis plan

DMP = Data Monitoring Plan; FDA = Food and Drug Administration; IRB = institutional review board; LMP = first day of the last menstrual period; MS = multiple sclerosis; PASS = postauthorization safety study; PMR = postmarketing requirement; SAP = statistical analysis plan; TORCH = toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19, Zika virus), rubella, cytomegalovirus, and herpes infections.

6. MILESTONES

After regulatory endorsement of the protocol, the study will be registered with the EU PAS Register (ENCePP 2023). In each of the participating data sources, the study observation period (study period) will start with the first dispensing/prescription of ocrelizumab, which will vary by country (anticipated Q2 2017 in the US), and will end at varying times depending on the accrual of patients and pregnancy outcomes in each data source (anticipated within the period Q2 2028-Q2 2029), with anticipated study completion in June 2029 (Figure 1). Currently, data extraction from the first data source is anticipated in Q2 2028, with data extraction potentially occurring at different dates for each data source. This date depends on the drug uptake, which will in turn depend on the date of drug approval by health authorities, local reimbursement, availability of reimbursement codes (e.g., Healthcare Common Procedure Coding System procedure codes), and administrative procedures within the selected data sources and the data source lag time for the data release to research. For example, with a launch date of Q2 2017, data collection (i.e., extraction) from a data source would start in Q2 2028 assuming a 3- to 4-month lag in data availability (Figure 1).

Figure 1 Study Timeline



Study milestones are summarized in Table 1. The number of ocrelizumab-exposed pregnancies and live births have been monitored annually from 2020 to 2023 in all data

sources; characteristics of pregnancies (ocrelizumab-exposed pregnancies and pregnancies in comparison groups) and frequency of outcomes in all study cohorts (spontaneous abortion, elective termination, stillbirth, major congenital malformations, and small for gestational age) will also be monitored annually from 2024 onward. The annual monitoring will inform the study size, update the predicted study power, and determine the final study data set creation date. Completion of the final study report is planned for June 2030, or earlier if study size (i.e., the target number of linked live births) is reached earlier. Progress reports will be provided to the health authorities through scheduled regulatory safety reporting (periodic adverse drug experience reports [PADERs] and/or periodic benefit-risk evaluation reports [PBRERs], as agreed with health authorities).

Table 1 Study Milestones

Milestone	Planned Date
Registration of protocol in the EU PAS Register	28 February 2020 (effective date)
Start of study observation	Q2 2017
Monitoring of counts of ocrelizumab-exposed pregnancies and live births	30 June 2020 (submission effective date)
Monitoring of counts of ocrelizumab-exposed pregnancies and live births	25 June 2021 (submission effective date)
Monitoring of counts of ocrelizumab-exposed pregnancies and live births	29 June 2022 (submission effective date)
Monitoring of counts of ocrelizumab-exposed pregnancies and live births	June 2023
Monitoring of counts of ocrelizumab-exposed and comparison pregnancies, live births, and other study outcomes	June 2024
Monitoring of counts of ocrelizumab-exposed and comparison pregnancies, live births, and other study outcomes	June 2025
Monitoring of counts of ocrelizumab-exposed and comparison pregnancies, live births, and other study outcomes	June 2026
Monitoring of counts of ocrelizumab-exposed and comparison pregnancies, live births, and other study outcomes	June 2027
Monitoring of counts of ocrelizumab-exposed and comparison pregnancies, live births, and other study outcomes	June 2028
End of study observation	Q2 2028-Q2 2029
Start of data collection (EMA definition)[a]	Q2 2028
End of data collection (EMA definition)[b]	Q2 2029
Study completion	Jun 2029
Study progress report	According to PADER/PBRER schedule
Final report of study results (CSR)	June 2030
Registration of the results in the EU PAS Register	July 2030 (within 1 month of submission of final report to FDA)

CSR = clinical study report; EU PAS Register = European Union electronic Register of Post-Authorisation Studies; PADER = periodic adverse drug experience report; PBRER = periodic benefit-risk evaluation report.

Note: Contracts between the sponsor and research organization(s) and approvals by data protection, data custodian, ethics, and scientific and regulatory review bodies are complete. If monitoring counts indicate that the target study size (live births with mother-infant linkage) (Section 9.5) might be attained earlier than anticipated, the final study analyses will be launched earlier, allowing for earlier submission of the study report to the FDA.

[a] Start of data collection for secondary data use is "the date from which data extraction starts. Simple counts in a database to support the development of the study protocol, for example, to inform the sample size and statistical precision of the study, are not part of this definition" (EMA 2017b).

[b] End of data collection for secondary data use is "the date from which the analytical data set is completely available" (EMA 2017b).

7. RATIONALE AND BACKGROUND

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). Its etiology is not fully understood, but is thought to be a complex interaction of genetic susceptibility and environmental factors (Milo and Kahana 2010). Multiple sclerosis affects approximately 2.3 million people worldwide, with the highest prevalence found in North America and Europe (140 and 108 patients with MS per 100,000 population, respectively) (MSIF 2013). Overall, MS is more frequent in women than men, with a sex ratio of 2 to 3 women for every 1 man (Orton et al. 2006; Trojano et al. 2012), except in individuals with primary progressive form of the disease, which presents with similar prevalence by sex (NMSS 2023b). Multiple sclerosis is commonly diagnosed during reproductive ages, between 20 to 50 years (NMSS 2023d), with 30 years being the estimated average age of onset (MSIF 2013).

About 85% of people with MS have relapsing-remitting MS, a form of MS with exacerbations or relapses during which new symptoms appear or previous symptoms worsen and periods of partial or complete remission. If left untreated, most patients who are diagnosed with relapsing-remitting MS will eventually progress to a chronic form characterized by progressive worsening of neurologic function over time with occasional relapses; which is categorized as secondary progressive MS. Approximately 15% of people with MS are diagnosed with primary progressive MS (PPMS), a form of MS with steadily worsening neurologic symptoms from the onset of disease and no clear relapses (Lublin et al. 2014; NMSS 2023c).

Evidence suggests that inflammation is present in the CNS throughout all MS clinical courses, from relapsing-remitting MS to secondary progressive MS and in PPMS (Frischer et al. 2009). Differences between disease phenotypes are due to the differential contribution of each of the inflammatory and neurodegenerative processes to the pathophysiology of CNS damage over time (Frischer et al. 2009; Frischer et al. 2015).

OCREVUS® (ocrelizumab) was approved by the United States (US) Food and Drug Administration (FDA) on 28 March 2017 for the treatment of adult patients with relapsing

forms of MS (RMS) and PPMS (OCREVUS® PI 2022). Subsequently, OCREVUS® was approved in the EU, Switzerland, Australia, Canada, and other countries. In 2019, the RMS indication was expanded to include "clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease" (OCREVUS® PI 2022).

Ocrelizumab is a recombinant humanized monoclonal immunoglobulin G1 (IgG1) antibody that selectively targets CD20-expressing (CD20+) B cells. Two identical, randomized, active-controlled studies (OPERA I [Study WA21092] and OPERA II [Study WA21093]) have demonstrated superior efficacy outcomes versus interferon beta-1a in RMS (Hauser et al. 2017); one randomized, placebo-controlled study (ORATORIO [Study WA25046]) demonstrated superior efficacy in PPMS versus placebo (Montalban et al. 2017). Results of these studies show that depletion of CD20+ B cells leads to a significant impact on a broad range of clinical measures of disease, including disability progression, in addition to an impact on magnetic resonance imaging (MRI) outcomes related to disease progression and reflective of neural tissue loss, thus further supporting the hypothesis that B cells are central to the pathogenesis of both relapsing and primary progressive MS. Ocrelizumab has demonstrated a favorable safety profile in patients with RMS and PPMS (Hauser et al. 2017; Montalban et al. 2017). The proportion of patients with adverse events was similar in patients treated with ocrelizumab and patients treated with interferon beta-1a (both 83.3%) or placebo (95.1% vs. 90.0%). The proportion of patients experiencing a serious adverse event was similar between ocrelizumab and the comparator groups—in RMS: 6.9%, ocrelizumab, and 8.7%, interferon beta-1a; in PPMS: 20.4%, ocrelizumab, and 22.2%, placebo.

7.1 STUDY BACKGROUND

Birth defects—structural (e.g., cleft lip/palate, heart defects, neural tube defects, abnormal limbs) and functional/developmental (e.g., sensory problems, metabolic disorders, nervous system problems, degenerative disorders)—affect about 3.0 per 100 live births in the US (CDC 2008) and are the leading cause of infant deaths (about 20% of all infant deaths) (Matthews et al. 2015). The European Surveillance of Congenital Anomalies (EUROCAT) estimated the prevalence of major congenital anomalies to be 23.9 per 1,000 live births from 2003 to 2007 (Dolk et al. 2010). It is uncertain whether MS has an impact on the risk of adverse pregnancy and infant outcomes. Some studies suggest there is little evidence that MS increases the risk of adverse pregnancy, delivery, or infant outcomes including perinatal mortality, congenital malformations, and delivery complications (Dahl et al. 2005; Houtchens 2007; Mueller et al. 2002). Other studies suggest pregnancies in women with MS are associated with more frequent operative deliveries, decreased infant birth weight, and infants small for gestational age compared with women without MS (Dahl et al. 2008; Dahl et al. 2005; Kelly et al. 2009).

Ocrelizumab is a humanized monoclonal antibody of an immunoglobulin G1 subtype, and immunoglobulins are known to cross the placental barrier. B-cell levels in human neonates following maternal exposure to ocrelizumab have not been studied in clinical studies. 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 (Chakravarty et al. 2011; Klink et al. 2008).

It is not known whether ocrelizumab can affect pregnancy outcomes or infant outcomes in humans. However, based on pathophysiological considerations, ocrelizumab might theoretically affect pregnancy outcomes and infant outcomes in the following ways:

- By direct exposure of the fetus to ocrelizumab, which is assumed to occur after the 16th week of gestation as receptor-mediated transplacental transfer of IgG1; this is minimal during the first trimester of pregnancy (Palmeira et al. 2012; Simister 2003).
- Indirectly due to known or unknown infections or infectious complications in the mother exposed to ocrelizumab during pregnancy, which may affect infants, where the infection may be associated with ocrelizumab exposure.
- Indirectly due to effects of ocrelizumab on the placenta.

Based on the average ocrelizumab terminal half-life of 26 days reported in the studies of MS (USPI), it is expected that ocrelizumab would be eliminated from the body approximately 4.5 months after the last administration. Considering the interpatient variability (the longest terminal half-life recorded in women was 53 days) and the absence of placental transfer of immunoglobulins during the first trimester of pregnancy, it is recommended that women of childbearing potential should use contraception while receiving ocrelizumab and for 6 months after the last infusion of ocrelizumab. However, women may get pregnant during this period due to noncompliance with contraception or failure of contraceptive methods.

Clinical studies of the effects on pregnancy and infants associated with the use of ocrelizumab during pregnancy, during lactation, and/or before the first day of the last menstrual period (LMP) have not been performed, and experience from ocrelizumab clinical trials is very limited. As of 31 January 2017, 25 pregnancies were reported during ocrelizumab trials in MS. Of these 25 pregnancies, 7 were electively terminated, and no abnormalities were found in the embryos or products of conception; 1 pregnancy ended in stillbirth at approximately 7-8 months of gestation; 2 live, preterm births had abnormal findings (benign nasopharyngeal neoplasm, jaundice, respiratory distress, and low birth weight for one infant and temperature instability, feeding difficulties, bradycardia, respiratory distress, and anemia for the other); 11 pregnancies ended in a live, full-term birth; and 4 pregnancies were still ongoing at the time of analysis (Vukusic et al. 2017).

In an embryo-fetal development study in cynomolgus monkeys, there was no evidence of teratogenicity or embryotoxicity (Study 04-1272-1342). Also in monkeys, using doses similar to or larger than those used clinically on a mg/kg basis, increased perinatal mortality (in some cases associated with bacterial infections), depletion of circulating B cells, and toxicity to kidneys (glomerulopathy and inflammation), bone marrow (lymphoid follicle

formation), and testis (reduced weight) were seen in the offspring in the absence of toxicity in the mother (USPI). Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants of women treated during pregnancy with other drugs with the same mechanism of action. Ocrelizumab was excreted in the milk of treated monkeys. The effects on the infant of ocrelizumab exposure through lactation are not known (USPI).

Roche proposes a non-interventional multidatabase postmarketing safety study to assess pregnancy-related safety data from women with MS exposed to ocrelizumab. Research partners (Carelon Research, Inc.; Optum; RTI Health Solutions [RTI-HS]; and Aarhus University) will conduct the work in each data source, and a coordinating center (RTI-HS) will lead/oversee the development of study documents, coordinate research activities, and pool results from individual data sources. This study will be conducted to fulfill part of the FDA postmarketing requirements (PMR 3194-4) for approval of ocrelizumab in the US. The study is listed as additional pharmacovigilance activity to address the missing information on drug use during pregnancy and lactation in the proposed European Union Risk Management Plan.

8. RESEARCH QUESTION AND OBJECTIVES

To assess and characterize pregnancy and infant outcomes of women with MS exposed to ocrelizumab during the 6 months before the estimated LMP or at any time during pregnancy.

The objectives are as follows:

- To estimate the frequency of selected adverse pregnancy outcomes in women with MS exposed to ocrelizumab during the defined exposure window (i.e., spontaneous abortions, fetal death/stillbirths, elective abortions, preterm births, C-sections, and urinary and other infections in pregnancy)
- To estimate the frequency of selected adverse fetal/neonatal/infant outcomes at birth and up to the first year of life of infants from pregnancies in women with MS exposed to ocrelizumab—i.e., major congenital malformations (primary study outcome), small for gestational age, adverse effects on immune system development (e.g., severe infectious disease in the first year of life)
- To compare the frequency of each safety event of interest, including major congenital malformations (primary study outcome), between ocrelizumab-exposed pregnant women with MS and two comparison cohorts: (1) primary comparison cohort—pregnancies in women with MS who have not been exposed to ocrelizumab (overall and in two strata—pregnancies exposed to any non-ocrelizumab disease-modifying therapies [DMTs] approved for the treatment of MS or any new DMT approved during the study period [subcohort 1a], and pregnancies not exposed to these DMTs [subcohort 1b]) and (2) secondary comparison cohort—pregnancies in women without MS who have not been exposed to ocrelizumab.

9. RESEARCH METHODS

In addition to a prospective product-specific pregnancy registry (PMR 3194-3, protocol WA40063) in the US, Germany, and possibly other countries, Roche proposes this study, in which secondary data sources will be used to ensure collection of sufficient data to reach scientifically valid conclusions on the safety of ocrelizumab use before LMP and during pregnancy as soon as possible after marketing authorization. Roche is aware that marketing authorization holders of other MS treatments (e.g., fingolimod, natalizumab, alemtuzumab, and teriflunomide) have attempted to generate pregnancy safety data by establishing drug-specific pregnancy registries. It has been noted by both the FDA and the EMA that product-specific pregnancy registries very often fail to provide clinically meaningful information in a timely manner, because of inadequate enrollment, loss to follow-up, selection bias, limited statistical power, and lack of suitable comparator populations (Gelperin et al. 2017; Sahin 2014). A recent analysis of pregnancy registries found that among products that had a stated target enrollment in the pregnancy registry protocol (22 of 59 registries [37%]), only 14% (3 of 22) achieved target enrollment (Sahin 2014). In the case of MS, two therapy-specific pregnancy exposure registries had to be terminated early because of low enrollment, and other ongoing pregnancy registries have experienced delays due to recruitment challenges (Anthony and Krueger 2016). Given these known challenges and limitations in obtaining quality pregnancy exposure data for newly launched drugs, Roche aims to obtain more timely information on the safety of the use of ocrelizumab before and during pregnancy by utilizing health care databases from the US and Europe. Analyses of existing databases with prospectively collected data have been proven useful to evaluate many drug safety questions, including questions on drug safety in pregnancy (Broms et al. 2014; Charlton et al. 2014; Hviid et al. 2013; Johansson et al. 2015; Li et al. 2014; Mines et al. 2014; Molgaard-Nielsen et al. 2016). Using existing databases minimizes the risk of self-selection into the study that is inherent to pregnancy exposure registries. Self-selection into a study may affect generalizability in that volunteers may be different from the average patient who is treated in routine practice. Additionally, the validity of relative risk estimates may be affected if subsets of women enroll late in registries (after the at-risk period for early pregnancy outcomes such as spontaneous abortions) or if the likelihood that women will enroll depends on their risk for outcomes such as congenital malformations.

In the past, pregnancy exposure registries were considered the first line of evidence because they are able to enroll women as soon as the drug is in the market. Standardization of protocols, methods development, and international collaborations are now allowing the creation of nested pregnancy cohorts within health care databases that are pooled, resulting in larger sample sizes in a shorter time.

Because the number of eligible subjects may be small in any given database, this non-interventional postmarketing safety study will integrate results from multiple data sources that prospectively collect relevant pregnancy data. Mother-child linked data will be extracted from existing health care claims databases in the US and population-based patient registries in Denmark. These two countries have a high prevalence of MS (>100 people with MS per

100,000 population) (MSIF 2013) and are generally quick in the uptake of new medications. Specifically, in Denmark, the prevalence of MS was 250 per 100,000 persons, with a female to male ratio of 2 to 1 in 2017 (personal communication from Melinda Magyari, head of The Danish Multiple Sclerosis Registry, July 2017). Suitability of the data sources in relation to reimbursement status has been determined. Furthermore, drug uptake will be monitored every year to assess when the target study size (i.e., the target number of linked live births) is reached.

9.1 STUDY DESIGN

This is a matched cohort study using multiple sources of prospectively collected secondary data. Selected outcomes will be validated in the data sources in which this is possible. Study subjects will include pregnant women and their children born during the study period.

The following cohorts will be assembled:

- Pregnancies in women with MS and exposure to ocrelizumab initiating or continuing within 6 months before LMP and/or at any time during pregnancy, and the children born to these pregnancies (exposed cohort). For analyses on congenital malformations, the exposure period will be 6 months before LMP or any time during the first trimester of pregnancy. For analyses on spontaneous abortions and elective terminations, the exposure period will start 6 months before LMP; it will end at the earliest of the end of the first trimester or the end of pregnancy.
- Pregnancies in women with MS but no ocrelizumab exposure in the 6 months before LMP or at any time during pregnancy who are matched to ocrelizumab-exposed pregnancies, and the children born to these pregnancies during the study period (primary comparison cohort). Results will be presented for the overall cohort and for two strata:
  - Pregnancies in women with MS exposed to any non-ocrelizumab DMTs approved for the treatment of MS or to any new DMTs approved during the study period (primary comparison subcohort 1a) within 5 half-lives of the corresponding DMT before LMP or any time during pregnancy. For analysis on congenital malformations, spontaneous abortions, and elective terminations, the exposure windows for non-ocrelizumab DMTs will end as described for ocrelizumab
  - Pregnancies in women with MS not exposed to DMTs approved for the treatment of MS (primary comparison subcohort 1b)
- Pregnancies in women without MS or ocrelizumab use who are matched to ocrelizumab-exposed pregnancies, and the children born to these pregnancies during the study period (secondary comparison cohort).

The checklist for reporting in perinatal pharmacoepidemiology (Margulis et al. 2022) is presented in Appendix 5.

9.2 SETTING

The data sources for this study include health care claims from the US and country-level registries from Denmark, including the Danish MS Registry.

A common core protocol will be adapted to each data source so that methods are as homogeneous as possible across data sources but also tailored to the specific characteristics of each source.

9.2.1 Eligibility Criteria

In each data source, the study will include all matched pregnancies in women with a pregnancy in the study period with continuous enrollment with pharmacy benefits in the 6 months before the estimated beginning of pregnancy and throughout the pregnancy and who are aged 18 to 50 years at LMP, and the children born to these pregnancies during the study period. For pregnancy outcomes, linkage to infants is not required (i.e., pregnancies not linked to an infant will be retained). For infant outcomes, linkage between the mother and infant is required.

Matching will be based on an exposure propensity score, which is described in Section 9.7.4.

A woman with MS and two recorded pregnancies in the study period who received ocrelizumab in one pregnancy and another drug to treat MS in the other pregnancy will contribute one pregnancy to each of two cohorts. Singleton and multifetal pregnancies, in addition to pregnancies carrying fetuses with major or minor malformations or with chromosomal abnormalities and ending in a live or non-live birth, will be considered for eligibility.

Women who used both ocrelizumab and a non-ocrelizumab DMT defining comparison subcohort 1a in the exposure window will be excluded from the comparative analyses, because their information will not be useful to understand whether any effect seen is associated with ocrelizumab or a comparator drug. Counts of pregnancies and counts of outcomes from these pregnancies, by drug combinations, will be presented in the study report. This situation is expected to occur in a small number of pregnancies. Women will be excluded from the study if they received—within the DMT-specific 5–half-life time window before pregnancy or during pregnancy—rituximab, a monoclonal antibody with the same mechanism of action as ocrelizumab that is used off-label for the treatment of MS (Salzer et al. 2016); ofatumumab; or other drugs with the same mechanism of action that may become available during the study period.

Eligibility criteria for children are inclusion of their mother in one the three study cohorts (i.e., successful mother-child linkage is required) and continuous enrollment covering outpatient care and hospitalizations (disenrollment or gaps in enrollment will stop follow-up, as specified in Section 9.2.3, Follow-up).

9.2.2 Study Period

The study observation period (study period) will start with the first dispensing/prescription of ocrelizumab in each of the participating data sources, which will vary by country. Accrual and follow-up of pregnant women and their infants will start with the first ocrelizumab prescription following approval on 28 March 2017 in the US and on 8 January 2018 in the European Union and will end at the latest date with data collected from each data source (expected in 2028). The latest date with data may vary across data sources, because the study will attempt to include the largest possible number of pregnancies from each data source (see Section 6, Figure 1).

9.2.3 Follow-up

Follow-up of women will start at the estimated beginning of pregnancy and will finish at the end of pregnancy; follow-up of infants will start at birth and finish at 1 year of age. For mothers and infants, follow-up will finish at the earliest of death, disenrollment from the data source, or end of the study period. In addition, for each outcome of interest that can occur multiple times, follow-up for that outcome will stop at its first occurrence (e.g., urinary tract infections in pregnancy, infections requiring hospitalization in pregnancy). Follow-up will continue for other outcomes.

9.3 VARIABLES

9.3.1 Exposure

The exposure of interest is ocrelizumab; other DMTs approved for MS, which will be the basis for forming comparison subcohort 1a, are listed in Table 2. Other MS DMTs that may become available during the study period will be considered for inclusion in this list (except those listed for exclusion [Section 9.2.1]). Such new drugs will be documented in the statistical analysis plan (SAP).

The exposure window will start 6 months before LMP for ocrelizumab, and a DMT-specific 5–half-life time window before LMP for each of the other DMTs. For ocrelizumab and other DMTs, the exposure window will end at the end of pregnancy for end-of-pregnancy and infant outcomes, at the end of the first trimester for analyses on congenital malformations, at the earliest of end of the first trimester or the end of pregnancy for analyses on spontaneous abortions or elective terminations, or at the date of occurrence of outcomes that may occur before the end of pregnancy (e.g., infections during pregnancy). The interval of 6 months before LMP takes into account ocrelizumab half-life, as described in Section 7, Rationale and Background, and is based on the prescribing information in the US at the time of approval (March 2017). As noted, for other DMTs, the exposure window will be based on 5 times the drug-specific half-life before LMP. Non-ocrelizumab DMTs used before their corresponding 5–half-life time window before LMP will not play a role in determining entry into comparison subcohorts in the primary analysis.

Exposure will be defined based on records of one or more dispensed prescriptions (treatment initiation or continuation) with dispensing dates within the noted exposure windows. Additional details are provided in Table 7 in Section 9.7.1, Study Cohorts.

The sources for ascertainment of medication use will be pharmacy claims and product-specific administration procedure codes in claim databases and treatment information in the MS Registry in Denmark (in Denmark, pharmacies do not dispense MS treatments). The timing of medication use relative to the beginning of pregnancy will be estimated, if needed, using previously described methods (Margulis et al. 2015).

Table 2 Ocrelizumab and Other Multiple Sclerosis Disease-Modifying Therapies

ATC Code[a]	Substance[b]	Route and Frequency of Administration[b]	Duration of Contraception After Last Course of Treatment[c]	Half-life (5 half-lives)[d]
L04AA34	Alemtuzumab	IV infusion in two blocks (5 and 3 days) 12 months apart	4 months	4–5 days (25 days)
L04AA40	Cladribine	Oral with 1 week of treatment at the start of treatment, another week of treatment 1 month later, and a second cycle in the second year	6 months	1 day (5 days)
L04AC01	Daclizumab[e]	SC once a month	Not specified	21 days (105 days)
L04AX07	Dimethyl fumarate	Oral twice daily	Not specified	1 hour (1 day)
L04AX09	Diroximel fumarate	Oral twice daily	Not specified	1 hour (1 day)
L04AA27	Fingolimod	Oral daily	2 months	6–9 days (45 days)
L03AX13	Glatiramer acetate	SC every day or 3 times a week	Not specified	<24 hours (5 days)
L03AB07	Interferon beta-1a	IM once a week or SC 3 times a week	Not specified	50–60 hours (13 days)
L03AB08	Interferon beta-1b	SC every other day	Not specified	5 hours (2 days)
L01DB07 (as antineoplastic drug)	Mitoxantrone	IV infusion every 3 months	Not specified	23–215 hours (45 days)
Not assigned	Monomethyl fumarate	Oral twice daily	Not specified	24 hours (5 days)
L04AA23	Natalizumab	IV infusion every 28 days	Not specified	11±4 days (75 days)
L04AA36	Ocrelizumab	IV infusion every 2 weeks as a starting dose and every 6 months later	6 months	26 days (130 days)

ATC Code[a]	Substance[b]	Route and Frequency of Administration[b]	Duration of Contraception After Last Course of Treatment[c]	Half-life[c] (5 half-lives)[d]
L04AA52	Ofatumumab	SC weekly for 3 weeks; then SC once monthly	6 months	16 days (80 days)
L04AA38	Ozanimod	Oral once daily	3 months	11 days (55 days)
L03AB13	Peginterferon beta-1a	SC every 14 days	Not specified	78 hours (17 days)
L04AA50	Ponesimod	Oral once daily	1 week	33 hours (7 days)
L04AA42	Siponimod	Oral once daily	10 days	30 hours (7 days)
L04AA31	Teriflunomide	Oral daily	Until plasma concentrations of teriflunomide have been verified to be less than 0.02 mg/L (0.02 mcg/mL), or 2 years	19 days (95 days)

ATC = Anatomical Therapeutic Chemical; IM = intramuscular; IV = intravenous; NMSS = National Multiple Sclerosis Society; SC = subcutaneous; WHO = World Health Organization.

[a] WHO (2022).

[b] NMSS (2023a).

[c] Sources: Drugs@FDA: FDA Approved Drug Products https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm; European product information at https://www.ema.europa.eu/en/medicines.

[d] Calculated as 5 times the half-life of the respective medication rounded up to the next integer in days (e.g., 5 hours is rounded up to 1 day). When the sources indicated a range of half-lives, the longest half-life was used.

[e] Withdrawn as of 2 March 2018.

9.3.2 Outcomes

Outcomes will be defined homogeneously across the data sources to the fullest extent possible based on the available information. The study outcomes are listed below. For diagnoses that are less commonly studied in health care databases, references supporting the feasibility of the approach are provided. When outcomes definitions vary across data sources, explanatory text is provided.

(1) Pregnancy outcomes and pregnancy complications

- Spontaneous abortion [pregnancy loss at <20 completed weeks (ACOG 2009)]. Abortion events with codes for ectopic pregnancy will not be considered events of spontaneous abortion.
- Elective termination: the reason for termination (e.g., therapeutic abortion, abnormal findings in fetus in prenatal tests, ectopic pregnancy) will be ascertained to the extent to which data are available.
- Fetal death/stillbirth (≥20 completed weeks). The standard definition of stillbirth in the Danish Medical Birth Registry uses 22 weeks of gestational age as the threshold, but it will be adapted to the preferred definition in this study; earlier fetal demises will be considered spontaneous abortions.
- Preterm delivery (live birth at <37 completed weeks).
- C-section (emergency or elective cesarean sections).
- Urinary tract infection during pregnancy (acute cystitis or asymptomatic bacteriuria in data from ambulatory care and dispensing of appropriate antibiotics). Danish registries will not capture mild episodes treated only in the primary care setting; for these occurrences, the outcome will be based on dispensed antibiotics.
- Infections requiring hospitalization during pregnancy (hospitalizations with main discharge diagnosis being an infectious disease or chorioamnionitis in any position). Chorioamnionitis will be reported separately.

(2) Fetal/neonatal/infant outcomes

- Major congenital malformations. This is the primary study outcome. Definitions and potential groupings will be based on guidelines from the European Surveillance of Congenital Anomalies program (EUROCAT 2021). In addition to major congenital malformations diagnosed in liveborn infants, information on major congenital malformations from spontaneous abortions, stillborns, and elective terminations will also be used, if available. Patent foramen ovale and persistent ductus arteriosus in preterms and undescended testes will not be included among major congenital malformations; patent foramen ovale, persistent ductus arteriosus, and possibly other cardiac malformations will be presented separately in a category named “unspecified cardiac defects.” The rationale is that these malformations are often physiologically expected in preterm births or are the result of improved technology, with little clinical significance for a large proportion of cases.
- Specific categories of major congenital malformations (e.g., cardiovascular) and specific malformations will be explored depending on the number of events observed

(e.g., hypospadias, cleft lip with or without cleft palate, and cardiac malformations [or subtypes]). Major congenital malformations are not expected through direct effects of the drug, as transplacental transfer of IgG1 is minimal before the 16th week of gestation (Palmeira et al. 2012; Simister 2003).

- Minor malformations will be examined to the extent available. Codes to define minor malformations will be based on guidelines from EUROCAT (2022). Underrecording is expected in all data sources. A category for unspecified cardiac defects will be included.
- Small for gestational age (defined by birth weight <10th percentile of the gestational-age-specific birth weight for data sources for which birth weight data are available, or diagnosis codes for small for gestational age). A secondary algorithm will be based on the fifth percentile.
- Infant growth (length, weight, and head circumference), including measurements at birth and during follow-up, will be explored where available. Danish registries are anticipated to contain some information on head circumference at birth.
- Infant development will be explored to the extent available.
- The following adverse effects on the immune system in the first year:
  - Hospitalizations due to infectious diseases, stratified by neonatal infections (within 28 days of birth) and later infections. The rationale for this stratification is that fever in neonates generally triggers a much more intensive sepsis workup.
  - Any cancer, including leukemia.
  - Vaccine-preventable diseases and vaccine-associated poliomyelitis in the first year of life: composite outcome of hepatitis B, whooping cough, tetanus, diphtheria, rotavirus diarrhea, invasive *Haemophilus influenza* b disease, invasive pneumococcal disease, poliomyelitis, and vaccine-associated poliomyelitis. Included in this composite outcome are infectious diseases for which children are typically immunized before 1 year of age. Among all possible occurrences of these conditions, an event will be considered to be a study outcome only if the event occurs between the age of first immunization (as listed in the country-specific immunization guidelines and recommendations) for the condition and 1 year of age of the infant.

Outcomes will be ascertained from diagnosis codes and procedure codes in US and Danish data sources in maternal and infant inpatient and outpatient records; dispensed drugs will be used in both types of data sources for ascertainment of treatment of urinary infections. Outcome definitions will be expanded in the SAP.

The ability of data sources to support validation efforts was considered in the feasibility assessment. Of the proposed data sources, outcome validation is feasible in HIRD and DAPI data. In MarketScan data, outcomes will be identified using algorithms validated in other US claims data sources. The approach for validation may include review of electronic medical records, medical chart abstraction, and review of claims, with estimation of the positive predictive values of outcome codes or algorithms (point estimate and 95% confidence interval). Cases of selected outcomes in the matched cohorts might be validated, subject to availability of medical charts, if the chosen validation method requires

review of medical charts. The selection of outcomes for validation will be informed by experts in the subject matter and in the data sources so that efforts are focused on the outcomes more susceptible to misclassification. The description of this process will be incorporated in the data validation plan, along with the strategy for estimating the target number of events for validation and the strategy for sampling events. These strategies will be determined in collaboration with the research partners to ensure that nuances of each data source are taken into consideration.

As a part of the outcome validation process, and if no validated algorithms for preterm birth using ICD-10 codes are available before the conduct of the analysis, three electronic algorithms for ascertaining preterm birth will be assessed; the prevalence of preterm birth will be estimated using these three algorithms in US data sources and one in Danish data (Appendix 3). Similarly, if no validated algorithms for small for gestational age (SGA) using ICD-10 codes are available before conduct of the analyses, three electronic algorithms will be assessed in US data sources, and the prevalence of SGA will be estimated using these three algorithms in US data sources (Appendix 3). In Danish data, prevalence of SGA will be estimated using primary and secondary algorithms (Appendix 3). Validation efforts conducted in US data sources will determine which algorithms for preterm birth and SGA will be selected for use in subsequent analyses in US data sources. For selected outcomes, if validated algorithms are not available for implementation in MarketScan, the number of outcomes observed in MarketScan will be placed into context by estimating the number of outcomes that would be expected had the algorithm performed with the same accuracy as in DAPI and HIRD.

A side-by-side comparison of estimated prevalences from the various study data sources (without statistical tests) is planned to help the research team interpret similarities and differences across data sources.

To the extent possible, validated algorithms (validated within this study or published) will be used to identify outcomes. As the transition from ICD-9 to ICD-10 codes happened relatively recently in US claims data (1 October 2015), limited validation work has been published at this point. Algorithms to define key study endpoints are presented in Appendix 3; it was not possible to define these endpoints with validated ICD-10 codes. Validated algorithms for other endpoints will be sought and specified in the SAP. If validated algorithms using ICD-10 or ICD-10-CM codes in US claims data with positive predictive value (PPV) (point estimate) ≥80% become available before the conduct of this study, those validated algorithms will be considered for use instead of the ones proposed in Appendix 3.

Details are defined in a data validation plan that has been developed and will be applied in consultation with clinicians with appropriate expertise within each collaborating institution (e.g., teratology or pediatrics with expertise in birth defects) who will support the clinical review process.

9.3.3 Covariates

Patient and pregnancy characteristics of interest are listed in Table 3. These variables were selected to provide a general description of the health and characteristics of the study cohorts and to explore potential confounding. The level of detail and completeness will vary across data sources. In claims data, the period for ascertaining baseline characteristics will be limited by the period of enrollment in the health care plan. Obesity, smoking habits, alcohol abuse and drug abuse may be very incompletely captured in all data sources. Their inclusion in analyses will be decided based on the information available (e.g., percentage of missing values).

Table 3 Covariates

Covariate	Comments	Availability in Data Sources			
		Carelon Research HIRD	IBM MarketScan	Optum DAPI	Danish National Health Databases
Maternal characteristics at LMP					
Age	In years	X	X	X	X
Calendar year	In years	X	X	X	X
Race and ethnicity	Imputed variable using an algorithm/model based on mother's information	X	NA	X	NA
Maximum education attained	In categories (to be specified)	NA	NA	NA	X
Obesity	Diagnosis codes and through proxies (treatment); likely to be incompletely captured in all sources	X	X	X	X
Smoking habits	Defined through proxies (treatment) or diagnosis codes, likely underrecorded in all sources	X	X	X	X
Alcohol abuse	Defined through diagnosis codes and proxies (treatment), likely underrecorded in all sources	X	X	X	X
Drug abuse	Defined through diagnosis codes and proxies (treatment)	X	X	X	X
MS type	E.g., RRMS. ICD-10 and ICD-10-CM do not have entries for MS types In Denmark, information will be extracted from the MS Registry	NA	NA	NA	X

Covariate	Comments	Availability in Data Sources			
		Carelon Research HIRD	IBM MarketScan	Optum DAPI	Danish National Health Databases
Duration of MS	In claims, time since first diagnosis code (risk of underascertainment due to left censoring, or restricted look-back period). In Denmark, based on year of onset as recorded in the MS Registry	X	X	X	X
Number of MS relapses in 6 months previous to LMP	In claims, relapses will be identified using the same algorithm across data sources. Published algorithms with their validation results are presented in Table 4. The selected algorithm will be specified in the SAP. In Denmark, information will be extracted from the MS Registry.	X	X	X	X
DMTs approved for MS received in the 12 months before the exposure window	From list in Table 2 Dispensed prescriptions and product-specific administration procedure codes In Denmark, information will be extracted from the MS Registry.	X	X	X	X
Other drugs used for MS received before LMP (e.g., methotrexate, azathioprine, cyclophosphamide, rituximab)	Dispensed prescriptions and product-specific administration procedure codes	X	X	X	X
Drugs to treat MS symptoms (e.g., amantadine, baclofen)	From dispensed prescriptions	X	X	X	X

Covariate	Comments	Availability in Data Sources			
		Carelon Research HIRD	IBM MarketScan	Optum DAPI	Danish National Health Databases
Hypertension	Defined through diagnoses, or use of medications in previous 12 months, not including gestational hypertension	X	X	X	X
Diabetes	Defined through diagnoses or use of medication in previous 12 months, not including gestational diabetes	X	X	X	X
Thyroid disease	Defined through diagnosis codes and applicable medications	X	X	X	X
Heart disease	Defined through diagnosis codes and applicable medications	X	X	X	X
Respiratory disease, incl. asthma	Defined through diagnosis codes and applicable medications	X	X	X	X
Liver disease	Defined through diagnosis codes and applicable medications	X	X	X	X
Kidney disease	Defined through diagnosis codes and applicable medications and procedures	X	X	X	X
Non-MS chronic neurologic disease	Defined through diagnosis codes and applicable medications	X	X	X	X
Malignancies except nonmelanoma skin cancer and in situ cancer	Defined through diagnosis codes and applicable medications	X	X	X	X
Anxiety/depression	Defined through diagnoses or use of medication in previous 12 months	X	X	X	X
Severe mental health conditions	Hospitalizations or institutionalization, not including depression	X	X	X	X

Covariate	Comments	Availability in Data Sources			
		Carelon Research HIRD	IBM MarketScan	Optum DAPI	Danish National Health Databases
Gravidity	Defined through diagnosis codes in claims data (limited by duration of enrollment before cohort entry) and in Medical Birth Registry in Denmark. Spontaneous abortions and terminations may be underrecorded	X	X	X	X
Parity	As number of deliveries or C-sections. Limitations as above. In Denmark, information will be extracted from the Danish Medical Birth Registry.	X	X	X	X
Spontaneous abortions in previous pregnancies	Defined through diagnosis codes. Likely underrecorded in all sources. In Denmark, information will be extracted from the Danish National Patient Registry (DNPR).	X	X	X	X
Pregnancy terminations in previous pregnancies	Defined through diagnosis codes. Likely underrecorded in all sources. In Denmark, information will be extracted from the Danish National Patient Registry (DNPR).	X	X	X	X
Health care utilization in the 6 months before LMP					
Psychotropic medications	Defined through dispensed prescriptions	X	X	X	X
Medications not used to treat MS or its symptoms	Defined through dispensed prescriptions	X	X	X	X
Number of medical encounters	Count of encounters with different date	X	X	X	X

Covariate	Comments	Availability in Data Sources			
		Carelon Research HIRD	IBM MarketScan	Optum DAPI	Danish National Health Databases
Descriptive data for this pregnancy					
Multiple pregnancy	Defined through diagnosis codes. In Denmark, information will be extracted from the Medical Birth registry	X	X	X	X
Gestational diabetes	Defined through diagnosis codes. In Denmark, information will be extracted from the Danish National Patient Registry (DNPR)	X	X	X	X
Preeclampsia/ eclampsia	Defined through diagnosis codes. In Denmark, information will be extracted from the Danish National Patient Registry (DNPR).	X	X	X	X
Number of MS relapses during pregnancy	Please see definition of proxy for relapses provided earlier in this table and in Table 4. In Denmark, information will be extracted from the MS Registry.	X	X	X	X
Sex of the infant	Administrative records	X	X	X	X
Use of oral contraceptives around LMP	Defined through dispensed prescriptions in the 3 months before pregnancy and the first month of pregnancy	X	X	X	X
TORCH infections	Defined through diagnosis codes for toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19, Zika virus), rubella, cytomegalovirus, and herpes infections during pregnancy (Stegmann and Carey 2002). Only infections that triggered contact with health care will be identified.	X	X	X	X

Covariate	Comments	Availability in Data Sources			
		Carelon Research HIRD	IBM MarketScan	Optum DAPI	Danish National Health Databases
Teratogenic medications	Prescriptions dispensed from 6 months before LMP to end of first trimester and end of third trimester of pregnancy for drugs in list of teratogenic medications in Eltonsy et al. (2016)	X	X	X	X
Vaccines	Dispensed prescriptions (vaccines offered at work, e.g., flu, will be underrecorded)	X	X	X	X

DMT = disease-modifying therapies; HIRD = Healthcare Integrated Research Database; ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th Revision; ICD-10-CM = International Classification of Diseases, 10th Revision, Clinical Modification; LMP = first day of the last menstrual period; MCM = major congenital malformation; MS = multiple sclerosis; NA = not available; RRMS = relapsing-remitting multiple sclerosis; TORCH = toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19, Zika virus), rubella, cytomegalovirus, and herpes infections; X = information available.

Table 4 Published Algorithms to Identify Relapses of Multiple Sclerosis in Claims Data

Reference, Data Type, and Country	Summary of Algorithm	Validation Results
Chastek et al. (2010) Health care claims from the US	Relapses were identified as follows: ▪ Hospitalizations with a primary diagnosis of MS at any time during hospitalization, OR ▪ A corticosteroid claim following an outpatient visit with a code for MS in the primary or secondary position	Validation of cases was conducted against medical charts for 300 patients. ▪ PPV = 67.3% ▪ NPV = 70.0%
Wang et al. (2015) Health care claims from Optum Research Database, US	Relapses were identified as follows: Algorithm 1: ▪ High dose (≥500 mg per day) of oral prednisone, prednisolone, or methylprednisolone for up to 15 days; OR ▪ ACTH ≥80 U per day for 5 days or more; OR ▪ Any IV methylprednisolone (regardless of dosage) for up to 15 days. Algorithm 2: ▪ High dose (≥500 mg per day) of oral prednisone, prednisolone, or methylprednisolone for up to 15 days; OR ▪ ACTH ≥80 U per day for 5 days or more; OR ▪ Hospitalization episode associated with MS (ICD-9 code 340)	No direct validation, but authors report that these algorithms identified relapses in 1.4% and 2.1% of patients treated with dimethyl fumarate for 6 or 12 months, respectively, while previous reports were around 6% in patients 6 and 12 months after initiation of dimethyl fumarate.

ACTH = adrenocorticotropic hormone; ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification; MS = multiple sclerosis; NPV = negative predictive value; PPV = positive predictive value.

9.4 DATA SOURCES

This is a multisource study involving population-based patient registries and health care databases that prospectively collect data in the US and Europe. The specific data sources were determined in a feasibility study conducted to identify the most appropriate sources for this study. Availability of mother-infant linked data, birth certificates, and other data, and ability to support partial outcome validation was assessed in the feasibility study (Anthony et al. 2016). The assessment evaluated specific information on the totality of data available in the databases and operational aspects that could confirm the ability to identify specific cohorts, pregnancies, medication exposure, and outcomes of interest for the study of ocrelizumab in pregnancy.

The study is to be conducted in health care claims databases in the US and national health registries in Denmark:

United States

- Healthcare Integrated Research Database (HIRD). Analyses will be conducted by Carelon Research.
- Optum Dynamic Assessment of Pregnancies and Infants™ (DAPI). Analyses will be conducted by Optum.
- IBM MarketScan Commercial Claims and Encounters Database (formerly Truven MarketScan Commercial Claims and Encounters Database). Analyses will be conducted by RTI-HS.

Denmark

- National Health Databases in Denmark and the Danish Multiple Sclerosis Registry. Analyses will be conducted by Aarhus University.

The top three choices for US claims databases were HIRD, DAPI, and MarketScan, based on the availability of the required information for the study on exposures, patient characteristics, and outcomes; the possibility to link mother and infant data; and the largest numbers of patients with MS among the databases evaluated. HIRD and DAPI both have access to medical records for at least a portion of their participants, so outcomes can be validated. While MarketScan might provide the largest number of ocrelizumab-exposed pregnancies, outcome validation against medical records cannot be done, but accuracy of results could be evaluated by comparing results from data sources with outcome validation.

The Danish National Health Databases and The Danish Multiple Sclerosis Registry are nationwide registries that offer the possibility of maternal data to be linked with birth defect registries, in which completeness of ascertainment and quality of diagnosis has been shown to be high. In addition, linking health, civil, and administrative data enriches the amount of data available beyond individual data sources, and follow-up of patients is virtually lifelong.

Key characteristics of the study data sources are described in Appendix 4.

9.4.1 Carelon Research Healthcare Integrated Research Database

Carelon Research is a wholly owned subsidiary of Elevance Health, which is the largest health benefits company in terms of medical membership in the US. Elevance Health is an independent licensee of the Blue Cross and Blue Shield Association. Carelon Research is the health services research entity for Elevance Health that integrates the public health, pharmacoepidemiologic, health outcomes, and pharmacoeconomic concerns of these companies and their clients to conduct outcomes analyses. Carelon Research maintains the Healthcare Integrated Research Database (HIRD®) for use in health services research. As of July 2022, 84.5 million unique individuals with medical coverage and more than 66 million lives with medical and pharmacy claims information may be included for research using the HIRD.

The HIRD is a broad, clinically rich, and geographically diverse spectrum of longitudinal medical and pharmacy claims data from health plan members in the Northeastern, Mid-Atlantic, Southeastern, Midwestern, Central, and Western regions of the US. The database represents claims information from one of the largest commercially insured populations in the US. Patient enrollment data, inpatient and outpatient medical care, outpatient prescription drug use, outpatient laboratory test results, and health care charges may be tracked for each patient in the database dating back to 2006 (HealthCore 2017). Carelon Research had integrated mortality data from various sources—including the Social Security Administration Death Master File, an online obituary, inpatient discharge, and disenrollment—which were validated against the gold standard National Death Index (NDI) with a sensitivity of 89% (95% confidence interval, 88%-90%) and PPV of 93% (95% confidence interval, 93%-94%) (Jamal-Allial et al. 2022b).

In the HIRD, diagnoses and procedures will be identified by the following types of codes for both outpatient visits and inpatient stays: *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM); *International Classification of Diseases, 10th Revision, Clinical Modification* (ICD-10-CM); Current Procedural Terminology; and Healthcare Common Procedure Coding System. Drug claims are captured by National Drug Codes, which can then be translated to broader categories of coding such as Generic Product Identifier codes. Information on physician specialty is also available in the HIRD. In addition, the HIRD has the ability to (1) link claims data to complementary data sources, including inpatient and outpatient medical records for the health plan members represented in the HIRD; (2) identify and contact providers and members for survey research through vendor relationships; and (3) link data to national vital records, such as the NDI, for date and cause of death (CDC 2020).

Carelon Research implements the mother-infant linkage table following the approach developed for Sentinel (Sentinel Coordinating Center 2019). As of March 2021, the HIRD has 1.9 million mothers and 3.4 million infants, resulting in 1.4 million mother-infant linkages

(~73.4%) (Jamal-Allial et al. 2022a). A mother will be classified as linked to her infant if the infant's date of birth is within the time period from 3 days before the admission date for the delivery through the discharge date. Past studies involving other methods of linkage of mothers and their infants found that about 3 of 4 completed pregnancies could be connected to a qualifying infant (Mines et al. 2014; Nkhoma et al. 2012).

9.4.2 Optum Dynamic Assessment of Pregnancies and Infants

Within the Optum data source, DAPI data will be used to identify pregnancies and link the health care data of mothers with that of their infants within a large health care claims database that covers members of a large health insurer affiliated with Optum. The database contains medical claims and enrollment data dating back to 1994. Patient and physician data are linked to pharmacy and medical claims, medical record data, socioeconomic measures, and clinical laboratory results. Estimates from recent years show that the size of the source database provides approximately 95,000 pregnancies each year, on average, of which, 84% resulted in live births, and 86% of live births have the mother linked to the infant. Data of mothers and infants is linked through a family identifier and by matching the dates of delivery and infant's birth. The fraction of identified deliveries that cannot be matched to an infant is likely due to the infant being carried under a different health insurance from the mother, in other instances, this is due to pregnancies that did not end in a delivery. Approximately 30% to 40% of identified pregnancies cannot be linked to an infant (Wyszynski et al. 2016).

Because the linkage is made within an identifiable health insurance database affiliated with Optum, Optum can (with appropriate approvals) access medical records for mothers or infants to ascertain covariate information or to confirm outcomes.

9.4.3 IBM MarketScan Commercial Claims and Encounters Database

The MarketScan claims database is a large convenience sample with more than 41.1 million covered lives in the most recent full data year. The database encompasses employees, their spouses, and their dependents covered by employer-sponsored private health insurance. More than 300 employers and 40 contributing health plans throughout the US are represented in the fully integrated databases, covering more than 245 million patients since 1995 (IBM 2021). The commercial database primarily consists of employer-sourced and health plan–sourced data containing medical and drug utilization data for several million individuals annually. Medical claims in the commercial database include complete payment and charge information, including amount of patient responsibility. Other standardized items on each medical claim include but are not limited to dates and place of service (e.g., inpatient, outpatient, emergency), diagnoses, procedures, and detailed information on hospitalizations, including admission and discharge dates. Pharmacy claims in the commercial database include complete outpatient prescription drug information, which consists of patient co-payments, mail order drugs, injectables, drugs from specialty pharmacies, and all standardized prescription-level fields collected on a typical pharmacy claim (e.g., date of fill/refill, drug name and class, strength, quantity, and days' supply). The

data include co-payment information for inpatient, outpatient, and pharmacy claims. All claims are paid and adjudicated, and the MarketScan research databases fully comply with the Health Insurance Portability and Accountability Act of 1996. Data validation against the original source and/or access to medical records is not available (IBM 2021).

Maternal and infant records in MarketScan can be linked using the common family identifier, timing of delivery from the mother's file, and birth from the infant's file (MacDonald et al. 2019a). The family identifier clusters family members under the same insurance plan. The date of delivery can be derived from the date of delivery procedures in the mother's record, and the date of birth can be approximated by the date of the first claim in the infant's record. In a recent study using MarketScan, this method allowed linkage of 69% of infants (MacDonald et al. 2019a). Application of more stringent criteria relating the timing of delivery and birth resulted in the loss of 7% of mother-infant pairs. In the end, 50% of all identified pregnancies (ending in a live birth or otherwise) was linked to an infant.

9.4.4 Danish National Health Databases and the Multiple Sclerosis Registry

The Danish health care system provides universal coverage to all Danish residents (5.6 million inhabitants; http://international.ucl.dk/life-in-denmark/the-danish-health-care-system). Health care coverage includes free visits to general practitioners and specialists, hospital admissions, and outpatient visits. The costs of medications are partially covered by the Danish health system. The centralized Civil Registration System in Denmark allows for personal identification of each person in the entire Danish population and for the possibility of linkage to all Danish registries containing civil registration numbers, such as the Danish National Patient Registry, Danish National Prescription Registry, and the Danish Registry of Causes of Death. Data collected in these registries are available for research purposes. The process requires collaboration with a local university or investigator affiliated with a research institute to access the data and ethics committee notification or approval to handle data (Danish Data Protection Agency 2011; Danish Health Authority 2016). All applications must be submitted in Danish.

Denmark's primary health care sector, which includes general practitioners, specialists, and dentists, generates about 96% of the prescription sales, most of which are reimbursable and are dispensed by community pharmacies. Each dispensing record contains information on the patient, drug, and prescriber. Dispensing records retain the patient's universal personal identifier, allowing for individual-level linkage to all Danish registries and medical databases. Two national registries (Danish National Patient Registry and Danish National Prescription Registry) and the Danish National Database of Reimbursed Prescriptions will be of particular interest for implementation of the ocrelizumab postauthorization safety study (PASS). Moreover, the Danish National Civil Registration System will be used to obtain information on death and migration status (Schmidt et al. 2014).

The Danish Medical Birth Registry

This registry contains computerized records of all births in Denmark since 1 January 1973. Data are recorded by the midwives or the physicians attending the deliveries (Knudsen and Olsen 1998). The registry includes information on maternal age, parity, multiplicity of gestation, birth weight, gestational age, self-reported maternal smoking status, and data about delivery.

The Danish National Patient Registry

This registry includes data on all hospital admissions since 1 January 1977 and on outpatient clinic and emergency department visits since 1995 (Danish Health Authority 2016; Lynge et al. 2011; Schmidt et al. 2014). Hospital discharge diagnoses and information on surgical procedures, in-hospital deaths, and some selected drugs are recorded. After 1993, hospital discharge diagnoses are coded using ICD-10 codes.

The Danish National Prescription Registry

Individual-level data on all prescription drugs sold in Danish community pharmacies have been recorded since 1994 in the Registry of Medicinal Products Statistics of the Danish Medicines Agency. The subset, termed the Danish National Prescription Registry, contains information on dispensed prescriptions, including variables at the level of the drug user, the prescriber, and the pharmacy (Kildemoes et al. 2011). The National Prescription Registry collects data on reimbursed and unreimbursed drugs.

The Danish National Database of Reimbursed Prescriptions

This data source encompasses the reimbursement records of all reimbursed drugs sold in community pharmacies and hospital-based outpatient pharmacies in Denmark since 2004 (Johannesdottir et al. 2012). On average, approximately 3.5 million users are recorded in the database each year. Individuals are identified by the unique central personal registration number assigned to all persons born in or immigrating to Denmark. This data source avoids restrictions imposed on data use at the Danish National Prescription Registry. Most importantly, central personal registration numbers are reversibly encrypted, which allows re-identification of drug users. These features are very important for validation purposes.

The Danish Multiple Sclerosis Registry

The Danish Multiple Sclerosis Registry (DMSR, http://www.dmsr.dk/) was formally established in 1956 and is a nationwide population-based follow-up registry for all Danish patients with MS. Since 1996, the DMSR includes data on all patients who have received DMT. The former Danish Multiple Sclerosis Treatment Registry, established in 1996 to collect data on Danish patients with MS and clinically isolated syndrome who are treated with DMTs, is now integrated into the DMSR. Reporting of patients on DMTs is mandatory (Koch-Henriksen et al. 2015; Magyari et al. 2020; Magyari et al. 2016). By regular data collection, the DMSR makes it possible to follow the therapeutic effect of DMTs such as relapses, adverse effects, and disability (Bronnum-Hansen et al. 2011). At present, more than 11,000 patients treated with DMT have been registered in this. database. Data are

continuously entered into a central database from all sites in Denmark at start and at regular visits. Population-based studies combining health and social registries can optimally be carried out in Denmark, due to linkage between registries at the individual level by a unique personal identification number (CPR number), which is used by all national registries. Thereby, the DMSR can be linked to a number of population-based registries to obtain additional patient information, such as hospitalization, cause of death, comorbidities, prescription drugs, and reproductive issues. The minimum data set of DMSR includes information about age, sex, year of disease onset, year of first diagnosis, basic clinical information, and information about treatment, side effects, relapses, and patient neurological status expressed by Functional Systems Score (FSS) and Expanded Disability Status Scale (EDSS) score. Notification is done at treatment start, and thereafter at every scheduled clinical visit, 3 months after treatment start and thereafter every 6 months. The longitudinally collected information about disease activity and side effects make it possible to investigate the clinical efficacy and adverse events of different DMTs.

Due to the unique CPR number in Denmark, patient follow-up is lifelong, as long as the patient remains in the country. Currently, serious adverse events are available through linkage to other registries. Prospective inclusion of adverse drug reaction or serious adverse events as part of the minimum data set will be possible, due to an expansion, via addition of a safety module, of the online data collection platform COMPOS DK.

9.5 STUDY SIZE

The target size for this study was calculated so that the upper limit of the 95% confidence interval for the relative risk for the association of pregnancy exposure to ocrelizumab and major congenital malformations is below 2.5 with 0.8 probability. This number is estimated at approximately 1,005 exposed pregnancies and 3,015 unexposed pregnancies in primary comparison subcohort 1a, in primary comparison subcohort 1b, and in the secondary comparison cohort counting subjects from the four proposed data sources. Estimated counts are as follows:

- 1,005 exposed and 3,015 unexposed pregnancies (in each of the mentioned cohorts) would be accrued by combining the four data sources
- Of these, 62% would result in live births (623 exposed and 1,869 unexposed)
- Of these records, 65% would be linkable to infant records, resulting in 405 exposed and 1,215 unexposed newborns, per Table 5

Actual study size will depend on medication utilization among the target population in the data sources selected for the study, as well as on the observed percentage of live births among the study pregnancies and success of mother-infant record linkage. Should the actual proportion of live births (assumed to be 62%) or the proportion of infant records linked to maternal records (assumed to be 65%) exceed the noted percentages, fewer pregnant women would be necessary to achieve the target number of newborns with mother-infant linkage.

The estimations for ocrelizumab exposure, potentially the limiting factor for reaching the study target size in this study, are described in Table 5 and associated text, below.

Table 5 Study Sizes Needed for the Upper Limit of the 95% Confidence Intervals to be Below Selected Thresholds With a Probability of 0.8

Panel A.

Outcome	Prevalence of Outcome	Thresholds on the Relative Risk Scale for the Upper Limit of 95% CI …	Exposed:Unexposed Pregnancies Needed
Stillbirth	6 per 1,000[a]	11	300:900
		8	400:1,200
		5	675:2,025
		3	1,440:4,320
		2.5	2,065:6,195
		2	3,610:10,830
Preterm birth	10%[b]	5	37:111
		4	50:150
		3	80:240
		2.5	115:345
		2.2	160:480
		2	200:600
		1.95	215:645
		1.85	250:750
		1.75	300:900
		1.5	575:1,725
Spontaneous abortions	23%[c]	5	14:42
		4	19:57
		3	30:90
		2.5	42.126
		2	73:219

Panel B.

Outcome	Prevalence of Outcome	Thresholds on the Relative Risk Scale for the Upper Limit of 95% CI …	Exposed:Unexposed Linkable Live Births Needed
Cardiac congenital malformations	1%[d]	12.75	160:480
		8.99	215:645
		6.5	300:900
		5	400:1,200
		4	540:1,620
		3	860:2,580
		2.5	1,235:3,705
		2	2,160:6,480
Major congenital malformations (combined)	3%[e]	5	130:390
		4.3	160:480
		4	177:531
		3.5	215:645
		3	280:840
		2.9	300:900
		2.5	405:1,215
		2	705:2,115

CDC = Centers for Disease Control and Prevention; CI = confidence interval; MS = multiple sclerosis; US = United States.

Note: Outcomes are listed in order of increasing prevalence. Assumptions underlying these calculations:

- No difference in risk between the exposed and unexposed (i.e., risk ratio = 1), regardless of comparison cohort (women with MS without ocrelizumab exposure, women without MS).
- Matching ratio of exposed to unexposed was 1:3.
- Probability that the upper limit of 95% CI will be as stated = 0.8.
- Calculations were done using the “Study Size” tool in Episheet (Rothman 2015).

[a] MacDorman and Gregory (2015).

[b] CDC (2022).

[c] MacDonald et al. (2019b). This prevalence is larger than reported in other publications, such as the 13% reported in Norway from 2009 to 2013 (Magnus et al. 2019) or 11% among all pregnancies or 17% among pregnancies with known outcome in the general population in US claims from 1997 to 2001 (Seeger et al. 2007).

[d] CDC (2020).

[e] CDC (2008).

The potential number of pregnancies exposed to ocrelizumab per year was estimated using counts provided by the database holders, several assumptions related to pregnancy rates in the general population and in women with MS, and the projected average use of ocrelizumab (Table 6). The potential accrual of pregnancies per year presented in Table 6

represents approximate estimates with many uncertainties. Concretely, the pregnancy rate may be lower than assumed (based on the general population), and the rate of treatment discontinuation before pregnancy can be higher than assumed (50%).

Each year, the observed mean number of women with MS with a delivery code in DAPI and who used DMTs currently approved for the treatment of MS for years 2012 to 2016 were consistent with estimates for ocrelizumab in Table 6 (data provided by Optum).

Table 6 Estimated Number of Pregnancies Exposed to Ocrelizumab in Women With Multiple Sclerosis in Selected US Data Sources, per Year

Data Source	Number of Women Aged 15–45 Years With MS per Year	Estimated Number of Pregnancies per Year[a]	Projected Number of Pregnancies Exposed to Ocrelizumab per Year[b]	Adjusted to 50% Withdrawn From Ocrelizumab Before Pregnancy[c] (per Year)	Adjusted Assuming 10% Loss to Follow-up (per Year)	Adjusted Assuming 30% Loss to Follow-up (per Year)
HIRD (US)	31,295 (Jan 2006–Apr 2016) ~9,400 per year	990	57	29	26	20
MarketScan (US)	25,729 (2014)	2,700	157	79	71	55
DAPI (US)	7,421 (2015)	780	45	23	21	16
Danish Registries		73 (observed average 2007–2012)	4	2	2	1
Total	--	4,543	263	133	120	92

HIRD = Healthcare Integrated Research Database; MS = multiple sclerosis; DAPI = Optum Dynamic Assessment of Pregnancies and Infants™; US = United States.

[a] Assuming a pregnancy rate of 10.5% in US women aged 15-44 years (Ventura et al. 2012).

[b] Assuming an average proportion of patients with MS treated with ocrelizumab of 5.8%, which could be slightly lower if use is strictly restricted to the approved indications of primary progressive and relapsing forms of MS.

[c] Assuming a 50% lower estimated number of pregnancies exposed due to the possible decision to stop treatment before becoming pregnant.

Individually, none of these data sources would provide a sufficient number of pregnancies with potential exposure to ocrelizumab by 5 years after launch to provide adequate power to draw meaningful conclusions. Hence the multidatabase approach and the need to monitor

the actual number of pregnant women in each database during the first years to confirm the feasibility and timing of the study start.

Per the estimated 92 exposed pregnancies that may be observed yearly (Table 6), attaining the estimated target study size would take approximately 11 years. All eligible pregnancies observed during the study period will be included in the study. Because some of the assumptions used in these calculations may be too conservative (for example, in Danish data, practically all deliveries are linkable to infant records), it is possible that this number of pregnancies is observed earlier, and analyses can proceed earlier than planned.

A common monitoring plan and a common SAP will guide analyses. The monitoring plan will be developed before data for the first monitoring report are extracted, will describe the analyses to be conducted periodically for monitoring accrual of ocrelizumab-exposed pregnancies and live births, and will update the predicted study power. Briefly, counts of ocrelizumab-exposed pregnancies and live births will be obtained from each data source using the most recently updated data available; the live birth proportion in each data source will be estimated. The SAP will be developed before database lock and data extraction and will provide details on the study core analyses and meta-analysis. Data from monitoring reports will inform the SAP.

The number of ocrelizumab-exposed pregnancies and live births will be monitored yearly in all databases in years 2020 to 2028. Results from monitoring counts, along with any updated figures on the success rate of mother-infant linkage in the US data sources, will allow study researchers to estimate when the target study size will be attained and the anticipated duration of the study.

In the monitoring count report in June 2020, in MarketScan, DAPI, and HIRD combined, 6,446 pregnancies were identified in women with MS with continuous enrollment and with both medical and pharmacy benefits in the 6 months before the estimated beginning of pregnancy and throughout pregnancy. Data from the Danish National Health Databases were not available. Of the 6,446 pregnancies identified, 6,395 pregnancies had not been exposed to ocrelizumab. These pregnancies can be seen as the starting point for the primary comparison cohort. If the study accrues the planned ocrelizumab-exposed cohort size (1,005 pregnancies anticipated to result in 405 exposed linked mother-infant pairs), with the current number of unexposed pregnancies (6,395 pregnancies anticipated to result in 2,577 unexposed linked mother-infant pairs), the study would be powered to exclude a relative risk for major congenital malformations between 2 and 2.5 (or greater) with probability 0.8, if the true relative risk is 1 (Table 5).

The proportion of pregnant women with MS who received DMTs in the 3 months before pregnancy in MarketScan from 2011 to 2015 was reported as 35% (MacDonald et al. 2019b). Use in the 6 months before LMP through the end of the first trimester (as defined in the BA39732 study for major congenital malformations) was not reported. Among the 6,395 pregnancies in women with MS who were not exposed to ocrelizumab in the

2020 monitoring report, assuming 35% would be exposed to a DMT (i.e., subcohort 1a) and that 65% would not (i.e., subcohort 1b), each subcohort would have a size allowing for the identification of up to 3 unexposed matches for each ocrelizumab-exposed cohort member. The 35% reported by MacDonald et al. (2019b) may be an underestimate of the exposure in the present study, given the differences in the exposure definition between the referenced publication and the present study; still, this does not change the conclusion that pregnancies in both subcohorts, 1a and 1b, if the reported pattern holds in the study population for study BA39732, are expected to achieve a variable matching ratio of up to 1:3 exposed to unexposed pregnancies.

Following this logic, 35% of the 6,395 unexposed pregnancies from the 2020 monitoring counts (2,238 pregnancies anticipated to result in 902 mother-infant linked pairs) can be seen as the basis for subcohort 1a. If the planned ocrelizumab-exposed cohort size is accrued, given the currently observed number of unexposed pregnancies, the study would be able to exclude relative risks for major congenital malformations between 2.5 and 2.9 (or larger) with the noted assumptions. Likewise, 65% of the 6,395 unexposed pregnancies from the 2020 monitoring counts (4,157 pregnancies anticipated to result in 1,675 linked mother-infant pairs) can be seen as the basis for subcohort 1b. If the planned ocrelizumab-exposed cohort size is accrued, given the currently observed number of unexposed pregnancies, the study would be able to exclude relative risks for major congenital malformations of 2.5 (or larger) with the noted assumptions.

FDA has recommended that the study be extended as needed to attain the target study size. If the target study size is achieved, but the number of pregnancies available in one data source is not large enough to support the planned analyses, descriptive or unadjusted analyses will be considered for that data source.

9.5.1 Observed Data From the Monitoring Phase

In Annual Monitoring Report No. 3 in 2022, 214 ocrelizumab-exposed pregnancies in women with MS were observed, resulting in 118 live births, combining counts from all the data sources. If the number of ocrelizumab-exposed pregnancies in women with MS increases by an average of 35% each year in the coming years (which would be consistent with the increases observed during the monitoring phase through the noted monitoring report), the target size for the ocrelizumab-exposed cohort is expected to be reached within the anticipated study duration.

9.6 DATA MANAGEMENT

Files from the various data sources will be kept separate behind firewalls, with each research partner analyzing data from different data sources, and individual-level data will not be merged.

Routine procedures will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality-control checks of all

programs. The study is conducted by multiple research partners, and each research partner will maintain any patient-identifying information securely on site according to internal/local standard operating procedures or guidance documents. Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except selected study staff.

Appropriate data storage and archiving procedures will be followed, with periodic backup of files. Standard procedures will be in place at each research center to restore files in the event of a hardware or software failure.

Each research partner will follow its own established procedures and generate results according to the analysis plan and specifications. All summary tables of results, and no individual patient identifiers, will be provided to RTI Health Solutions (RTI-HS), which will compile the results and develop the report in collaboration with research partners. RTI-HS will follow quality-control procedures regarding transfer of data.

For requests to access to data for audit purposes, only aggregated data from all research centers will be available at the coordinating center. The audit trail will consist of a detailed description of the methods to extract and process the electronic health records or claims data, as applicable. Access to raw data at each database research center will require the data requestor to obtain a license or apply for approval at a research committee and to fulfill the conditions required under the governance rules of each database research center.

9.7 DATA ANALYSIS

9.7.1 Study Cohorts

The study cohorts are summarized in Table 7.

Table 7 Study Cohorts

	Exposed Cohort	Primary Comparison Cohort		Secondary Comparison Cohort
		Comparison Subcohort 1a	Comparison Subcohort 1b	
Cohort definition	Pregnancies in women with MS and exposure to ocrelizumab	Pregnancies in women with MS exposed to non-ocrelizumab DMTs approved for the treatment of MS	Pregnancies in women with MS not exposed to DMTs approved for the treatment of MS	Pregnancies in women without MS or ocrelizumab use
MS diagnosis	Required	Required	Required	Absence of diagnosis required
Drugs	Required: Use of ocrelizumab in the 6 months before LMP or any time during pregnancy (first trimester only for analysis on MCM)	Required: Use of DMTs in the DMT-specific 5–half-life time window before LMP or any time during pregnancy (first trimester only for analysis on MCM) No use of ocrelizumab in the 6 months before pregnancy or any time during pregnancy (first trimester only for analysis on MCM)	No use of DMTs in the DMT-specific 5–half-life time window before LMP or any time during pregnancy (first trimester only for analysis on MCM)	No use of ocrelizumab in the 6 months before LMP or any time during pregnancy

DMT = disease-modifying therapy; LMP = first day of the last menstrual period; MCM = major congenital malformation; MS = multiple sclerosis.

In Denmark, MS will be ascertained from the MS Registry. The ascertainment of MS in claims is not straightforward. For US data, the algorithm selected for MS identification requires a person to have three or more MS-related claims from any combination of inpatient visit, outpatient visit, or DMT use within 2 years (no minimum number of claims of any given type is required) (Culpepper et al. 2019); this algorithm has shown satisfactory performance in various data sources, including US claims data (Culpepper et al. 2019) (Table 8). Codes during pregnancy are included because they are understood to represent a diagnosis that was present before pregnancy but is recorded only during pregnancy. To define absence of MS (secondary comparison cohort), it will be required that patient records do not contain MS diagnosis codes or entries for DMTs to treat MS.

Table 8 Published Algorithms to Identify Cases of Multiple Sclerosis in Claims Data

Reference, Database, and Country	Summary of Algorithm	Validation Results
Bargagli et al. (2016) Health administrative data including the Hospital Discharge Registry and the PHARMED database of dispensed medications within the Italian National Health System; Italy	Selected patients with hospital records with a primary or a secondary diagnosis of MS (ICD-9-CM, 340.0); with at least one pharmacy claim in the study period for at least one MS DMT; and patients with records of MS-related disability.	No validation results.
Culpepper et al. (2006) Several data sets, including administrative and health data and electronic medical charts, from the Veterans Health Administration data sources; United States	The database algorithm classified patients as not having MS if they did not have, on average, at least one health care encounter each year with MS coded as the primary diagnosis (ICD-9-CM, 340), did not have a service-connected disability for MS (this was related to compensation and pensions), or did not use a DMT. If any of these criteria were met, the case was classified as MS/possible MS.	In validation against medical charts, sensitivity was 0.93; specificity, 0.92; PPV, 0.92; and negative predictive value, 0.93. In an analysis in which cases classified as unknown in the medical chart review were retained, sensitivity was 0.93; specificity, 0.90; PPV, 0.88; and negative predictive value, 0.94.
Culpepper et al. (2019) Four administrative health claims data sets representing different health care systems and geographic regions: Veterans Health Administration data sources and Kaiser Permanente Southern California in the US and Manitoba and Saskatchewan in Canada	The recommended algorithm to define MS required a patient to have three or more MS-related claims from any combination of inpatient visit, outpatient visit, or DMT use within 1 year (no minimum number of claims of any given type was required). MS diagnosis code (ICD-9 code 340 or ICD-10 G35) recorded as one of the diagnoses, in any position. Another version of the algorithm allowed 2 years for the code requirements to be met.	1-year window: in validation against medical charts, sensitivity was 85.5%–93.4%; specificity, 66.1%–82.2%; PPV, 95.4%–97.8%; NPV, 41.4%–56.8%; and interrater reliability (Youden J), 0.60–0.69 2-year window: sensitivity, 88.1%–95.1%; specificity, 60.0%–78.4%; PPV, 94.7%–97.4%; NPV, 44.2%–61.9%; interrater reliability, 0.55–0.68
Higuera et al. (2016) Claims data from commercial plans, individual and family health plans, managed Medicaid and Medicare plans, and dual Medicaid/Medicare plans in the upper Midwest of the United States.	Patients had to have an ICD-9 code for MS (340 or 340.0) and a prescription filled for an MS DMT in any year of data (this was a study on adherence to DMTs).	No validation results.

Reference, Database, and Country	Summary of Algorithm	Validation Results
Marrie et al. (2010) Health claims from the Manitoba Health and Healthy Living program—including physician claims, hospitalization records and outpatient dispensed prescriptions—from the Drug Programs Information Network; Canada.	The authors validated several algorithms requiring different numbers of and combinations of claims for hospitalization, general practitioner encounters, and prescriptions. The base cohort from which cases were selected had codes for signs and symptoms that may be related to MS. One version of the algorithm required at least two MS claims (physician, hospital, or DMT prescriptions). ICD-9-CM and ICD-10-CA codes used for MS were 340 and G35, respectively. A simpler version required one claim of any of the three types.	Validation was conducted against medical records. Two claims required: sensitivity was 95.7%, sensitivity, 44.3%; PPV, 73.2%; and NPV, 86.7%. One claim required: sensitivity was 97.9%, specificity, 17.0%; PPV, 65.2%; and NPV, 83.3%.

DMT = disease-modifying therapy; ICD-10-CA = *International Classification of Diseases, 10th Revision, Canadian Modification*; ICD-9 = *International Classification of Diseases, 9th Revision*; ICD-9-CM = *International Classification of Diseases, 10th Revision, Clinical Modification*; MS = multiple sclerosis; NPV = negative predictive value; PPV = positive predictive value.

9.7.2 Descriptive Analyses

In each data source, the study cohorts (exposed cohort, comparison cohort 1, subcohorts 1a and 1b, and comparison cohort 2) will be characterized based on the covariates listed in Section 9.3.3. Characteristics of the unmatched and matched cohorts, and frequency of the endpoints, will be shown in a table. Balance in matching will be assessed by examining the distribution of variables in the cohorts and the standardized difference. No statistical tests are planned for this comparison, but variables with standardized differences above 0.1 may lead to a re-evaluation of the propensity score estimation.

9.7.3 Measures of Frequency

In each data source, crude measures of frequency of the study outcomes with associated 95% confidence intervals will be estimated within matched cohorts (exposed cohort, primary comparison cohort, subcohorts 1a and 1b, and secondary comparison cohort; see next subsection).

9.7.4 Measures of Association

Table 9 presents the measures of association planned for each outcome. Regression models will be used to compare women with MS who received ocrelizumab during the exposure window with women in the primary comparison cohort and subcohorts 1a and 1b, and in the secondary comparison cohort, which have been described above. Point estimates and 95% confidence intervals from crude analyses within the matched cohorts will be presented. The number of pregnancies will be considered when determining which analyses can be conducted.

To control for confounding and channeling effect (see Section 9.9), women in the ocrelizumab-exposed cohort will be matched to women in the primary comparison subcohort 1a, primary comparison subcohort 1b, and the secondary comparison cohort (separately) in a 1:3 ratio in a variable matching ratio based on an exposure propensity score (i.e., if only one pregnancy from the primary comparison cohort is available for a given exposed pregnancy, that matched set will have one exposed pregnancy and one comparison pregnancy), using greedy matching.

An advantage of matching is that “crude” results are adjusted for the matching variables. The main disadvantage is the loss of precision associated with the loss of unmatched subjects in the context of a rare exposure and rare outcomes. However, because many more pregnancies are expected in the two comparison cohorts unexposed to ocrelizumab (please see Section 9.5), it is unlikely that ocrelizumab-exposed pregnancies will be left without appropriate matches. Therefore, this disadvantage is not a major concern in this setting. The variable matching ratio has the advantage of minimizing the loss of exposed pregnancies due to lack of matches while increasing precision due to multiple matches for easily matchable exposed pregnancies.

Logistic regression will be used to estimate an exposure propensity score as the probability of being exposed to ocrelizumab or not (separately for the primary comparison subcohort 1a, the primary comparison subcohort 1b, and the secondary comparison cohort). Variables considered for inclusion in the propensity score will be those related to the exposure and to any of the outcomes; the method for variable selection will be specified in the SAP. The propensity score model for the secondary comparison cohort will be a reduced model to avoid overfitting. Details will be provided in the SAP.

A strength of propensity scores is that they allow for the selection of the best set of variables within each data source. For example, Danish data will be richer with regard to information on MS (to be used in propensity scores in cohorts of women with MS only [exposed cohort and primary comparison cohort]). Propensity scores will allow the investigators to use this information to obtain a locally optimal control of confounding. Furthermore, flexibility in variable selection may allow the investigators to reduce overall confounding in this setting in which confounding factors will likely vary across data sources, given differences in insurance, health care systems, and patient characteristics. Propensity scores with subsequent pooling of data source–specific information have been used in multidatabase studies (Rassen et al. 2010; Toh et al. 2013). A single propensity score will be used for all outcomes in comparisons of ocrelizumab-exposed pregnancies and pregnancies in the primary comparison subcohort 1a, another propensity score will be used for all outcomes in comparisons of ocrelizumab-exposed pregnancies and pregnancies in the primary comparison subcohort 1b, and another propensity score will be used for all outcomes in comparisons of ocrelizumab-exposed pregnancies and pregnancies in the secondary comparison cohort.

9.7.5 Missing Data

Using automated health care data, missing data for exposure, outcome, and comorbidities are not expected; in the presence of records for the condition, it is assumed the condition is present, and in the absence of such records, it is assumed that the condition is absent. Otherwise, where relevant, the percentage of missing data will be reported.

9.7.6 Statistical Analyses

A summary of the analyses proposed for each outcome can be found in Table 9. The feasibility of the proposed approaches will be reassessed taking into account the number of observed outcomes.

For analyses of urinary tract infections in pregnancy and infections requiring hospitalization during pregnancy, person-time will accrue from the beginning of the pregnancy until the end of the woman's follow-up, as described in Section 9.2.3, Follow-up. For analyses on adverse effects on the infant immune system, i.e., vaccine-preventable diseases and vaccine-associated poliomyelitis in the infant, person-time will accrue from the date of birth until the end of the infant's follow-up, as described in Section 9.2.3, Follow-up, and in

Table 9, in the column “Timing of Outcome Ascertainment” (this column notes that some person-time analyses will have multiple cut-off ages).

Table 9 Proposed Statistical Analyses

Outcome	Measure of Frequency	Measure of Association (Regression Model)	Timing of Outcome Ascertainment	Timing of Exposure Ascertainment	Unit of Analysis
Spontaneous abortion	Incidence rate	Hazard ratio (proportional hazards regression)	Before week 20 of pregnancy	6 months before LMP for ocrelizumab and DMT-specific 5–half-life window before LMP for other DMTs, up to and including first trimester of pregnancy or end of pregnancy if before end of first trimester	Pregnancy
Fetal death/ stillbirth	Cumulative incidence	Relative risk (log-binomial regression)	At or after week 20 of pregnancy	6 months before LMP for ocrelizumab and DMT-specific 5–half-life window before LMP for other DMTs or any time in pregnancy (i.e., before the time of fetal death)	Pregnancy
Elective termination	Cumulative incidence	Relative risk (log-binomial regression)	At any time of follow-up	6 months before LMP for ocrelizumab and DMT-specific 5–half-life window before LMP for other DMTs, up to and including first trimester of pregnancy or end of pregnancy if before end of first trimester	Pregnancy
Preterm delivery	Cumulative incidence	Relative risk (log-binomial regression)	At birth	6 months before LMP for ocrelizumab and DMT-specific 5–half-life window before LMP for other DMTs or any time in pregnancy	Pregnancy

Outcome	Measure of Frequency	Measure of Association (Regression Model)	Timing of Outcome Ascertainment	Timing of Exposure Ascertainment	Unit of Analysis
C-section	Cumulative incidence	Relative risk (log-binomial regression)	At birth	6 months before LMP for ocrelizumab and DMT-specific 5–half-life window before LMP for other DMTs or any time in pregnancy	Pregnancy
Urinary tract infection	Incidence rate	Hazard ratio (proportional hazards regression)	At any time in pregnancy (or end of follow-up for the patient)	6 months before LMP for ocrelizumab and DMT-specific 5–half-life window before LMP for other DMTs, until the end of follow-up for the patient for this outcome	Pregnancy
Infection requiring hospitalization during pregnancy	Incidence rate	Hazard ratio (proportional hazards regression)	At any time in pregnancy (or end of follow-up for the patient)	6 months before LMP for ocrelizumab and DMT-specific 5–half-life window before LMP for other DMTs, until the end of follow-up for the patient for this outcome	Pregnancy
Major congenital malformations	Cumulative incidence	Relative risk (log-binomial regression)	At birth or during infant follow-up	6 months before LMP for ocrelizumab and DMT-specific 5–half-life window before LMP for other DMTs, up to and including first trimester of pregnancy	Live births (fetuses, if the information is available for terminations or stillbirths) or infants

Outcome	Measure of Frequency	Measure of Association (Regression Model)	Timing of Outcome Ascertainment	Timing of Exposure Ascertainment	Unit of Analysis
Adverse effects on the immune system	Incidence rate	Hazard ratio (proportional hazards regression)	The hazard ratio will be evaluated at several ages because the incidence may vary widely with age (e.g., first month of life, and at the end of infant follow-up). Subgroup analyses on infants who died because of infectious disease or had a full year of follow-up may be explored. For vaccine-preventable diseases and vaccine-associated poliomyelitis, the outcome will be ascertained between age for first dose of vaccines and end of first year of life.	6 months before LMP for ocrelizumab and DMT-specific 5–half-life window before LMP for other DMTs or any time in pregnancy	Infants
Vaccine-preventable diseases and vaccine-associated poliomyelitis	Incidence rate	Hazard ratio (proportional hazards regression)	The hazard ratio will be evaluated at several ages because the incidence may vary widely with age (e.g., first month of life, and at the end of infant follow-up). The outcome will be ascertained between age for first dose of vaccines per guidelines and end of first year of life.	6 months before LMP for ocrelizumab and DMT-specific 5–half-life time window before LMP for other DMTs or any time in pregnancy	Infants

Outcome	Measure of Frequency	Measure of Association (Regression Model)	Timing of Outcome Ascertainment	Timing of Exposure Ascertainment	Unit of Analysis
Small for gestational age	Cumulative incidence	Relative risk (log-binomial regression)	At birth	6 months before LMP for ocrelizumab and DMT-specific 5–half-life time window before LMP for other DMTs or any time in pregnancy	Fetuses (live births)

C-section = cesarean section; DMT = disease-modifying therapy; LMP = first day of the last menstrual period.

Note: With variable matching ratios, regression analyses will be weighted to account for the matched sets. Pregnancies no longer at risk for one outcome will be excluded (e.g., a pregnancy that ended in a spontaneous abortion is not at risk for preterm delivery). The date or gestational age at the time of the event may need to be estimated for spontaneous abortions, elective terminations, and stillbirth, as generally they are not well recorded. For each outcome of interest that can occur multiple times, follow-up for that outcome will stop at its first occurrence (e.g., urinary tract infections in pregnancy, infections requiring hospitalization in pregnancy). Follow-up will continue for other outcomes.

9.7.7 Data Integration

Results will be presented separately for each data source. Data analysis will be performed by data custodians at their sites and behind firewalls, and individual-level data will not be available for data integration. Overall results (e.g., relative risks for major congenital malformations) will be summarized using meta-analytic techniques. It is proposed to use direct meta-analytic techniques (meta-analytic techniques with direct comparisons) with random effects as results are expected to have some heterogeneity across data sources; the random-effects model will allow assessment of heterogeneity. Standard meta-analysis graphic displays and diagnostics (Forest plots and I^2) will be conducted to assess heterogeneity of effect across data sources.

Outcomes for data integration include all outcomes listed, plus subgroups of major congenital malformations (e.g., cardiac malformations, cleft lip with or without cleft palate). Results from sensitivity analyses (e.g., using various exposure windows) may be pooled if numbers are adequate.

9.7.8 Subgroup Analyses

Possible stratifications (depending on counts) may include strata of maternal age (e.g., 20-24 years, 25-29 years), calendar year, and others.

9.7.9 Sensitivity Analyses

Ocrelizumab has a mean half-life of 26 days. It is expected that after 5 mean half-lives (i.e., 130 days) after the last ocrelizumab administration, ocrelizumab would be eliminated from the women's bodies. Accordingly, the following sensitivity analyses related to the definition of unexposed are proposed:

- Women would be considered unexposed if their last recorded exposure to ocrelizumab took place 26 or more days before the beginning of pregnancy (1 mean half-life).
- Women would be considered unexposed if their last recorded exposure to ocrelizumab took place 90 or more days before the beginning of pregnancy (3.5 mean half-lives).
- Women would be considered unexposed if their last recorded exposure to ocrelizumab took place 130 or more days before the beginning of pregnancy (5 mean half-lives).

Other sensitivity analyses will consider last exposure of ocrelizumab took place within the first, second or third trimester of pregnancy. Exposure during the second and third trimester may be combined for the outcome major malformation to maximize study size, taking into consideration that the critical time window for this outcome is the first trimester.

Other sensitivity analyses will be planned around key analytical aspects: exposure by trimester, age at diagnosis of major congenital malformation, changes in health care utilization due to COVID-19, matching, proportional hazards assumption, and residual confounding. Additional sensitivity analyses will (1) remove potential data overlap between data in HIRD or DAPI and MarketScan data by excluding MarketScan results from pooled

analyses, and (2) stop accrual of pregnant women well before the end of data availability, to give all pregnancies the opportunity to reach term.

9.8 QUALITY CONTROL

Data management and analysis will be conducted by each research partner in each database. Standard operating procedures or internal process guidance at each research center will be used to guide the conduct of the study. These procedures include internal quality audits and the opportunity for external audits; rules for secure and confidential data storage, backup, and recovery; methods to maintain and archive project documents; quality-control procedures for programming; standards for writing analysis plans; and requirements for scientific review by senior staff. A quality-assurance audit of this study may be conducted by the sponsor or the sponsor's designees. Each of the database research centers will follow its own quality and audit trail procedures. The quality and audit trails at each center may be different.

At the coordinating center, an independent Office of Quality performs audits and assessments that involve various aspects of its projects, including but not limited to documentation of education and training, data entry, data transfer, and approval of the institutional review board at RTI International, of which RTI-HS is a research unit. Such audits at RTI-HS will be conducted by the Office of Quality according to established criteria in standard operating procedures and other applicable procedures.

All programming written by one study analyst will be reviewed independently by a different analyst, with oversight by a senior statistician. All key study documents, such as the analysis plan, data abstraction forms, and study reports, will undergo quality-control review, senior scientific review, and editorial review.

External reviewers with expertise in drug safety in pregnancy and MS provided advice on the design of the study and have reviewed this protocol; they will provide advice on the conduct of the study and will review results, reports, and other important documents.

9.9 LIMITATIONS OF THE RESEARCH METHODS

Data-related limitations of the study will depend on the accuracy of codes and algorithms used to identify outcomes, completeness of the data contained in the data sources, and the availability of records for validation of selected outcomes. Of the three health care claims databases included in this study, only MarketScan does not have access to medical records. Optum has the ability to access medical records for data abstraction and validation of study endpoints, and claims data in HIRD can be linked to medical records. Definitions for and algorithms to identify study endpoints will be homogeneous across databases; given that the same algorithm will be applied and that US claims data sources share basic features, positive predictive values obtained from DAPI and HIRD are expected to be applicable to MarketScan. In Denmark, it is possible to apply for access to the medical files to retrieve additional data or to validate registry-based information, if needed.

Not all of the outcomes of interest have been validated in administrative claims data, and the performance of ICD-10 codes, which have only been used since October 2015 in the US, has not been well characterized in this setting. Existing validation studies are referenced in SAP version 4.0, Section 3.2.1.2.

Exposure ascertainment will be based on pharmacy claims in US data sources. Given the type of medication, it is expected that filled prescriptions will be used (as opposed to use-on-demand medications, such as pain killers), although the precise timing of use will be uncertain. In Denmark, exposure ascertainment will be more robust thanks to the MS registry. Exact timing of exposure relative to start of pregnancy will need to be estimated in claims because claims data sources do not include date of LMP or records of gestational age at birth. However, multiple methods for this estimation using data available in claims have been evaluated and found to be appropriate (Margulis et al. 2015). Information on breastfeeding will be limited or unavailable.

Unsuccessful linkage of mothers and infants may reveal some differences between mothers linked to infants and mothers without linked infants. Bias due to non-linkage is not expected unless the characteristics associated with linkage or lack thereof are simultaneously associated with the exposure and the outcomes, which is not likely.

Similar to the design other pregnancy safety studies (e.g., pregnancy registries), early pregnancy outcomes, such as spontaneous abortions, will be incompletely captured in pregnancy studies based on existing databases, because they may happen before the pregnancy is known to the health care system. Information related to pregnancy terminations and reasons for termination will be incomplete. Outcomes that occur during the first year of life will be captured only in infants who stay enrolled for that time period.

Information on some potential confounding factors, such as use of supplements, tobacco, alcohol, and illicit drugs, is limited in these data sources. Information on lifestyle factors such as smoking, alcohol consumption, and body mass index is not typically available in claims databases. However, the presence of diagnoses related to obesity, smoking, and alcohol abuse or dependence can be used to approximate the patient profile relating to health habits in databases where this information is missing. Danish data include some lifestyle information, as it is captured and recorded during prenatal care. Information on race and ethnicity is incomplete or not available in claims databases and not collected in the Danish registries. Race and ethnicity will be imputed in two claims data sources using algorithms that may present some limitations. Misclassification of race and ethnicity is likely to occur. Research has shown a good performance of algorithms for White race and less optimal results for other racial or ethnic groups (Lin et al. 2020). In claims data, the period for ascertaining baseline characteristics will be limited by the period of enrollment in the health care plan; underrecording of diagnoses only recorded well before pregnancy is expected. For certain diagnosis that are mainly recorded at the primary care level, some degree of underascertainment is expected in the Danish databases if the patients did not

receive inpatient or outpatient hospital care for those conditions. Over-the-counter medications, including folic supplementation at the regular dose and prenatal vitamin use, are not captured in these data sources. Claims data will also provide limited or no information on type of MS, duration of the disease, and other MS-related details. Some degree of residual confounding due to this can be expected, although the proposed method to adjust for confounding should remove most confounding.

Currently, several drugs are available to treat relapsing MS (ocrelizumab is the first medication approved for the indication of PPMS). At this point, one can only speculate about which patients would receive prescriptions for ocrelizumab. Matching on patient characteristics will aim to minimize confounding due to channeling effect, although it will not remove it completely. Because of the Danish MS Registry, Danish data will be more robust in this respect. This study is not designed to study the effect of ocrelizumab in patients without MS or patients with isolated clinical syndromes who do not have a diagnosis of MS.

Due to the low frequency of exposure and outcomes, this study will reach limited precision within a reasonable timeframe. While a smaller study size (e.g., a minimum of 100 ocrelizumab-exposed pregnancies) would ensure the study is conducted even in the case of low uptake of ocrelizumab, results would be very imprecise for all but the most common study outcomes.

It is possible that some pregnancies are represented in more than one participating US claims databases. Membership in the HIRD and DAPI is health care plan–based, while membership in MarketScan is employer-based. Thus, women and infants can be represented in either HIRD or DAPI and also in MarketScan if health care is provided by an employer represented in MarketScan and through a health insurance plan represented in HIRD or DAPI. No information is directly available in any of the data sources to identify the overlap in data sources. A sensitivity analysis will address this by excluding results from MarketScan from the pooled analysis.

It is possible that women with MS and their children are subjected to more intensive surveillance during pregnancy and in childhood, respectively, possibly resulting in higher recorded prevalence of non–life-threatening malformations than women without MS. If this is true, we should expect to see higher prevalence of malformations in infants born to women with MS, even if MS or MS treatments do not carry such increased risk. If increased surveillance is not differential by MS treatment, comparisons between ocrelizumab and other DMTs approved for MS should not be affected.

10. PROTECTION OF HUMAN SUBJECTS

This is a non-interventional study using secondary data and does not pose any risks for patients. All data collected in the study will be de-identified with no breach of confidentiality with regard to personal identifiers or health information. Each US database research partner will apply for an independent ethics committee review according to local regulations;

in addition, as the coordinating center, RTI-HS will obtain approval from the RTI International institutional review board (IRB) (see Section 10.1). In Denmark, following local regulations, approval from the Data Protection Authorities will be obtained. Data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

In the case of secondary data collection for validation purposes (e.g., medical chart abstraction), every effort will be made to protect participant confidentiality according to local and international data privacy and medical record confidentiality guidance and requirements.

10.1 RTI INTERNATIONAL

RTI International holds a Federal-wide Assurance from the Department of Health and Human Services Office for Human Research Protections that allows the organization to review and approve human subjects protocols through its IRB committees. RTI International currently has two IRB committees available to review research protocols. One IRB committee is constituted to review medical research and has two members who are physicians. These IRBs have been audited by the FDA and are fully compliant with applicable regulatory requirements.

10.2 CARELON RESEARCH HEALTHCARE INTEGRATED RESEARCH DATABASE

Carelon Research maintains Data Sharing Agreements and Business Associate Agreements with all covered entities who provide data to the HIRD. Carelon Research's access, use, and disclosure of protected health information (PHI) are in compliance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (45 CFR Part 160 and Subparts A and E of Part 164). Carelon Research does not access, use, or disclose identifiable PHI unless under a specific waiver of authorization (e.g., a HIPAA Waiver of Authorization from an IRB). Carelon Research accesses the data in a manner that complies with federal and state laws and regulations, including those related to the privacy and security of individually identifiable health information.

As PHI must be accessed to acquire medical records to validate electronic case-finding algorithms, a HIPAA Waiver of Authorization will be applied for from an IRB. Carelon Research will submit the protocol to a central IRB for review and approval. If changes to the protocol are required, Carelon Research will submit an amendment to the IRB.

At no time during the conduct of this study will Carelon Research provide patient- or provider-identifying information to RTI-HS or Roche. Only aggregated data will be reported to RTI-HS or Roche. Carelon Research will keep all needed documents and provide a copy of the final approvals/waivers to RTI-HS (the coordinating center) for completeness of study records.

10.3 OPTUM DYNAMIC ASSESSMENT OF PREGNANCIES AND INFANTS™

Optum has obtained approval from health plans and an IRB as per standard procedures. Optum will communicate directly with the IRB to address questions or provide additional information as needed. The IRB will be asked to re-approve the study with the periodicity established by standard procedures. In addition to IRB approval, internal review and approval are also required. Optum will keep all needed documents and provide a copy of the final approvals/waivers to RTI-HS (the coordinating center) for completeness of study records.

10.4 IBM MARKETSCAN COMMERCIAL CLAIMS AND ENCOUNTERS DATABASE

RTI-HS obtained a "not human research" designation from the RTI International IRB on 30 April 2020 (IRB ID STUDY00021100).

10.5 DANISH NATIONAL HEALTH DATABASES AND DANISH MULTIPLE SCLEROSIS REGISTRY

For the Danish National Health Databases, approval will be requested from the Danish Data Protection Agency.

10.6 OTHER GOOD RESEARCH PRACTICE

This study adheres to the *Guidelines for Good Pharmacoepidemiology Practices (GPP)* of the International Society for Pharmacoepidemiology (ISPE 2015) and has been designed in line with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology* (ENCePP 2022). The ENCePP Checklist for Study Protocols (ENCePP 2018) is included in Appendix 2.

The study is a PASS and will comply with the definition of the non-interventional observational study referred to in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use tripartite guideline Pharmacovigilance Planning E2E (ICH 2004) and provided in the EMA *Guideline on Good Pharmacovigilance Practices (GVP) Module VIII: Post-Authorisation Safety Studies* (EMA 2017b), and with the 2012 European Union pharmacovigilance legislation, adopted 19 June 2012 (European Commission 2012). The study will comply with the study reporting requirements specified in Module VIII Section VIII.B.6.3.2. "Final Study Report" of the GVP (EMA 2017b).

The study is registered in the EU PAS Register (EUPAS33879) (ENCePP 2023).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

For non-interventional studies that are solely based on secondary use of data, reporting of adverse events/adverse drug reactions is not required. Based on current guidelines from the ISPE (ISPE 2015) and the EMA GVP Module VI - Management and Reporting of Adverse Reactions to Medicinal Products (EMA 2017a), non-interventional studies such as the one described in this protocol conducted using aggregated patient data from electronic health care records do not require expedited reporting of suspected adverse events/reactions. Based on the data planned for this study, no suspected adverse events/reactions are expected.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Regardless of the outcome of this study, Roche is dedicated to openly providing information on this safety study to health care professionals and to the public, both at scientific congresses and in peer-reviewed journals. Roche will comply with all requirements for publication of study results. Roche will submit all study reports to the health authorities through scheduled regulatory safety reporting (periodic adverse drug experience report [PADERs] and/or periodic benefit-risk evaluation report [PBRERs], as agreed with health authorities).

The study protocol and progress and final study reports will be included in regulatory communications in line with the risk management plan, PADERs/PBRERs, and other regulatory milestones and requirements. Study reports will be prepared using a template following GVP, Module VIII, Section B.6.3 (EMA 2017b).

Any publications will follow guidelines, including those for authorship, established by the International Committee of Medical Journal Editors (ICMJE 2021). When reporting results of this study, the appropriate STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist will be followed (STROBE statement 2007).

In the contracts for the implementation of this study, Roche and the principal investigators (e.g., the principal investigators at the study coordinating center and at the research partner centers) agreed upon a publication policy allowing the principal investigators to independently prepare publications based on the study results, irrespective of data ownership and sponsorship. The design of this study has been presented as a conference abstract (Margulis et al. 2018).

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Appendix 1
Contact Details for Collaborating Institutions

Collaborating Institutions

Carelon Research, USA
Stephan Lanes, PhD, MPH; Senior Scientist Aziza Jamal-Allial, PhD, MS; Principal Investigator

OptumInsight Life Sciences, Inc., USA
John D. Seeger, PharmD, DrPH; Chief Scientific Officer

Aarhus University, Denmark
Henrik Toft Sørensen, MD, PhD; Principal Investigator Mette Nørgaard, PhD; Project Leader Vera Ehrenstein, MPH, DSc; Senior Epidemiologist Lars Pedersen, MD, PhD; Senior Biostatistician

Appendix 2
ENCePP Checklist for Study Protocols

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is “Yes,” the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer ‘N/A’ (Not Applicable) can be checked, and the “Comments” field included for each section should be used to explain why. The “Comments” field can also be used to elaborate on a “No” answer.

This Checklist should be included as an Annex by marketing authorization holders when submitting the protocol of a non-interventional postauthorization safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional postauthorization safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Multisource Surveillance Study of Pregnancy and Infant Outcomes in Ocrelizumab-Exposed Women With Multiple Sclerosis

EU PAS Register® number:
Study reference number: BA39732 (protocol number)

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	4, 6
1.1.2 End of data collection[2]	☒	☐	☐	4, 6
1.1.3 Progress report(s)	☒	☐	☐	4, 6, 12
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results	☒	☐	☐	6

Comments:

No interim progress reports are planned; ocrelizumab use monitoring reports are planned annually from 2020 through 2028.

Section 2: Research Question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g., to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	4, 7
2.1.2 The objective(s) of the study?	☒	☐	☐	4, 8
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☒	☐	

Comments:

There are no a priori hypotheses in this study.

Section 3: Study Design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g., cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary, or combined data collection?	☒	☐	☐	9, 9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7.2

[1] Date from which information on the first study is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical data set is completely available.

Section 3: Study Design		Yes	No	N/A	Section Number
3.4	Does the protocol specify measure(s) of association? (e.g., relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm [NNH])	☒	☐	☐	9.7.4
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g., adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and Study Populations		Yes	No	N/A	Section Number
4.1	Is the source population described?	☒	☐	☐	9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2.2
	4.2.2 Age and sex	☒	☐	☐	9.2.1
	4.2.3 Country of origin	☐	☐	☒	
	4.2.4 Disease/indication	☒	☐	☐	9.1, 9.2.1
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.3
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1

Comments:

Eligibility in the study is independent of country of origin.

Section 5: Exposure Definition and Measurement		Yes	No	N/A	Section Number
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g., operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☒	☐	☐	9.9
5.3	Is exposure categorized according to time windows?	☒	☐	☐	9.3.1
5.4	Is intensity of exposure addressed? (e.g., dose, duration)	☐	☐	☐	

Section 5: Exposure Definition and Measurement	Yes	No	N/A	Section Number
5.5 Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	7, 9.3.1
5.6 Is (are) an appropriate comparator(s) identified?	☒	☐	☐	4, 8, 9

Comments:

Section 6: Outcome Definition and Measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g., HRQoL, QALYs, DALYS, health care services utilization, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☒	☐	☐	9.7.4
7.2 Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☒	☐	☐	9
7.3 Does the protocol address information bias? (e.g., misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Section 8: Effect Measure Modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g., collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

Effect modification is not considered at this point.

Section 9: Data Sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3.1
9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.2
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
9.2.2 Outcomes? (e.g., date of occurrence, multiple events, severity measures related to event)	☒	☐	☐	9.4
9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4
9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.4 Is a linkage method between data sources described? (e.g., based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Section 10: Analysis Plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.2
10.4 Are stratified analyses included?	☒	☐	☐	9.7.8
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.4

Section 10: Analysis Plan	**Yes**	**No**	**N/A**	**Section Number**
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.3.2
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.5
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	4, 9.7.9

Comments:

Section 11: Data Management and Quality Control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g., study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

Section 13: Ethical Issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	

Section 13: Ethical Issues	**Yes**	**No**	**N/A**	**Section Number**
13.3 Have data protection requirements been described?	☒	☐	☐	9.6, 10

Comments:

There has not been any ethical review procedure yet.

Section 14: Amendments and Deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for Communication of Study Results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g., to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Erwan Muros-Le Rouzic

Date: see cover page

Signature: _____

Appendix 3
Algorithms to Identify Key Study Endpoints

Algorithms to Identify Key Endpoints

Endpoint	ICD-10 Codes	Window for Outcome Ascertainment	Maternal or Infant Files
Major congenital malformations	Included: D21.5, D82.1, D18.10, P35.0, P35.1, P37.1. Not included (codes for minor malformations[a]) per EUROCAT (2022): Q04.61, Q07.80, Q07.82, Q10.1, Q10.2, Q10.3, Q10.3, Q10.3, Q10.5, Q13.5, Q17.0, Q17.0, Q17.1, Q17.2, Q17.3, Q17.4, Q17.5, Q17.9, Q18.0, Q18.1, Q18.2, Q18.4, Q18.5, Q18.6, Q18.7, Q18.80, Q18.9, Q21.11, Q24.6, Q25.41, Q26.1, Q27.0, Q31.4, Q31.40, Q31.5, Q32.0, Q32.2, Q33.00, Q33.1, Q33.10, Q35.7, Q38.1, Q38.2, Q38.50, Q40.0, Q40.1, Q40.21, Q43.0, Q43.20, Q43.81, Q43.82, Q44.4, Q45.83, Q50.1, Q50.10, Q50.11, Q50.2, Q50.5, Q52.3, Q52.5, Q52.7, Q53, Q53.0, Q54.4, Q55.20, Q55.21, Q56.4, Q61.0, Q62.7, Q63.3, Q65.3, Q65.5, Q65.6, Q65.8, Q65.9, Q66.1, Q66.2, Q66.3, Q66.4, Q66.5, Q66.6, Q66.7, Q66.8, Q66.80, Q66.9, Q67.0, Q67.1, Q67.2, Q67.3, Q67.4, Q67.40, Q67.41, Q67.5, Q67.6, Q67.7, Q67.8, Q68.0, Q68.10, Q68.21, Q68.3, Q68.4, Q68.5, Q74.00, Q75.2, Q75.3, Q76.0, Q76.43, Q76.5, Q76.60, Q76.62, Q76.71, Q82.5, Q82.50, Q82.51, Q82.52, Q82.80, Q82.81, Q83.3, Q84.5, Q84.6, Q89.11, Q89.9, Q95, Q95.2. Additional minor malformations: Q25.0 and Q25.6 if gestational age at birth < 37 weeks (i.e., pregnancy end date minus LMP is < 259 days)	Birth through first year of life	Either
Spontaneous abortion	Ascertained as part of the pregnancy identification process	Before gestational week 20	Maternal
Stillbirth	Ascertained as part of the pregnancy identification process	At or after gestational week 20	Maternal
Small for gestational age	US data sources: 1. O36.51 and O36.59 P05.1 2. Combinations of estimated gestational age at birth (derived from codes Z3A), sex, and codes for birth weight (codes P07) based on US growth standards (Oken et al. 2003) 3. #1 or #2	30 days before or after delivery	Either

Endpoint	ICD-10 Codes		Window for Outcome Ascertainment	Maternal or Infant Files
	Danish registries: 1. Birth weight <10th percentile of birth weight by gestational age at birth and sex (primary algorithm) 2. Birth weight <5th percentile of birth weight by gestational age at birth and sex (secondary algorithm)			Infant
Preterm birth[b]	1. ICD-10 codes mapped from ICD-9 codes retained in the final model of the method developed by Eworuke et al. (2012). Mapping will use the mapping tools developed by the Centers for Medicaid and Medicaid Services.[c]	Per Table 5 in Eworuke et al.	7 days before LMP through 30 days after LMP	Either
	2. Gestational age at birth <37 completed weeks using the estimated gestational age at birth (e.g., codes Z3A.x)			
	3. #1 or #2			

EUROCAT = European Surveillance of Congenital Anomalies (program); ICD-10 = *International Classification of Diseases, Tenth Revision*; ICD-9 = *International Classification of Diseases, Ninth Revision*; LMP = first day of the last menstrual period; US = United States.

Note: Algorithms and codes using other coding systems are presented in more detail in the statistical analysis plan.

[a] Some of these codes represent more than one minor malformation.

[b] In Denmark, preterm birth will be identified as births before 37 completed gestational weeks using gestational age at birth as recorded in the Danish Medical Birth Registry. In US data, validation efforts will determine which algorithm will be preferred.

Appendix 4
Characteristics of Study Data Sources

Characteristics of Study Data Sources

Description	HIRD[a]	DAPI and Optum Research Database[b]	MarketScan Databases[c]	Danish National Registries[d]	Danish MS Registry[e]	Danish MS Treatment Registry[f]
Year available	2006	1993	1995	1977	1956	1996
Database type	Health care claims	Health care claims	Health care claims	Nationwide health record databases capable of linkage with other databases through a unique personal identification number	Disease-specific registry	DMT-treated, disease-specific registry
Purpose	Administrative	Administrative	Administrative	Administrative	Research database	Clinical quality monitoring, safety surveillance, and research database
Country	United States	United States	United States	Denmark	Denmark	Denmark
Database size	As of June 2017: 60 million individuals with multiple health plans coverage and over 44 million lives with medical and pharmacy coverage at any point since 2006.	Over 100 million lives since 1993	225 million unique patients since 1995 62.9 million covered lives in the most recent update	5.6 million Nationwide	Nationwide	Nationwide
Representa-tiveness of patients	Commercially insured population	Commercially insured population	Commercially insured population	Total population	All patients with MS	All patients with MS treated with DMTs (mandatory registration)

Description	HIRD[a]	DAPI and Optum Research Database[b]	MarketScan Databases[c]	Danish National Registries[d]	Danish MS Registry[e]	Danish MS Treatment Registry[f]
Type of health care contact or source of data	Physician, specialist, and emergency room visits, and hospital stays	Inpatient hospital, outpatient hospital, emergency room, physician's office, surgery center, etc.) for virtually all types of services provided, including specialty, preventive, and office-based treatments	Inpatient hospital, outpatient hospital, emergency room, physician's office	Inpatient, outpatient (ambulatory) clinics, or emergency department	1,322 departments of neurology, private neurologists, MS rehabilitation clinics, the Danish MS Treatment Registry, the Danish MS Society, and neuropathologists. Two neurologists extract data from medical records Online data collection by the neurologist in the MS clinics and monthly quality-control checks of the data by the registry staff	All Danish departments of neurology through notification at treatment start, and during follow-up at month 3 from start and every 6 months thereafter

Description	HIRD[a]	DAPI and Optum Research Database[b]	MarketScan Databases[c]	Danish National Registries[d]	Danish MS Registry[e]	Danish MS Treatment Registry[f]
Data on medications	Approved prescription drug and biologic products dispensed in pharmacies, specialty pharmacies, outpatient settings, and hospitals	Pharmacy claims or procedure claims for approved drug and biologic products dispensed in pharmacies or specialty pharmacies or dispensed or administered in outpatient settings and hospitals	Pharmacy claims, claims for mail order prescriptions and specialty pharmacies	Pharmacy-dispensed prescriptions, reimbursed and non-reimbursed	Available as the online data collection platform; serves as data source for the clinical quality database where notification on all patients with MS treated with DMT is mandatory	
Medication information available	Dispensed date, product, strength, days' supply, quantity dispensed, and prescriber specialty	Drug name, drug strength, fill date, quantity dispensed, and days of supply, along with administration date for medications administered by a health care provider	Dispensed date, product, strength, days' supply, quantity dispensed	Formulation strength, DDD (dose unit) and DDDs per package, units per package, date dispensing		
Dose	Based on pharmacy dispensing data	Based on pharmacy dispensing data	Based on pharmacy dispensing data	Dose optional, in free text	Not available for DMTs	
Duration	Based on pharmacy dispensing data	Based on pharmacy dispensing data	Based on pharmacy dispensing data	Based on prescription refills	Not available for DMTs	

Description	HIRD[a]	DAPI and Optum Research Database[b]	MarketScan Databases[c]	Danish National Registries[d]	Danish MS Registry[e]	Danish MS Treatment Registry[f]
Drug dictionary codes	NDC linked to 14-digit GPI For some drugs and biologic therapy products used in outpatient physician offices, clinics, and inpatient settings: CPT, HCPCS, or, depending on the type of product, ICD-9-CM	NDC	NDC	ATC classification code	ATC classification code	
Diagnosis/ clinical indication	No	No	No	Optional, in free text. Based on proxies	MS disease course, date of onset, date of diagnosis, symptoms at onset, diagnostic accuracy, EDSS	MS disease course, date of onset, date of diagnosis, symptoms at onset, diagnostic accuracy, EDSS, number of relapses in last 12 or 24 months
Outpatient diagnosis	Yes	Yes	Yes	Only outpatient hospital diagnoses	Linkage with Danish National Registries	Linkage with Danish National Registries
Hospital diagnosis	Yes	Yes	Yes	Yes	Linkage with Danish National Registries	Linkage with Danish National Registries
Disease codes	ICD-9-CM, ICD-10-CM	ICD-9-CM, ICD-10-CM	ICD-9-CM, ICD-10-CM	ICD-10-CM	ICD-10	

Description	HIRD[a]	DAPI and Optum Research Database[b]	MarketScan Databases[c]	Danish National Registries[d]	Danish MS Registry[e]	Danish MS Treatment Registry[f]
Procedure codes	CPT, HCPCS	CPT, HCPCS	CPT, HCPCS	NCSP		
Diagnostic examinations	CPT, HCPCS	CPT, HCPCS	CPT, HCPCS	NCSP (no results)	Evoked potentials, MRI, CSF	Radiological examination (with results)
Laboratory tests	Standard LOINC coding	Procedure and test results available	Procedure		JCV, NAb, Tysabri antibody, CSF analyses	Some tests (with results)
Lifestyle risk factors	No	No	No	Yes	No	No
Source of data for validation	Inpatient and outpatient medical records; patient and provider surveys	Inpatient and outpatient medical records	Not available	Not available	Inpatient and outpatient medical records	Not available
Linkage to other data sources	National mortality, cancer, and vaccine registries	National mortality and birth registries, surveys, and medical records[g]	EMR, mortality	Danish National Registries	Danish National Registries	Danish National Registries
Approximate time lag (updates per year)	3 months (monthly update)	6 months (semi-annually/quarterly)	6 months (quarterly update)	6 to 8 months (annually)		

ATC = Anatomical Therapeutic Chemical; CPT = Current Procedural Terminology; CSF = cerebrospinal fluid; DAPI = Dynamic Assessment of Pregnancies and Infants; DDD = defined daily dose; DMT = disease-modifying therapy; EDSS = Expanded Disability Status\ Scale; EMR = electronic medical record; GPI = Generic Product Identifier; HCPCS = Healthcare Common Procedure Coding System; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*; ICD-10-CM = *International Classification of Diseases, 10th Revision, Clinical Modification*; ICD-9-CM = *International Classification of Diseases, 9th Revision, Clinical Modification*; JCV = JC

virus; LOINC = Logical Observation Identifiers Names and Codes; MRI = magnetic resonance imaging; MS = multiple sclerosis; NA = not applicable; NAb = neutralizing antibodies; NCSP = NOMESCO classification of surgical procedures; NDC = National Drug Codes.

[a] Source: HealthCore (2017).

[b] Source: Wyszynski et al. (2016).

[d] Sources: Kildemoes et al. (2011); Lynge et al. (2011); Pedersen et al. (2016); Schmidt et al. (2015).

[e] Sources: Bronnum-Hansen et al. (2011); Flachenecker et al. (2014).

[f] Sources: Flachenecker et al. (2014); Magyari et al. (2016). The Danish Multiple Sclerosis Treatment Registry has been integrated into The Danish Multiple Sclerosis Registry and is no longer available as a stand-alone data source for research.

[g] In limited instances where personally identifiable information is available and appropriate approvals are obtained.

Appendix 5
Checklist for Reporting in Perinatal Pharmacoepidemiology

This checklist identifies methods-related elements that are key in perinatal pharmacoepidemiology research. The columns for yes, no, or not applicable (N/A) reflect whether each element is specified in the present document. The column for section number reflects where in the document the element is specified (if applicable).

#	Element	Yes	No	N/A[a]	Section
Source of information on beginning and end of pregnancy					
1	Source of information for start of pregnancy (e.g., electronic algorithm, ultrasound)	X			SAP 3.1.3, SAP Appendices
2	Source of information for pregnancy outcome date (e.g., recorded codes for spontaneous abortion, date estimated using an algorithm)	X			SAP Section 3.1.3, SAP Appendices
Composition of the study population					
3	Multifetal pregnancies included in study population?	X			Protocol 9.2.1 SAP 3.1.2
4	More than one pregnancy per woman included in study population?	X			Protocol 9.2.1 SAP 3.1.2
5	Fetuses with chromosomal abnormalities included in study population?	X			Protocol 9.2.1 SAP 3.1.2
6	Fetuses with major malformations included in study population?	X			Protocol 9.2.1 SAP 3.1.2
7	Fetuses with minor malformations included in study population?	X			Protocol 9.2.1 SAP 3.1.2
8	Non-live births included in denominator?	X			Protocol 9.2.1 SAP 3.1.2
Mother-infant and father-infant linkages					
9	If mother-infant linkage was implemented, was the process described?	X			SAP 3.1.4, SAP Appendices
10	If mother-infant linkage was implemented, was the success rate reported?			X	
11	If mother-infant linkage was implemented, was the information taken from maternal vs. infant files?	X			SAP 3.1.4
12	If father-infant linkage was implemented, was the process described?			X	
13	If father-infant linkage was implemented, was the success rate reported?			X	
Analytical aspects					
14	Unit of analysis for pregnancy outcomes	X			SAP 3.2.1.2

#	Element	Yes	No	N/A[a]	Section
15	Unit of analysis for fetal or infant outcomes	X			SAP 3.2.1.2
16	Gestational age at start of follow-up	X			SAP 3.1.3, SAP Appendices
17	Was intrafamily correlation considered?		X		

Comments: Linkages not implemented yet; father-infant linkage will not be sought. Some elements are specified in the study SAP and not in the study protocol: the corresponding SAP section is presented in this checklist.

N/A = not applicable; SAP = statistical analysis plan.

[a] If elements are not applicable, please specify the reasons in the Comments field.

Source: Margulis AV, Kawai AT, Anthony MS, Rivero-Ferrer E. Perinatal pharmacoepidemiology: how often are key methodological elements reported in publications? Pharmacoepidemiol Drug Saf. 2022 Jan;31(1):61-71. doi:10.1002/pds.5353.

Appendix 6
Approval Pages

Approval page for RTI Health Solutions

RTI-HS Project No.: 0304767

Sponsor: Roche Registration Ltd/F. Hoffmann-La Roche Ltd

Signature:

Elena Rivero	Date
Senior Director, Epidemiology	
RTI Health Solutions	

Approval page for Aarhus University

RTI-HS Project No.: 0304767

Sponsor: Roche Registration Ltd/F. Hoffmann-La Roche Ltd

Signature:

Henrik Toft Sørensen	Date
Head of Department of Clinical Epidemiology	
Aarhus University	

Approval page for Carelon Research

RTI-HS Project No.: 0304767

Sponsor: Roche Registration Ltd/F. Hoffmann-La Roche Ltd

Signatures:

Aziza Jamal-Allial, PhD Research Scientist of Epidemiology, Safety & Epidemiology **Carelon Research**	Date

Approval page for Optum

RTI-HS Project No.: 0304767

Sponsor: Roche Registration Ltd/F. Hoffmann-La Roche Ltd

Signature:

John D. Seeger, PharmD, DrPH Chief Scientific Officer, Epidemiology **Optum**	Date

PROTOCOL

TITLE:	**A PHASE IIIb, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OCRELIZUMAB IN ADULTS WITH PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS**
PROTOCOL NUMBER:	WA40404
VERSION NUMBER:	5
EUDRACT NUMBER:	2018-001511-73
IND NUMBER:	100,593
NCT NUMBER:	*NCT04035005*
TEST PRODUCT:	Ocrelizumab (RO4964913) (OCREVUS®)
SPONSOR:	F. Hoffmann-La Roche Ltd
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**
5	See electronic date stamp on the final page of this document.	—	—	—
4	1 February 2021	—	—	—
3	4 August 2020	—	—	—
2	12 March 2020			
1	14 February 2019	Italy	1	13 August 2019
		Ireland	1	30 June 2019
		United Kingdom	1	26 June 2019

PROTOCOL AMENDMENT, VERSION 5: RATIONALE

Protocol WA40404 has been amended in line with the change in the study design from an event-driven study to a fixed-duration study (i.e., eligible patients will switch from the double-blind, placebo-controlled treatment to the open-label treatment of ocrelizumab at 144 weeks). Changes to the protocol, along with a rationale for each change, are summarized below:

- The name and contact information of the Medical Monitor have been removed as per new template (title page, Protocol Amendment Acceptance Form, and Section 5.4.1).
- The terms "intent-to-treat (ITT)" or "ITT population" have been updated to “all randomized patients” throughout the protocol to align with the guideline to precisely define analysis sets for estimands (Sections 1.3, 2.1.3, 6.4.1.3, 6.4.3, and Table 1, Table 2).
- Benefit–risk assessment and guidance on the conduct of the study during the coronavirus disease 2019 (COVID-19) pandemic and concomitant administration of COVID-19 vaccines with ocrelizumab have been added (Sections 1.3.2 and 1.3.3).
- Males and females (all randomized patients, MRI-active subgroup and MRI-inactive subgroup) has been added to the patient subgroup for the exploratory efficacy objective based on Health Canada feedback (Sections 2.1.3 and 6.4.3).
- The biomarker objective, rationale and analyses have been updated to include more specific assessments of neurofilament light chain as a pharmacodynamic and prognostic/predictive biomarker based on current advances in knowledge (Sections 2.5, 3.3.5, and 6.8)
- Based on regulatory authority feedback on ways to mitigate the slower than anticipated recruitment to the study, the study design has been changed from an event-driven study to fixed-duration study. As a result, the following changes have been made:
  - The duration of the double-blind treatment phase for patients has been updated to 144 weeks (6 study drug doses, with each dose 24 weeks apart) (Sections 3.1, 3.1.1.2, and 3.2, and Appendix 1).
  - The timing of the primary analysis has been updated to be performed after the last randomized patient reaches 144 weeks of double-blind treatment (+12 weeks to allow for the confirmation of the latest event) (Sections 3.1, 3.1.1.2, and 6.4.1.3).
  - Text has been modified to specify that patients who prematurely discontinue from study treatment will continue in the follow-up 1 (FU1) phase until 144 weeks from randomization for each patient (Sections 3.1 and 3.1.1.2).
  - The study design and patient flow schemas have been updated (Section 3.1 [Figures 1 and 2]).

- Guidance has been added to describe that eligible patients will switch to the open-label extension (OLE) phase after they have completed 144 weeks of double-blind treatment (Sections 3.1 [Figure 1] and 3.1.1.5).
- A footnote has been added to the study design schema to describe the completion of the efficacy assessments, the duration of the OLE phase, the dosing in the OLE phase, and the follow up of patients who discontinue from the OLE phase (Section 3.1 [Figure 1]).
- The duration of the OLE phase has been updated to at least 2 years (at least 4 doses of ocrelizumab) for each patient (Sections 3.1 [Figure 1], 3.1.1.5, and 3.2, and Appendix 3).
- The dosing regimen in the double-blind treatment phase has been updated to 6 treatment doses (144 weeks), and the dosing regimen in the OLE phase has been updated to at least 4 treatment doses (Sections 3.1, 3.1.1.2, 3.2, and Figure 1).
- Text has been updated to indicate that patients may continue on post–double-progression ocrelizumab (PDP OCR) treatment until the end of the OLE phase (Section 3.1.1.3).
- The duration of the FU1 phase that will run in parallel with the double-blind treatment phase has been updated to "until 144 weeks from randomization for each patient" (Section 3.1.1.4 and Appendix 2).
- Text has been modified to indicate that all patients who are ongoing in the FU1 phase at 144 weeks from randomization for each patient will continue in the follow up 2 (FU2) phase (Sections 3.1.1.4, and 3.1.1.5) and will not participate in the OLE phase (Section 3.1.1.5).
- Text has been added to indicate that Study WA40404 will remain blinded until the primary analysis (Section 3.1.1.5).
- The criteria for patients who will move into the FU2 phase have been updated (Section 3.1.1.6).
- The expected total length of the study has been extended to 9.5 years (Section 3.2).
- Footnote "d" has been added to the schedule of activities for the OLE phase to provide clarification on the duration, assessments, and treatment discontinuation of the OLE phase (Appendix 3).

- The stratification factor for region has been updated to remove Iceland, Norway, and Liechtenstein, as these countries are not participating in the study (Section 3.1.1.1).
- Text has been added to indicate that screening for Floodlight remote patient monitoring (RPM) participation will close on November 2022 in order for the last Floodlight RPM patient enrollment to occur by the end of December 2022 (Sections 3.1.1.1 and 4.5.15).

- Clarification has been made that the exclusion criterion of known presence of other neurologic disorders as those that could interfere with the diagnosis of multiple sclerosis (MS) or assessments of efficacy and/or safety during the study (Section 4.1.2).
- The eligibility criterion for OLE phase for patients who meet the re-treatment criteria for ocrelizumab has been removed to allow future inclusion of patients into the OLE phase when patients meet the re-treatment criteria at a later timepoint (Section 4.1.3).
- The eligibility criterion of female contraception has been clarified to reference the Clinical Trial Facilitation Group guidance for the type of contraception methods (Sections 4.1.1 and 4.1.3).
- Text has been added to indicate that at the Week 120 visit for patients switching to PDP OCR treatment, mandatory MRI scans should be obtained within 4 weeks before the Week 120 visit because the assessments of the Week 120 visit, including MRI scans, should correspond to the double-blind treatment phase and therefore, should be performed before the infusion (Section 4.5.10 and Appendix 1).
- Clarification has been made that the Treating Investigator may have access to MRI scans performed during the OLE phase after primary analysis and the study will remain blinded until primary analysis (Section 4.5.10).
- Information about future use of screening blood and cerebrospinal fluid samples has been added (Section 4.5.11).
- Leftover samples from the main trial have been added to possible samples allowed for use as part of the Research Biosample Repository (RBR) for patients giving RBR optional consent as this allows greater flexibility to allow use of RBR samples already collected as part of the main trial for future research (Section 4.5.14.3).
- Instructions about patient withdrawal from the RBR after site closure have been modified to indicate that the investigator must inform the Sponsor of patient withdrawal by emailing the study number and patient number to global.rcrwithdrawal@roche.com (Section 4.5.14.6).
- The potential risk section for progressive multifocal leukoencephalopathy and hypersensitivity reactions has been updated to align with the most recent safety data (Section 5.1.1.2).
- Language has been added to indicate that the Informed Consent Form will instruct female patients to inform the investigator if they become pregnant (Section 5.4.3.1).
- Language of “more than 24 hours” has been deleted to facilitate a more accurate safety reporting-based investigator’s medical judgement of the prolongation of hospitalization, without operational constrains of time (Section 5.3.5.11).
- The description of the determination of sample size and the operating characteristics for true underlying hazard ratio values have been updated (Section 6.1).

- The definition of baseline for 9-Hole Peg Test (9-HPT) time has been clarified as measured before first dose administration (or randomization for non-treated patients) (Section 6.4.1).
- The term "MS disease-modifying therapy" has been applied throughout the protocol for clarity (Sections 6.4.1.1, 6.4.1.2, and 6.5).
- Text has been added to specify the duration that the Sponsor will retain study data to align with Roche model document wording (Section 7.6).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with Clinical Trials Regulation requirements (Section 8.4).
- The 9-HPT, Expanded Disability Status Scale, and Symbol Digit Modalities Test assessments have been removed from end of observation or withdrawal from follow-up in the schedule of activities for FU2 and B-cell monitoring (BCM) phases because it has been decided to not conduct those assessments at the end of the study as it has not been conducted during the FU2 and BCM phases (Appendix 4).

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

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PROTOCOL *AMENDMENT* ACCEPTANCE FORM

TITLE:	**A PHASE IIIb, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OCRELIZUMAB IN ADULTS WITH PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS**
PROTOCOL NUMBER:	WA40404
VERSION NUMBER:	5
EUDRACT NUMBER:	2018-001511-73
IND NUMBER:	100,593
NCT NUMBER:	*NCT04035005*
TEST PRODUCT:	Ocrelizumab (RO4964913) (OCREVUS®)
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 the Sponsor or their designee.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE IIIb, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OCRELIZUMAB IN ADULTS WITH PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS**
PROTOCOL NUMBER:	WA40404
VERSION NUMBER:	5
EUDRACT NUMBER:	2018-001511-73
IND NUMBER:	100,593
NCT NUMBER:	*NCT04035005*
TEST PRODUCT:	Ocrelizumab (RO4964913) (OCREVUS®)
PHASE:	IIIb
INDICATION:	Primary progressive multiple sclerosis
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of ocrelizumab (Ocrevus®) compared with placebo in patients with primary progressive multiple sclerosis (PPMS), including patients later in their disease course. Specific objectives and corresponding endpoints for the study are outlined below.

EFFICACY OBJECTIVES

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of ocrelizumab-treated patients compared with placebo-treated patients on upper extremity disability progression. This objective is measured on upper limbs on the basis of the following endpoint:

- Upper limb disability progression defined as time to 20% worsening from baseline in 9-Hole Peg Test (9-HPT) confirmed for at least 12 weeks in all randomized patients and in patients with magnetic resonance imaging (MRI) activity (MRI activity is defined as presence of T1 gadolinium (Gd)+ lesion[s] and/or new and/or enlarging T2 lesion[s] as detected by MRI scans during the screening phase).

Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of ocrelizumab compared with placebo for all randomized patients on the basis of the endpoints below, in hierarchical order. The secondary efficacy endpoints will also be evaluated as exploratory analyses for the MRI-active subgroup.

- Upper limb disability progression defined as time to 20% increase from baseline in 9-HPT confirmed for at least 24 weeks
- Time to 12-week confirmed disability progression (CDP) in Expanded Disability Status Scale (EDSS), defined as an increase in EDSS score that is confirmed for at least 12 weeks (an increase of ≥ 1.0 point from baseline EDSS score in patients with a baseline EDSS score ≤ 5.5 or an increase of ≥ 0.5 point in patients with a baseline EDSS score of > 5.5)
- Time to 24-week CDP in EDSS, defined as an increase in EDSS score that is confirmed for at least 24 weeks (an increase of ≥ 1.0 point from baseline EDSS in patients with a baseline EDSS score ≤ 5.5 or an increase of ≥ 0.5 point in patients with a baseline EDSS score of > 5.5)

- Percent change in total volume of T2 lesions from baseline up to Week 120
- Percent change in total brain volume from Week 24 to Week 120

Exploratory Efficacy Objective

An exploratory efficacy objective for this study is to evaluate the efficacy of ocrelizumab compared with placebo in patients, as measured by the primary and secondary endpoints in the following patient subgroups:

- Age >55 versus ≤ 55
- EDSS score ≤ 6.5 versus >6.5
- MRI-inactive versus MRI-active
- *Males and females (all randomized patients, MRI-active subgroup and MRI-inactive subgroup)*

Additional exploratory objectives include the efficacy of ocrelizumab compared with placebo inpatients from *all randomized patients* and *the* MRI-active subgroup as measured by the following endpoints:

- Proportion of patients free of disability progression on upper limbs by 9-HPT at Week 120 and at time of clinical cutoff of primary analysis
- Change from baseline to Week 120 in fatigue as measured by Modified Fatigue Impact Scale (MFIS)
- Change from baseline to Week 120 and from Week 24 to Week 120 in cervical spinal cord volume on MRI scans
- Change from baseline to Week 120 in a measure of manual ability for adults with upper limb impairments (ABILHAND)
- Change from baseline to Week 120 in the upper limb domain of a life quality measure for patients with neurological disorders (Quality of Life in Neurological Disorders-Upper Extremity Function [Neuro-QoL-UE])
- Change from baseline to Week 120 in the Patient Global Impression of Change for upper limb function (PGIC-UL)
- Change from baseline to Week 120 in the Patient Global Impression of Change for fatigue (PGIC-F)
- Change from baseline to Week 120 in the Multiple Sclerosis Impact Scale (MSIS)-29 physical score
- Proportion of patients at Week 120 with a clinically meaningful decline on the MSIS-29
- Change from baseline to Week 120 in the Symbol Digit Modalities Test (SDMT)
- Rate of decline in fine motor skills of upper extremities and manual/finger dexterity as measured by smartphone-based digital outcome assessment (Floodlight remote patient monitoring [RPM])
- The number of gadolinium (Gd)-enhancing T1 lesions and number of new or enlarging T2 hyperintense lesions as detected by mandatory MRI
- The change from baseline in total non-enhancing T1 lesion volume on MRI scan of the brain

Safety Objectives

The safety objectives for this study are to evaluate the safety of ocrelizumab compared with placebo, as well as over time, for all patients who received ocrelizumab and until they receive any other MS disease-modifying therapy (DMT).

Safety endpoints considered include adverse events, serious adverse events, adverse events leading to study treatment withdrawal, vital signs, change from baseline in laboratory test results, association of decrease in certain laboratory parameters, and serious infections.

Immunogenicity Objective

The immunogenicity objective is as follows:

- Immunogenicity, as the presence of anti-drug antibody (ADA) during the study relative to baseline. The relationship between ADA status and pharmacokinetics, pharmacodynamics, efficacy and safety may be explored.

Pharmacokinetic and Pharmacodynamic Objectives

The pharmacokinetic (PK) and pharmacodynamic objectives are as follows:

- Characterization of the ocrelizumab PK profile
- Evaluation of ocrelizumab pharmacodynamics, as measured by B-cell levels in blood

Biomarker Objective

The exploratory biomarker objective for this study is to identify 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., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint*s*:

- *Neurofilament light chain (NfL) levels (actual value and percentage change from baseline) at each visit up to time of clinical cutoff of primary analysis*
- *The prognostic or predictive relationship between baseline NfL and the study primary endpoint (20% worsening from baseline in 9-HPT confirmed for at least 12 weeks) and key secondary endpoints (20% worsening from baseline in 9-HPT confirmed for at least 24 weeks, 12-week CDP on EDSS, and 24-week CDP on EDSS)*
- *The prognostic relationship between on-treatment NfL (measured at Weeks 24 or 48) and subsequent disability progression on the same clinical outcomes listed above*
- Relationship between biomarkers in blood (plasma and/or serum) and/or cerebrospinal fluid (CSF) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

Health Status Utility Objective

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with ocrelizumab on the basis of the following endpoint:

- Relationship between EQ-5D-5L index score and clinical measurements that may support pharmacoeconomic modeling.

STUDY DESIGN

DESCRIPTION OF STUDY

Study WA40404 is a Phase IIIb, randomized, double-blind, placebo controlled, parallel group, multicenter study to evaluate efficacy on upper limb function and safety of ocrelizumab administered at 600 mg IV infusions every 24 weeks in patients with PPMS, including patients later in their disease course. This study will consist of the following phases: screening, double-blind treatment, *an optional post-double-progression ocrelizumab (PDP OCR) treatment,* follow up 1 (FU1), an optional open label extension (OLE), follow up 2 (FU2), and B-cell monitoring (BCM).

The screening phase will last up to 24 weeks. Two mandatory MRI scans performed at least 6 weeks apart or one mandatory MRI that can be compared with a historical MRI performed in the previous 1 year will be performed to verify the patient's MRI activity level. For patients who fail the initial screening, a maximum of two re screenings will be allowed.

Eligible patients will be randomized (1:1) in a blinded fashion to either placebo or ocrelizumab. The expected sample size will be approximately 1000 patients, with at least 350 patients in the MRI active subgroup. The MRI active subgroup will consist of patients with T1 Gd+ lesion(s) and/or new and/or enlarging T2 lesion(s) as detected by MRI scan during screening.

Patients will be treated for 144 weeks (6 study drug doses, with each dose 24 weeks apart) in the double-blind treatment phase. The primary analysis will be performed after the last randomized patient reaches 144 weeks of double-blind treatment (+12 weeks to allow for the confirmation of the latest event).

Patients who experience a double-progression event (DPE; defined as a confirmed 20% increase in 9-HPT time sustained for 24 weeks, and a CDP sustained for 12 weeks) during the double-blind treatment phase will be given the option to switch to post-double progression ocrelizumab (PDP OCR) after completing at least 120 weeks of the double-blind treatment phase.

All patients who discontinue prematurely from the double-blind treatment phase will enter the FU1 phase, including patients who receive other DMTs for MS, commercial ocrelizumab, or no treatment. The FU1 phase will run in parallel with the double-blind treatment phase until 144 weeks from randomization for each patient. Scheduled visits will be performed every 12 weeks analogically to the initial (double-blind) schedule of activities and will include both efficacy and safety assessments. In the FU1 phase, patients will remain blinded to their original (randomized) treatment assignment. Patients who withdraw from treatment should be encouraged to remain in the study for the full duration of the FU1 phase. All patients who are ongoing in the FU1 phase at 144 weeks from randomization for each patient will continue in the FU2 phase.

An optional OLE phase is planned for eligible patients who have completed 144 weeks of the double-blind treatment phase and, in the opinion of the investigator, could benefit from ocrelizumab treatment.

The OLE phase will be carried out for at least 2 years (at least 4 doses of ocrelizumab) for each patient. The 2-year duration of the OLE phase serves to further evaluate long-term safety and efficacy of ocrelizumab treatment in patients with PPMS.

The following patients will move into the FU2 phase:

- Patients who are ongoing in the FU1 phase at 144 weeks from randomization for each patient
- Patients who have completed 144 weeks of the double-blind treatment phase and will not enter the OLE phase
- Patients who have completed or withdrawn from the OLE phase or from PDP OCR treatment phase

Laboratory and safety assessments for the FU2 phase will be performed during the clinic visits that occur every 24 weeks (see Appendix 4). All patients will continue in the FU2 phase until the end of the phase. The end of the FU2 phase is defined as 48 weeks after the last patient to enter the OLE phase has had his or her last OLE visit.

At the end of the FU2 phase, all patients will move into BCM phase until the end of the study. This study will end when all patients who are not being treated with an alternative B cell-depleting therapy have repleted his or her B cells. A patient's B cells will be considered to be repleted once B-cell levels have returned to baseline value or the lower limit of normal (whichever is lower).

An independent Data Monitoring Committee (iDMC) will be employed to monitor and evaluate patient safety throughout the study, until the primary analysis is performed.

NUMBER OF PATIENTS

The expected sample size will be approximately 1000 patients, of which at least 350 patients are planned to be in the MRI-active subgroup.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Ability to provide written informed consent and be compliant with the study protocol
- Diagnosis of PPMS in accordance with the McDonald criteria
- Age 18–65 years at time of signing Informed Consent Form

- EDSS score at screening and baseline ≥ 3.0 to 8.0, inclusive
- Disease duration from the onset of MS symptoms relative to randomization date:

  Less than 20 years in patients with an EDSS score at screening 7.0–8.0

  Less than 15 years in patients with an EDSS at screening 5.5–6.5

  Less than 10 years in patients with an EDSS at screening ≤ 5.0
- Documented history or presence at screening of at least one of the following laboratory findings in a cerebrospinal fluid specimen (source documentation of laboratory results and method must be verified)

  Elevated IgG index

  One or more IgG oligoclonal bands detected by isoelectric focusing
- Screening and baseline 9-HPT completed in > 25 seconds (average of the two hands)
- Ability to complete the 9-HPT within 240 seconds with each hand at screening and baseline
- Neurological stability for ≥ 30 days prior to baseline.
- Patients previously treated with immunosuppressants, immunomodulators, or other immunomodulatory therapies must undergo an appropriate washout period according to the local label of the immunosuppressant/immunomodulatory drug used

  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 before deciding to enter the study of their treatment options and, that by participating in this study, they may be randomized to placebo for a period of 120 weeks or greater.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use adequate contraceptive methods during the treatment period and for 6 or 12 months (as applicable by the Ocrevus local label) after the final dose of ocrelizumab.

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

  The following contraceptive methods *are considered acceptable (failure rate > 1% [Clinical Trial Facilitation Group (CTFG)]): (1) progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action; (2) male or female condom with or without spermicide; (3) cap, diaphragm, or sponge with spermicide; (4) combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier method).*

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

  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 *individual*. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not *adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.*

For female patients without reproductive potential:

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

Exclusion Criteria

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

- History of relapsing-remitting or secondary progressive MS at screening
- Confirmed serious opportunistic infection including active bacterial, viral, fungal, mycobacterial infection or other infection, including tuberculosis or atypical mycobacterial disease
- Patients who have or have had confirmed or a high degree of suspicion of progressive multifocal leukoencephalopathy (PML)
- Known active malignancy or are being actively monitored for recurrence of malignancy
- Immunocompromised state, defined as one or more of the following:

  CD4 count $<250/\mu L$

  Absolute neutrophil count $<1.5\times10^3/\mu L$

  Serum IgG <4.6 g/L
- Receipt of a live-attenuated vaccine within 6 weeks prior to randomization
- Inability to complete an MRI (contraindications for MRI, including but not restricted to pacemaker, cochlear implants, intracranial vascular clips, surgery within 6 weeks of entry in the study, coronary stent implanted within 8 weeks prior to the time of the intended MRI, etc.) or contraindication to Gd administration.
- Patients requiring symptomatic treatment of MS (e.g., fampridine) and/or physiotherapy who are not on a stable regimen. Patients must not initiate symptomatic treatment of MS or physiotherapy within 4 weeks of randomization.
- Contraindications to mandatory premedications (i.e., corticosteroids and antihistamines) for infusion-related reactions, including:

  Uncontrolled psychosis for corticosteroids

  Closed-angle glaucoma for antihistamines
- Known presence of other neurologic disorders *that could interfere with the diagnosis of MS or assessments of efficacy and/or safety during the study*, including but not limited to, the following:

  History of *hemorrhagic or* ischemic cerebrovascular disorders (e.g., stroke, transient ischemic attack) or *hemorrhage or* ischemia of the spinal cord

  History or known presence of CNS or spinal cord tumor (e.g., meningioma, glioma)

  History of metabolic myelopathy or known presence of untreated causes of metabolic myelopathy (e.g., untreated vitamin B12 deficiency)

  History or known presence of infectious myelopathy (e.g., due to syphilis, Lyme disease, HTLV 1, herpes zoster)

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

  Neuromyelitis optica

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

  History or known presence of sarcoidosis

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

- Pregnant or breastfeeding, or intending to become pregnant during the study and for 6 or 12 months (as applicable by the Ocrevus local label) after last infusion of the study drug
- Lack of peripheral venous access
- Significant, uncontrolled disease, such as cardiovascular (including cardiac arrhythmia), pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine or gastrointestinal, or any other significant disease that may preclude patient from participating in the study
- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study
- History of alcohol or other drug abuse
- History of primary or secondary (non-drug-related) immunodeficiency
- Treatment with any investigational agent within 24 weeks prior to screening (Visit 1) or 5 half-lives of the investigational drug (whichever is longer), or treatment with any experimental procedure for MS (e.g., treatment for chronic cerebrospinal venous insufficiency)
- Previous treatment with B cell-targeting therapies (e.g., rituximab, ocrelizumab, atacicept, belimumab, ofatumumab, and alemtuzumab)
- Any previous treatment with bone marrow transplantation and hematopoietic stem cell transplantation
- Any previous history of transplantation or anti-rejection therapy
- Treatment with IV Ig or plasmapheresis within 12 weeks prior to randomization
- Systemic corticosteroid therapy within 4 weeks prior to screening

  The screening period may be extended for patients who have used systemic corticosteroids for MS before screening. For a patient to be eligible, systemic corticosteroids should also not have been administered between screening and baseline.
- Positive serum β-hCG measured at screening or positive urine β-hCG at baseline
- 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)
- Any additional exclusionary criterion as per ocrelizumab (Ocrevus®) local label, if more stringent than the above
- Lack of MRI activity at screening/baseline if more than 650 patients without MRI activity have already been enrolled, as defined by T1 Gd+ lesion(s) and/or new and/or enlarged T2 lesion(s) in the screening, to ensure that at least 350 patients with MRI activity will be randomized

Re-testing before baseline: In rare cases in which the screening laboratory samples are rejected by the central laboratory (e.g., hemolyzed sample) or the result is not assessable (e.g., indeterminate) or abnormal, the tests need to be repeated within 4 weeks. Any abnormal screening laboratory value that is clinically relevant should be retested to rule out any progressive or uncontrolled underlying condition. The last value before randomization must meet study criteria.

ELIGIBILITY CRITERIA FOR OPEN-LABEL EXTENSION PHASE

Patients who meet the following entry criteria may participate in the OLE phase:

- Completed the double-blind treatment phase of the trial and who, in the opinion of the investigator, may benefit from treatment with ocrelizumab

  Patients who withdrew from study treatment and received another disease-modifying therapy (DMT) or commercial ocrelizumab will not be allowed to enter in the OLE phase.

- Able and willing to provide written informed consent to participate in the OLE phase and to comply with the study protocol
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use adequate contraceptive methods during the treatment period and for 6 or 12 months (as applicable by the Ocrevus local label) after the final dose of ocrelizumab.

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

  The following contraceptive methods *are considered acceptable (failure rate >1% [CTFG]): (1) progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action; (2) male or female condom with or without spermicide; (3) cap, diaphragm, or sponge with spermicide; (4) combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier method).*

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

  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 *individual*. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not *adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.*
- For female patients without reproductive potential:

  Women may be enrolled if surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy) or post-menopausal (i.e., spontaneous amenorrhea for the past year confirmed by a FSH level > 40 mIU/mL) unless the patient is receiving a hormonal therapy for her menopause.

END OF STUDY

The end of the study will occur when all patients who are not being treated with an alternative B cell–depleting therapy have repleted his or her B cells (i.e., B-cell level of the patient has returned to the baseline value or the lower limit of normal, whichever is lower).

LENGTH OF STUDY

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately *9.*5 years (assuming that the last patient randomized after 3 years from the *start of the* study *has* receive*d* blinded treatment over *144* weeks, followed by OLE *phase for at least 2 years (at least 4 doses of ocrelizumab) for each patient*, 48 weeks of FU2 phase, and [variable] BCM phase).

INVESTIGATIONAL MEDICINAL PRODUCTS

TEST PRODUCT (INVESTIGATIONAL DRUG)

The ocrelizumab (or placebo) dose administered will be 600 mg every 24 weeks. The first dose of ocrelizumab will be administered as two 300 mg IV infusions given 14 days apart. For the subsequent doses, ocrelizumab will be administered as a single 600 mg infusion every

24 weeks. A minimum interval of 20 or 22 weeks, depending if the previous dose was administered in one or two infusion, should be maintained between each infusion.

NON-INVESTIGATIONAL MEDICINAL PRODUCTS

To reduce potential infusion-related reactions (IRRs), all patients must receive mandatory prophylactic treatment with 100 mg of methylprednisolone administered by slow IV infusion, to be completed approximately 30 minutes before the start of each ocrelizumab (or placebo) infusion. In the rare case when the use of methylprednisolone is contraindicated for the patient, use of an equivalent dose of an alternative steroid should be used as premedication prior to the infusion.

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

Analgesic/antipyretic such as acetaminophen/paracetamol (1 g) can also be considered.

STATISTICAL METHODS

PRIMARY ANALYSIS

The primary analysis will compare the time from randomization to 20% increase from baseline in the 9-HPT time that is sustained for at least 12 weeks between ocrelizumab and placebo in all randomized patients and in the MRI-active subgroup. If at least one of the two co-primary analyses is statistically significant, then the trial is considered positive. Type I error will be controlled using a fallback and loop-back procedure.

The 9-HPT time is the reciprocal of the score for the 9-HPT as described in the MS functional composite guide (National Multiple Sclerosis Society 2001). The score for the 9-HPT is an average of the four trials (2 for the dominant hand and 2 for the non-dominant hand), calculated as follows: the two trials for each hand are averaged, converted to the reciprocals of the mean times for each hand, and then the two reciprocals are averaged. The most recent 9-HPT measured before first dose administration *(or randomization for non-treated patients)* will be considered baseline.

The p-value will be calculated from a log-rank test, stratified by the randomization stratification factors.

The hazard ratio will be estimated from a Cox regression, stratified by the randomization factors. In addition, a sensitivity analysis that adjusts for sex and continuous baseline 9-HPT will be performed to assess the impact of these prognostic factors.

DETERMINATION OF SAMPLE SIZE

The primary objective for this study is to evaluate the efficacy of ocrelizumab compared with placebo on time to 20% worsening from baseline in 9-HPT time confirmed for at least 12 weeks in all randomized patients and in patients with MRI activity. The sample size was estimated on the basis of data from Study WA25046 (ORATORIO).

A two-group test of equal exponential survival is used to determine the sample size for the time to 12-week confirmed 20% worsening in the 9-HPT. With a sample size of 1000 patients (of which at least 350 patients are expected in the MRI-active population), a double-blind treatment phase of 144 weeks, an annual dropout rate of 10%, and a randomization ratio of 1:1, it is expected that approximately 355 events will be observed in all randomized patients (placebo progression rate: 40%), which will provide approximately 82.1% power to detect a hazard ratio of 0.70 at a type I error rate of 0.0146 and approximately 77.3% power to detect a hazard ratio of 0.75 at a type I error rate of 0.05. Likewise, it is expected that approximately 134 events will be observed in the MRI-active subgroup (placebo progression rate: 44%), which will provide approximately 81.5% power to detect a hazard ratio of 0.60 at a type I error rate of 0.04.

INTERIM ANALYSES

There is no planned interim analysis.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
9-HPT	9-Hole Peg Test
ADA	anti-drug antibody
ADL	activities of daily living
ANCOVA	analysis of covariance
BCM	B-cell monitoring
CDP	confirmed disability progression
COVID-19	*coronavirus disease 2019*
CSF	cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	*Clinical Trial Facilitation Group*
DMT	disease-modifying therapy
DPE	double-progression event
DSS	Disability Status Scale
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FSS	Functional System Scores
FU1	follow-up 1
FU2	follow-up 2
Gd	gadolinium
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRR	infusion-related reaction
IxRS	interactive voice or web-based response system

Abbreviation	Definition
JC	*John Cunningham*
MFIS	Modified Fatigue Impact Scale
MMRM	mixed effect model repeat measurement
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSIS	Multiple Sclerosis Impact Scale
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
Neuro-QoL-UE	Quality of Life in Neurological Disorders-Upper Extremity Function
NfL	neurofilament light chain
OLE	open-label extension
PDP OCR	post-double-progression ocrelizumab
PGIC	Patient Global Impression of Change
PGIC-F	Patient Global Impression of Change for fatigue
PGIC-UL	Patient Global Impression of Change for upper limb function
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PPMS	primary progressive multiple sclerosis
PRO	patient-reported outcome
PY	patient years
QoL	quality of life
RBR	Research Biosample Repository
RMS	relapsing multiple sclerosis
RPM	remote patient monitoring
RRMS	relapsing-remitting MS
SARS-CoV-2	*severe acute respiratory syndrome coronavirus 2*
SDMT	Symbol Digit Modalities Test
SmPC	summary of product characteristics
ULN	upper limit of normal
USPI	U.S. prescribing information
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic, inflammatory, and demyelinating disease of the CNS that affects approximately 2.3 million people worldwide (MSIF 2013). While MS is a global disease, its prevalence is highest in North America and Europe (140 and 108 per 100,000 people, respectively) (MSIF 2013). MS is commonly diagnosed during reproductive age, between 20 and 40 years (Tullman 2013). Overall, MS is approximately twice as prevalent in women as in men, except in individuals with the primary progressive- form of the disease, where there is no gender prevalence difference (MSIF 2013; Tullman 2013). Reasons for these observed differences are unclear. However, progression, once it begins, continues at similar rates in women and men (Leray et al. 2010).

In approximately 85% of patients, MS begins as a relapsing, episodic disorder with gradual complete or incomplete recovery (referred to as relapsing-remitting MS [RRMS]). If left untreated, the majority of these patients will transition to a progressive form characterized by worsening neurologic disability, either with or without occasional super-imposed relapses (relapsing or non-relapsing secondary progressive MS). Patients accumulate disability as a result of incomplete recovery from acute relapses and/or gradual disease progression (Tullman 2013). Primary progressive MS (PPMS) is a less common form of MS, accounting for approximately 10% of all cases (approximately 40,000 individuals in the United States). PPMS is characterized by a progressive course from disease onset, with infrequent superimposed discrete clinical attacks or relapses (Lublin et al. 2014). Unlike RRMS, the typical age of onset for PPMS is older at approximately 40 years, and men are affected nearly as often as women (Cottrell et al. 1999). The absence of relapses imposes special challenges for diagnosis, requiring clinical evidence that the disease has advanced for at least 1 year from symptom onset independent of clinical relapse (Thompson et al. 2018).

Natural history studies of patients with PPMS suggest a disabling course from symptom onset. In a well-characterized cohort of patients with PPMS from Ontario, Canada, the median time to the use of a unilateral cane or brace (Disability Status Scale [DSS] or DSS 6) was 8 years and the median time to wheelchair use (DSS 7) was under 20 years (Cottrell et al. 1999). A higher proportion of patients with PPMS present initially with motor impairment, cerebellar ataxia, and brainstem symptoms than relapsing-onset patients, and spastic paraparesis is a common early clinical presentation (Andersson et al. 1999). Evidence suggests that inflammation is present in the CNS throughout all MS clinical courses, from RRMS to secondary progressive MS, and in PPMS (Frischer et al. 2009). Differences between disease phenotypes are due to the differential contribution of each of the inflammatory and neurodegenerative processes to the pathophysiology of CNS damage over time (Frischer et al. 2009, 2015).

1.2 BACKGROUND ON OCRELIZUMAB

Ocrelizumab is a recombinant humanized, glycosylated, monoclonal IgG1 antibody that selectively targets and depletes CD20-expressing B cells, while preserving the capacity of B-cell reconstitution and preexisting humoral immunity. CD20 is a B-cell surface molecule that is restricted in expression to pre–B cells and mature B cells but is not expressed earlier in the development of B cells (Banchereau and Rousset 1992). Based on the results of ocrelizumab Phase III studies in patient populations with relapsing MS (RMS) and PPMS, ocrelizumab was approved by the US Food and Drug Administration (FDA) on 28 March 2017 for the treatment of adult patients with RMS and PPMS and by the European Medicines Agency (EMA) on 12 January 2018 for patients with active relapsing forms of MS defined by clinical or imaging features and for patients with early PPMS in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.

Two identical randomized, active-controlled studies (OPERA I [Study WA21092] and OPERA II [Study WA21093]) have demonstrated superior efficacy outcomes versus interferon β-1a in patients with RMS (Hauser et al. 2017); one randomized placebo-controlled study (ORATORIO [Study WA25046]) has demonstrated superior efficacy in PPMS versus placebo (Montalban et al. 2017). Results of these studies show that depletion of CD20+ B cells leads to a significant impact on a broad range of clinical measures of disease, including disability progression, in addition to an impact on magnetic resonance imaging (MRI) outcomes related to disease progression and reflective of neural tissue loss, thus further supporting the hypothesis that B cells are central to the pathogenesis of both RMS and PPMS. Ocrelizumab has demonstrated a favorable safety profile in patients with RMS and PPMS (Hauser et al. 2017; Montalban et al. 2017). The proportion of patients with adverse events was similar in patients treated with ocrelizumab compared with interferon β-1a (both 83.3%) or placebo (95.1% vs. 90.0%). The proportion of patients experiencing a serious adverse event was similar between ocrelizumab and the comparator groups (in RMS: 6.9% [ocrelizumab] and 8.7% [interferon β-1a]; in PPMS: 20.4% [ocrelizumab] and 22.2% [placebo]).

Refer to the Ocrelizumab Investigator's Brochure and/or local prescribing information for details on nonclinical and clinical studies of ocrelizumab.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

The pivotal Phase III Study WA25046 (ORATORIO) was a global, multicenter, randomized, parallel-group, double-blind, placebo-controlled trial evaluating the efficacy and safety of ocrelizumab in adults with PPMS. The primary endpoint was the time to onset of confirmed disability progression (CDP) during the treatment period, defined as an increase in the Expanded Disability Status Scale (EDSS) score that was sustained for at least 12 weeks. Disability was assessed using the EDSS (Kurtzke 1983). In Study WA25046, an event of disability progression was defined as an increase from

baseline EDSS of 1 point or more for patients with a baseline EDSS score of ≤5.5, or an increase of 0.5 point or more for patients with a baseline EDSS score of >5.5. This sustained increase in EDSS is considered a clinically meaningful change as described in the EMA MS Guideline of 2015 (EMA 2015). Study WA25046 met its primary endpoint (24% reduction in the risk of 12-week CDP compared with placebo [hazard ratio=0.76; 95% CI: 0.59, 0.98; p=0.0321]) and demonstrated significant reduction in both clinical and subclinical measures of disease progression compared with placebo. In Study WA25046, the results of the 9-Hole Peg Test (9-HPT), a pre-specified exploratory endpoint, showed a significant 44% reduction in progression for patients treated with ocrelizumab versus placebo (p=0.0004) (see Table 1 below and Section 5.1 in the Primary Clinical Study Report for Study WA25046).

Table 1 Analysis of Time to 12-Week Confirmed 20% Increase in 9-HPT Score (*All Randomized Patients*: Study WA25046)

Endpoint	Patients with Event		Hazard Ratio (95% CI)	p-value (log-rank)
	Placebo (N=244)	Ocrelizumab (N=488)		
20% increase in 9-HPT confirmed at 12 weeks	66/244	83/488	0.56 (0.41, 0.78)	0.0004

9-HPT=9-Hole Peg Test.

Source: Unpublished data.

Study WA25046 included patients aged 18–55 years with a baseline EDSS score ranging from 3.0 to 6.5. Within this population, patients with more advanced disability consisting of EDSS score ≥5.5 and patients with an abnormal 9-HPT time of >25 seconds at baseline showed more rapid rates of upper limb disability progression on the 9-HPT. In the post-hoc analyses of these more advanced subgroups of patients, ocrelizumab showed a significant 44% reduction in 20% 9-HPT progression versus placebo (p=0.0085 and p=0.003, respectively) (see Table 2). EDSS score >5.5 corresponds to patients with lower extremity impairment requiring unilateral assistance (e.g., cane or crutch) with or without upper extremity impairment. Thus, the Study WA25046 results imply that ocrelizumab may reduce the rate of progression of upper limb disability in patients even if significant lower extremity disability has ensued. 9-HPT times above a threshold of 25 seconds can be regarded as abnormal based on a reference population of patients aged 18–59 years (consistent with the age of the ORATORIO population) from a large-scale normative database (N = 4319) (Wang et al. 2015). Patients with an abnormal 9-HPT time of >25 seconds at baseline progressed more rapidly than patients with normal 9-HPT time of ≤25 seconds; however, both patient groups showed a comparable benefit from treatment with ocrelizumab (44% [hazard ratio=0.56; 95% CI: 0.38, 0.82; p=0.0023] and 49% [hazard ratio=0.51; 95% CI: 0.27, 0.97; p=0.0358] risk reduction, respectively) (see Table 2). Presence of inflammatory activity as detected by mandatory MRI at baseline correlates

with a greater treatment benefit. Pre-specified, non-powered, subgroup analysis of the primary endpoint (time to 12-week CDP progression) in Study WA25046 suggests that patients with T1 gadolinium (Gd)-enhancing lesions at baseline received a greater treatment benefit than patients without T1 Gd-enhancing lesions (with T1 Gd-enhancing lesions at baseline: HR=0.65 [95% CI: 0.40–1.06], without T1 Gd-enhancing lesions at baseline: HR = 0.84 [95% CI: 0.62–1.13]; EMA 2018). With regard to inflammatory activity and hand function, ocrelizumab-treated patients with MRI-detected T1 Gd-enhancing lesions at baseline experienced a significant 58% reduction in 20% 9-HPT progression versus placebo (p=0.0034); a reduction of 36% (p=0.0242) in 20% 9-HPT progression versus placebo was observed in ocrelizumab-treated patients without MRI-detected T1 Gd-enhancing lesions at baseline (see Table 2).

Table 2 Analysis of Time to 12-Week Confirmed 20% Increase in 9-HPT Score by Population (*All Randomized Patients*: Study WA25046)

Population	Percent of Patients with Event at Week 120 (Placebo Arm)[a]	Percent of Patients with Event at Week 120 (Ocrelizumab Arm)[a]	Hazard Ratio (95% CI)	p-value (log-rank)
EDSS≥5.5	39%	21%	0.56 (0.36, 0.87)	0.0085
T1 Gd+	39%	16%	0.42 (0.23, 0.76)	0.0034
T1 Gd–	18%	14%	0.64 (0.43, 0.95)	0.0242
9-HPT>25 seconds	33%	18%	0.56 (0.38, 0.82)	0.0023
9-HPT≤25 seconds	12%	9%	0.51 (0.27, 0.97)	0.0358

9-HPT=9-Hole Peg Test; EDSS=Expanded Disability Status Scale; Gd=gadolinium.

[a] Kaplan-Meier estimates.

Source: Unpublished data.

Therefore, given the encouraging results from Study WA25046, the primary objective of this study is to evaluate the efficacy of ocrelizumab compared with placebo on the preservation of upper limb function in a population that also includes patients with more advanced PPMS who acquired significant lower extremity impairment. The study will include patients with a baseline EDSS score from 3.0 to 8.0, inclusive, and evaluate upper limb function using the same 9-HPT measure that was used in Study WA25046. Moreover, the upper limit of age of the enrolled population will be 65 years, and the treatment effect of ocrelizumab will be explored according to the presence of inflammatory activity as detected by mandatory MRI at baseline. Additional secondary and exploratory objectives will evaluate the efficacy of ocrelizumab on its ability to reduce disease progression on other clinical and subclinical measures. These will include clinical measures of other neurological functional systems, subclinical imaging and biomarker measures, and measures of fatigue and quality of life.

1.3.1 Clinical Relevance of Upper Extremity Disability Progression, as Measured by the 9-HPT, in PPMS

Patients with PPMS with high EDSS scores, including those who are wheelchair-restricted, have a devastating reduction in quality of life if they lose any residual function in their arms and/or hands. For this reason, preserving upper limb function is highly relevant to the quality of life of the patient and an important therapeutic clinical goal in PPMS. Dysfunction of the upper limbs is clinically relevant as it significantly limits the ability to perform activities of daily living, affects the level of independence, and negatively impacts quality of life (Kraft et al. 2014). Patients with more advanced PPMS have been recognized as a much-underserved population with very limited therapeutic options (Kraft et al. 2014). Therefore, exploring the therapeutic effects of ocrelizumab in this PPMS population will be both consistent with and expand on the results of Study WA25046 as well as fulfill a significant medical need for these patients.

The 9-HPT has become one of the most frequently used measures of upper extremity function in MS (Earhart et al. 2011). The 9-HPT provides a brief, standardized approach to assess upper limb function and can be administered by a wide variety of trained examiners (Earhart et al. 2011). The test has high inter-rater reliability and good test-retest reliability (Erasmus et al. 2001). There is also evidence for concurrent and convergent validity as well as sensitivity to detect minor impairments of hand function (Parker et al. 1986; Wang et al. 2015). A 20% worsening in test time is commonly used to define clinically meaningful worsening (Feys et al. 2017) as it corresponds to predefined clinically meaningful changes of established clinician and patient-reported measures.

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 is any impact of the coronavirus disease 2019 (COVID-19) pandemic on the conduct of this study. Based on that assessment, no impact is anticipated, and the existing information on identified and potential risks, safety monitoring, and management guidelines and risk mitigation measures provided in the study protocol are considered adequate.

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

The protocol's eligibility criteria mitigate the known risk factors for severe SARS-COV-2 infection outcomes, such as older age, more advanced MS disease status, and presence of relevant comorbidities, and exclude patients with MS with any known

or suspected active infection (including SARS-CoV-2, based on the investigator's assessment) from participating in the study. As per Section 4.3.2.3, absence of active infection is also required for patients to receive further re-treatment with ocrelizumab. The risk of MS progression may potentially increase over time, if highly effective treatments are delayed.

In summary, protocol-mandated safety monitoring and management guidelines, study eligibility criteria, and 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 as infections caused by any other pathogen, as per local guidelines.

1.3.3 ***Benefit–Risk Assessment for Concomitant Use of COVID-19 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 interaction between the concomitant use of COVID-19 vaccines and ocrelizumab has been identified. There is no anticipated impact affecting the efficacy and safety of ocrelizumab in patients enrolled in ocrelizumab clinical trials. Existing key safety information as described in the protocol (namely immunizations [see Section 4.4.4], and impaired response to vaccination [see Section 5.1.1.1]), safety monitoring, and risk mitigation measures related to administration of vaccines (including COVID-19 vaccines) are considered adequate.

As described in Section 5.1.1.1 (impaired response to vaccination), data from the pivotal Phase III studies (WA21092/93, WA25046) of ocrelizumab in RMS and PPMS show that preexisting humoral immunity to common viral and bacterial antigens is not affected by ocrelizumab treatment. Additionally, for patients receiving vaccines while treated with ocrelizumab, the vaccination study BN29739 (VELOCE) showed that patients with MS treated with ocrelizumab were able to mount a humoral immune response to non-live vaccines and new antigens. The antibody immune response was considered protective in patients who received ocrelizumab, albeit with reduced levels of antibodies compared to patients in the control arm. Vaccines were given as early as 12 weeks following the first ocrelizumab infusion (as early as 10 weeks following the second ocrelizumab infusion of the first dose). Booster doses were given at least 4-weeks before the next dose of ocrelizumab. Other immune responses, such as cellular responses, were not investigated in the VELOCE study.

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

As with any other medication or vaccine, COVID-19 vaccines should be reported as concomitant medications by using the standard fields in the clinical database

(see immunizations [see Section 4.4.4], and medical history, baseline conditions, concomitant medications, and demographic data [see Section 4.5.2]).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of ocrelizumab (Ocrevus®) compared with placebo in patients with PPMS, including patients later in their disease course. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of ocrelizumab-treated patients compared with placebo-treated patients on upper extremity disability progression. This objective is measured on upper limbs on the basis of the following endpoint:

- Upper limb disability progression, defined as time to 20% worsening from baseline in 9-HPT confirmed for at least 12 weeks in all randomized patients and in patients with MRI activity (MRI activity is defined as presence of T1 Gd+ lesion[s] and/or new and/or enlarging T2 lesion[s] as detected by MRI scans during the screening phase)

The estimand of this endpoint will be discussed in Section 6.4.1.1.

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of ocrelizumab compared with placebo for all randomized patients on the basis of the endpoints below, in hierarchical order. The secondary efficacy endpoints will also be evaluated as exploratory analyses for the MRI-active subgroup.

- Upper limb disability progression defined as time to 20% increase from baseline in 9-HPT confirmed for at least 24 weeks
- Time to 12-week CDP in EDSS, defined as an increase in EDSS score that is confirmed for at least 12 weeks (an increase of $\geq$1.0 point from baseline EDSS score in patients with a baseline EDSS score $\leq$5.5 or an increase of $\geq$0.5 point in patients with a baseline EDSS score of $>$5.5)
- Time to 24-week CDP in EDSS, defined as an increase in EDSS score that is confirmed for at least 24 weeks (an increase of $\geq$1.0 point from baseline EDSS in patients with a baseline EDSS score $\leq$5.5 or an increase of $\geq$0.5 point in patients with a baseline EDSS score of $>$5.5)
- Percent change in total volume of T2 lesions from baseline up to Week 120
- Percent change in total brain volume from Week 24 to Week 120

The estimands for the time to CDP analyses will be discussed in Section 6.4.1.2.

2.1.3 Exploratory Efficacy Objective

An exploratory efficacy objective for this study is to evaluate the efficacy of ocrelizumab compared with placebo in patients, as measured by the primary and secondary endpoints in the following patient subgroups:

- Age >55 versus ≤ 55
- EDSS score ≤ 6.5 versus >6.5
- MRI-inactive versus MRI-active
- *Males and females (all randomized patients, MRI-active subgroup and MRI-inactive subgroup)*

Additional exploratory objectives include the efficacy of ocrelizumab compared with placebo in patients from *all randomized patients* and *the* MRI-active subgroup as measured by the following endpoints:

- Proportion of patients free of disability progression on upper limbs by 9-HPT at Week 120 and at time of clinical cutoff of primary analysis
- Change from baseline to Week 120 in fatigue as measured by Modified Fatigue Impact Scale (MFIS)
- Change from baseline to Week 120 and from Week 24 to Week 120 in cervical spinal cord volume on MRI scans
- Change from baseline to Week 120 in a measure of manual ability for adults with upper limb impairments (ABILHAND)
- Change from baseline to Week 120 in the upper limb domain of a life quality measure for patients with neurological disorders (Quality of Life in Neurological Disorders-Upper Extremity Function [Neuro-QoL-UE])
- Change from baseline to Week 120 in the Patient Global Impression of Change for upper limb function (PGIC-UL)
- Change from baseline to Week 120 in the Patient Global Impression of Change for fatigue (PGIC-F)
- Change from baseline to Week 120 in the Multiple Sclerosis Impact Scale (MSIS)-29 physical score
- Proportion of patients at Week 120 with a clinically meaningful decline on the MSIS-29
- Change from baseline to Week 120 in the Symbol Digit Modalities Test (SDMT)
- Rate of decline in fine motor skills of upper extremities and manual/finger dexterity as measured by smartphone-based digital outcome assessment (Floodlight remote patient monitoring [RPM])
- The number of Gd-enhancing T1 lesions and number of new or enlarging T2 hyperintense lesions as detected by mandatory MRI
- The change from baseline in total non-enhancing T1 lesion volume on MRI scan of the brain

2.2 SAFETY OBJECTIVES

The safety objectives for this study are to evaluate the safety of ocrelizumab compared with placebo, as well as over time, for all patients who received ocrelizumab and until they receive any other *DMT for MS*.

Safety endpoints considered include adverse events, serious adverse events, adverse events leading to study treatment withdrawal, vital signs, change from baseline in laboratory test results, association of decrease in certain laboratory parameters, and serious infections. For details on the analyses and the population, see Section 6.5.

2.3 IMMUNOGENICITY OBJECTIVE

The immunogenicity objective is as follows:

- Immunogenicity, as the presence of anti-drug antibody (ADA) during the study relative to baseline. The relationship between ADA status and pharmacokinetics, pharmacodynamics, efficacy, and safety may be explored.

2.4 PHARMACOKINETIC AND PHARMACODYNAMIC OBJECTIVES

The pharmacokinetic (PK) and pharmacodynamic objectives are as follows:

- Characterization of the ocrelizumab PK profile
- Evaluation of ocrelizumab pharmacodynamics, as measured by B-cell levels in blood

2.5 BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify 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., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint*s*:

- *Neurofilament light chain (NfL) levels (actual value and percentage change from baseline) at each visit up to time of clinical cutoff of primary analysis*
- *The prognostic or predictive relationship between baseline NfL and the study primary endpoint (20% worsening from baseline in 9-HPT confirmed for at least 12 weeks) and key secondary endpoints (20% worsening from baseline in 9-HPT confirmed for at least 24 weeks, 12-week CDP on EDSS, and 24-week CDP on EDSS)*
- *The prognostic relationship between on-treatment NfL (measured at Weeks 24 or 48) and subsequent disability progression on the same clinical outcomes listed above*

- Relationship between biomarkers in blood (plasma and/or serum) and/or cerebrospinal fluid (CSF) (listed in Section 4.5.11) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

2.6 HEALTH STATUS UTILITY OBJECTIVE

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with ocrelizumab on the basis of the following endpoint:

- Relationship between EQ-5D-5L index score and clinical measurements that may support pharmacoeconomic modeling

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

Study WA40404 is a Phase IIIb, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate efficacy on upper limb function and safety of ocrelizumab administered at a 600 mg IV infusion every 24 weeks in patients with PPMS, including patients later in their disease course. This study will consist of the following phases: screening, double-blind treatment, *an optional post-double-progression ocrelizumab (PDP OCR) treatment,* follow-up 1 (FU1), an optional open-label extension (OLE), follow-up 2 (FU2), and B-cell monitoring (BCM).

Patients providing informed consent will undergo screening prior to the study drug administration. Eligible patients will be randomized (1:1) in a blinded fashion to either placebo or ocrelizumab. Randomization will be performed through an interactive voice or web-based response system (IxRS).

The expected sample size will be approximately 1000 patients, with at least 350 patients in the MRI-active subgroup. The MRI-active subgroup will consist of patients with T1 Gd+ lesion(s) and/or new and/or enlarging T2 lesion(s) as detected by MRI scan during screening. If during the study conduct more than 650 patients have enrolled without MRI activity (referred to as MRI-inactive subgroup thereafter), then subsequently only patients with MRI activity may be enrolled to ensure that at least 350 patients with MRI activity will be randomized.

Patients will be treated for *144 weeks* (*6* study drug doses, with each dose 24 weeks apart) *in the double-blind treatment phase*. The primary analysis will be performed after the *last randomized patient reaches 144 weeks of double-blind treatment (+ 12 weeks to allow for the confirmation of the latest event)*. Patients who experience a double-progression event (DPE; defined as a confirmed 20% increase in 9-HPT time sustained for 24 weeks, and a CDP sustained for 12 weeks) during the double-blind treatment phase will be given the option to switch to PDP OCR after they have completed at least 120 weeks of double-blind treatment and 120-week visit assessments. See Section 3.1.1.3 for definitions of DPE and PDP OCR.

Patients will be recruited globally. Patients who prematurely discontinue from study treatment will continue to be followed *in the FU1 phase until 144 weeks from randomization for each patient* (see Section 3.1.1.4).

An independent Data Monitoring Committee (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.

Figure 1 presents an overview of the study design. Figure 2 shows the patient progression through the study. The schedules of activities are provided in Appendix 1, Appendix 2, Appendix 3, and Appendix 4. Overview of the dosing regimen across study phases is provided in Table 3.

Figure 1 Study Design

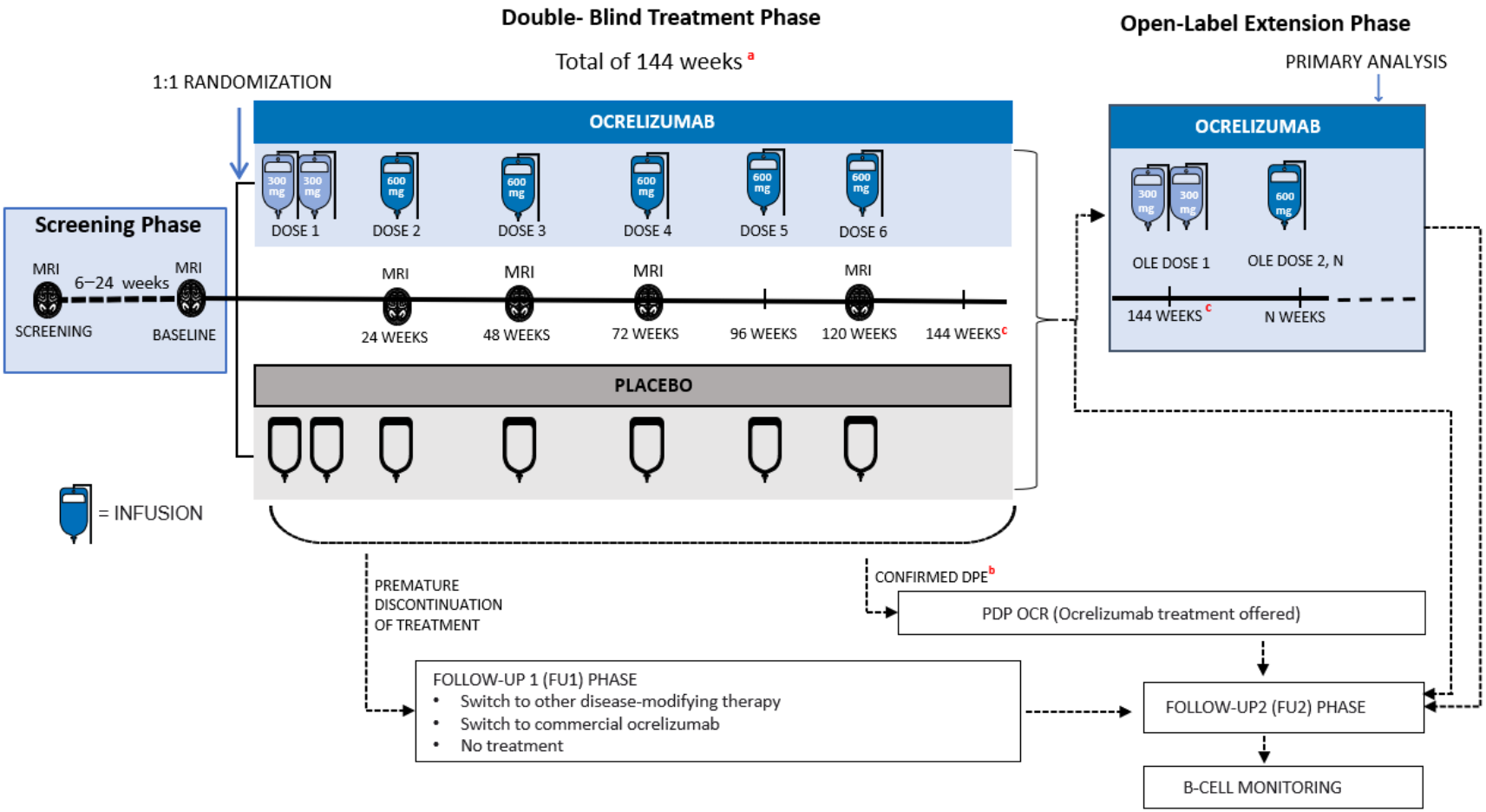


Figure 1 Study Design (cont.)

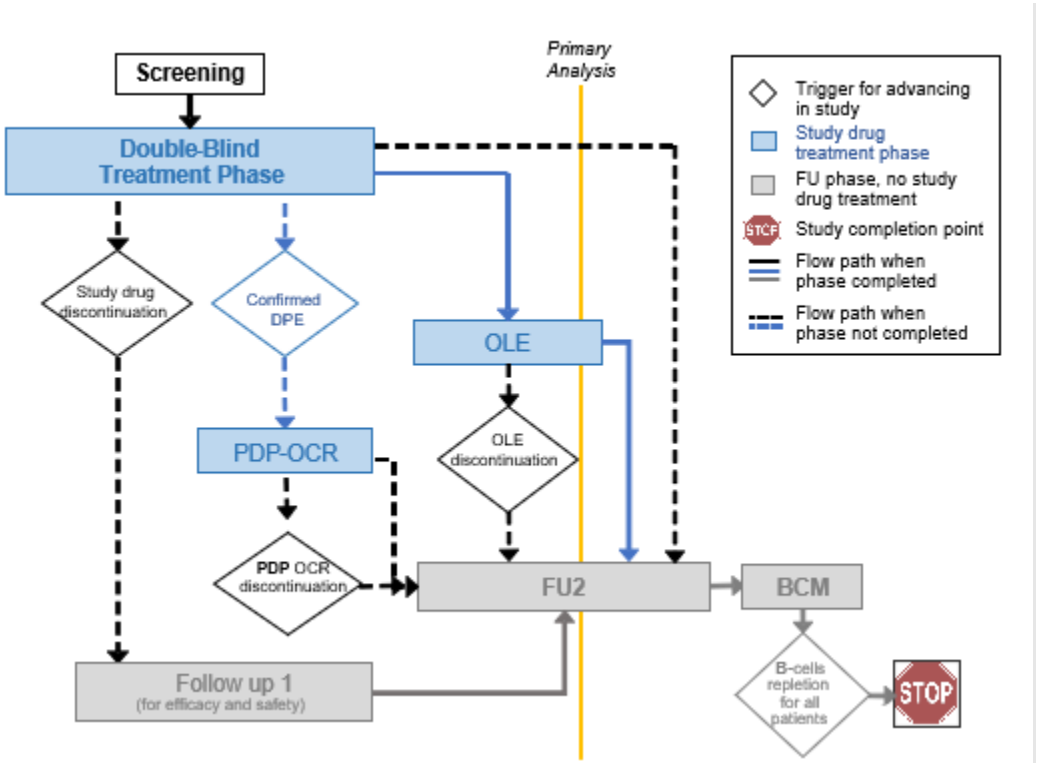
DPE = double-progression event; *FU1 = follow-up 1; FU2 = follow-up 2;* MRI = magnetic resonance imaging; *OLE = open-label extension;* PDP OCR = post-double-progression ocrelizumab.

[a] Patients will be treated in *the double-blind treatment phase for 144 weeks (6 study drug doses, with each dose 24 weeks apart). Eligible patients will switch to open-label treatment with ocrelizumab after completing 144 weeks of double-blind treatment. Patients who have reached 144 weeks of double-blind treatment at the time of the approval of this version of the protocol will be switched to the OLE phase at the next visit.*

[b] Patients who experience a DPE during the double-blind treatment phase will be given the option to switch to *the* PDP OCR *phase* after they completed at least 120 weeks of double-blind treatment and 120-week visit assessments (see Section 3.1.1.3 for definition*s* of DPE and PDP OCR). To maintain the blind*ing* in the treatment arm, the first dose of PDP OCR treatment will be two infusions of 300 mg given 14 days apart for all patients. Subsequent doses will then be 600 mg IV infusions every 24 weeks. Patients who discontinue from *the* PDP OCR *phase* may continue to be followed in *the* FU*2 phase*.

[c] *At the Week 144 visit, patients will complete the efficacy assessments in a blinded manner as part of the double-blind treatment phase and will receive open label ocrelizumab. Patients will remain in the OLE phase for at least 2 years (at least 4 doses of ocrelizumab) for each patient. To maintain the blinding in the treatment arm, the first dose of open-label treatment will be two infusions of 300 mg given 14 days apart for all patients. For subsequent doses, patients will continue open-label treatment with a single IV infusion of 600 mg ocrelizumab every 24 weeks. Patients who discontinue from the OLE phase may continue to be followed in the FU2 phase.*

Figure 2 Patient Flow Schema



BCM = B-cell monitoring; DPE = double-progression event; FU = follow up; OCR = ocrelizumab; OLE = open-label extension; PDP OCR = post-double-progression ocrelizumab.

Notes: A patient may discontinue treatment and/or discontinue from the study at any time. Qualifications for advancing and the duration of each study phase are detailed in Section 3.1.1. The size of the boxes in this diagram does not represent the duration of each phase; for visit schedule and assessments required, see the schedule of activities for each phase.

Table 3 Overview of the Dosing Regimen across Study Phases

	Double-Blind Treatment Phase							PDP OCR			OLE Phase		
	6 Treatment Doses (144 Weeks) [a, b, c, d]							Variable [b, d, e]			At Least 4 Treatment Doses [b, d, f, g]		
	Dose 1		Dose 2	Dose 3	Dose 4	Dose 5	Dose 6 [a, c] (Every 24 Wks)	PDP OCR Dose 1 [h]		PDP OCR Dose 2, 3, N	OLE Dose 1 [e, g] Double Infusion [g]		OLE Dose 2, N (Subsequent Treatment Doses) [g] (Every 24 Wks)
	Day 1	Day 15	Wk 24	Wk 48	Wk 72	Wk 96	Wk 120+	Day 1	Day 15	Day N	Day 1	Day 15	Day N
A OCR	300 mg	300 mg	600 mg	600 mg	600 mg	600 mg	600 mg	OCR 300 mg	OCR 300 mg	OCR 600 mg	OCR 300 mg	OCR 300 mg	OCR 600 mg
B Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	OCR 300 mg	OCR 300 mg	OCR 600 mg	OCR 300 mg	OCR 300 mg	OCR 600 mg

9-HPT = 9-Hole Peg Test; CDP = confirmed disability progression; DPE = double-progression event; OCR = ocrelizumab; OLE = open-label extension; PDP OCR = post–double-progression ocrelizumab; wk = week.

Note: Each study drug dose has a duration of 24 weeks (± 5 days).

[a] The double-blind treatment phase consists of a 144-week (6 study drug doses, with each dose 24 weeks apart) period.

[b] After the first infusion, an evaluation will be performed before each subsequent infusion to ensure the patient remains eligible for further treatment (see also Section 4.3.2.3 for re-treatment criteria for ocrelizumab).

[c] Enrolled patients will undergo ocrelizumab (or placebo) treatment of 6 treatment doses at 24-week intervals.

[d] A dose of 100 mg of methylprednisolone IV and oral or IV antihistamine (e.g., IV diphenhydramine 50 mg), or equivalent dose of alternative, will be administered prior to ocrelizumab or placebo infusions. In patients where methylprednisolone is contraindicated, equivalent doses of other IV steroids (e.g., dexamethasone) should be used as premedication.

[e] Patients who experience a DPE during the double-blind treatment phase will be given the option to switch to the PDP OCR phase after they have completed at least 120 weeks of double-blind treatment. A DPE is defined as a confirmed 20% increase in 9-HPT time sustained for 24 weeks, and a CDP sustained for 12 weeks that occurs during the double-blind treatment phase.

[f] The OLE phase for eligible patients begins after the completion of the double-blind treatment phase. The OLE phase can be terminated at any point (see Section 3.1.1.5).

Table 3 Overview of the Dosing Regimen across Study Phases (cont.)

[g] During the OLE phase, the first dose of ocrelizumab will be administered as two 300 mg IV infusions given 14 days apart. For the subsequent doses, patients will continue open-label treatment with a single IV infusion of 600 mg ocrelizumab every 24 weeks. The first infusion of ocrelizumab in the OLE phase may occur once the patient meets the re-treatment criteria (see Section 4.3.2.3) at a scheduled visit following communication with the Sponsor.

[h] To maintain the original blinding, PDP OCR will be offered to all patients who qualify regardless of their original treatment assignment. Patients who experience a DPE during the double-blind treatment phase will be given the option to switch to the PDP OCR phase after they have completed at least 120 weeks of double-blind treatment. The first dose of the PDP OCR will be administered as two 300 mg ocrelizumab infusions (given 14 days apart) 24 weeks after the last dose of blinded study drug.

3.1.1 Study Phases

This study will consist of the following study phases:

- Screening
- Double-blind treatment
- *An optional PDP OCR treatment*
- Follow-up 1
- Open-label extension
- Follow-up 2
- B-cell monitoring

The details of each study phase are described below and in Figure 1. The study duration will vary for each patient to maximize the safety and efficacy data collected.

3.1.1.1 Screening Phase

The screening phase will last up to 24 weeks. Patients who are candidates for enrollment in the study will be evaluated by the investigator to ensure all eligibility criteria are met (see Sections 4.1.1 and 4.1.2). All patients must sign the Informed Consent Form prior to screening and prior to any changes to their existing medication for the purposes of enrollment in the study.

Procedures at screening will include collecting medical history, medical examination, complete neurological examination, 9-HPT time and EDSS score, and blood and urine sampling (see Appendix 1 for further details on screening assessments and samples and Section 4.1 on eligibility criteria for the study). Because of the potentially long screening phase (up to 24 weeks), the investigator is required to verify that the patient still meets eligibility criteria prior to randomization. Patients must be neurologically stable for at least 30 days prior to randomization and baseline assessments. In particular, laboratory assessments related to eligibility should not be older than 6 weeks prior to randomization; otherwise, laboratory retests will be required (not applicable for CSF testing).

Two mandatory MRI scans performed at least 6 weeks apart or one mandatory MRI that can be compared with a historical MRI performed in the previous 1 year will be performed to verify the patient's MRI activity level. The MRI performed closer (i.e., from 6 weeks up to 10 days prior) to randomization will be considered the baseline MRI for the study analyses.

For patients who fail the initial screening, a maximum of two re-screenings will be allowed.

Central randomization will be performed by the IxRS and will be stratified by:

- MRI activity, defined as any T1 Gd+ lesion(s) and/or new and/or enlarging T2 lesion(s) during the screening period (yes vs. no)
- Age (≤55. vs.>55)
- EDSS score (≤6.5 vs.>6.5)
- Region (two regions: European Union, United Kingdom, and Canada vs. other)

To ensure a balanced distribution of patients, demographics across regions by patient access to commercial ocrelizumab and enrollment within randomization strata will be monitored. Enrollment caps will be implemented in the IxRS system (e.g., no more than 650 patients will be randomized to the MRI-inactive subgroup). Other dynamic enrollment caps may be added to ensure that distribution of patients according to stratification factors will be balanced across regions by patient's access to commercial ocrelizumab.

Patient eligibility information will be provided by the investigator or the investigator's research staff to the IxRS at randomization. The patient will be randomized and assigned a unique medication number and randomization number.

Depending on local availability, patients who choose to and consent to the optional smartphone-based digital outcome assessments (Floodlight RPM) at screening will be asked to begin performing digital assessments (see Appendix 1). *Screening for Floodlight RPM participation will close in November 2022 in order for the last Floodlight RPM patient enrollment to occur by the end of December 2022.*

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

The investigators will be notified by the Sponsor if the study is placed on clinical hold and when the study is completed or closed to further patient enrollment.

3.1.1.2 Double-Blind Treatment Phase

All patients will undergo *144* weeks of study treatment (see Table 3 for review of dosing regimen). Study assessments will be performed as described in the schedule of activities (see Appendix 1). Randomization (Day 1) will occur only after the patient has met all inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2). Patients will be randomized to either ocrelizumab or placebo control group.

Study drug (ocrelizumab or placebo) dose will be administered in this study every 24 weeks. The first dose of study drug will be administered as two 300 mg IV infusions given 14 days apart. For the subsequent doses, study drug will be administered as a single 600 mg IV infusion every 24 weeks. All patients will receive mandatory

premedication prior to each infusion. A minimum interval of 20 weeks should be kept between the ocrelizumab second infusion of Dose 1 (i.e., infusion Day 15) and the next infusion of Dose 2 (Week 24). A minimum interval of 22 weeks must be maintained between each dose of study drug. More detailed information on study drug administration and premedication is contained in Section 4.3.2.1 and in Table 3.

The first study drug infusion should occur within 24 hours of randomization. In exceptional cases where all baseline assessments cannot be completed within 24 hours, the first study drug infusion may be administered within 48 hours of randomization provided the investigator ensures that all inclusion and 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.

Patients who prematurely withdraw from study treatment during the double-blind treatment phase will remain blinded to treatment and will continue to be followed for safety and efficacy, regardless of switching to other medications *for 144 weeks after randomization for each patient* (FU1).

To maintain integrity of the trial results and to prevent potential unblinding of the assigned arm during the double-blind treatment phase as a result of adverse events or changes to laboratory results, several additional measures, including a "dual assessor approach" (i.e., two blinded investigators per site: Treating Investigator and Examining Investigator), will be implemented until the time of the primary analysis; see Section 4.2 for details and definitions.

The primary analysis will be performed after *the last randomized patient reaches 144 weeks of double-blind treatment (+12 weeks to allow for the confirmation of the latest event).*

3.1.1.3 *An Optional Post-Double-Progression Ocrelizumab Treatment Phase*

A double-progression event (DPE) is defined as a confirmed 20% increase in 9-HPT time sustained for 24 weeks, and a CDP sustained for 12 weeks. Patients who experience a DPE during the double-blind treatment phase will be notified by the Sponsor and given the option switch to ocrelizumab (PDP OCR) treatment after they have completed at least 120 weeks of double-blind treatment and 120-week visit assessments. Patients will have to provide his or her informed consent prior to switching to PDP OCR treatment. An iDMC will monitor the rate of DPE in the double-blind treatment period.

In order to maintain the original blind, the option for PDP OCR will be offered to all patients who qualify, regardless of their original treatment assignment. The first dose of the PDP OCR will be administered as two 300 mg IV infusions (given 14 days apart) 24 weeks after the last dose of study drug. *Subsequent doses will be 600 mg IV infusions every 24 weeks.* Patients may continue on PDP OCR treatment until *the*

end of the OLE phase. Patients who discontinue from the PDP OCR phase earlier may continue to be followed in the FU2 phase.

3.1.1.4 Follow-Up 1 Phase

All patients who discontinue prematurely from the double-blind treatment phase will enter the FU1 phase, including patients who receive other *DMTs* for MS, commercial ocrelizumab, or no treatment. The FU1 phase will run in parallel with the double-blind treatment phase until *144 weeks from randomization for each patient*. Scheduled visits will be performed every 12 weeks analogically to the initial (double-blind) schedule of activities and will include both efficacy and safety assessments (see Appendix 2). In the FU1 phase, patients will remain blinded to their original (randomized) treatment assignment. Patients who withdraw from treatment should be encouraged to remain in the study for the full duration of the FU1 *phase*. All patients who are ongoing in the FU1 *phase at 144 weeks from randomization for each patient* will continue in the FU2 *phase* (see Section 3.1.1.6).

3.1.1.5 Optional Ocrelizumab Open-Label Extension Phase

After the completion of the double-blind treatment phase, an optional OLE phase is planned for eligible patients who have *completed* the double-blind treatment phase and, in the opinion of the investigator, could benefit from ocrelizumab treatment. Patients who are ongoing in the FU1 *phase at 144 weeks from randomization for each patient will continue in the FU2 phase* and will not participate in the OLE *phase*.

The OLE *phase* will be carried out for *at least* 2 years (*at least* 4 doses of ocrelizumab) *for each patient*. The 2-year duration of the OLE phase serves to further evaluate long-term safety and efficacy of ocrelizumab treatment in patients with PPMS.

Patients will continue in the *OLE* phase or with PDP OCR treatment as per the schedule of activities (see Appendix 1 and Appendix 2) and Table 3.

All patients who do not participate in the OLE phase will enter the FU2 phase (see Section 3.1.1.6). For patients who have completed the double-blind treatment phase and who do not immediately enter the OLE phase once it starts, if eligible, they may reconsider their decision and enter the OLE phase up to 24 weeks after the OLE phase begins. This will occur on a case-by-case basis in consultation with the Sponsor.

Eligible patients will need to provide consent for participation in the OLE phase. Patients who consent to participate in the OLE phase will be required to meet the eligibility criteria for OLE prior to infusion with ocrelizumab (see Section 4.1.3).

During the OLE phase, the first dose of ocrelizumab will be given as two 300 mg IV infusions given 14 days apart. For the subsequent *OLE* doses, patients will continue open-label treatment with a single infusion of 600 mg ocrelizumab IV every 24 weeks (see Appendix 3 and Section 4.3.2.1). A minimum 22-week interval between the last

study ocrelizumab infusion *in the double-blind treatment phase* and the first OLE ocrelizumab infusion *must be respected*. The first infusion of ocrelizumab in the OLE phase may occur once the patient meets the re-treatment criteria (see Section 4.3.2.3) at a scheduled visit. Refer to Section 4.2 for additional information about study unblinding.

Patients who complete or withdraw from the OLE phase will enter the FU2 phase (see Section 3.1.1.6). The Sponsor may decide to terminate the OLE at any time (*see* Section 4.7.3).

Study WA40404 will remain blinded until the primary analysis. The mechanisms necessary to ensure that the blinding of the Examining Investigator is maintained are not necessary *after the primary analysis* during the OLE phase. All required assessments during the OLE phase should occur as described in OLE schedule of activities (see Appendix 3). It is recommended that the same Examining Investigator continues to perform the assessments throughout the OLE phase as in the double-blind phase.

Visits should be scheduled with respect to the date of first infusion during the OLE phase. *The* visit for the second infusion should be scheduled 14 days after the first infusion of the OLE *dose* (Dose 1). A minimum interval of 20 weeks must be kept between the ocrelizumab second infusion during the OLE *dose* (Dose 1) and the next infusion at OLE *dose* (Dose 2). A minimum of 22 weeks must occur between ocrelizumab single infusions administered from OLE Dose 2 onward.

To verify re-treatment criteria for OLE infusion Dose 2 *and subsequent doses,* patients must attend a scheduled visit approximately 2 weeks prior to the infusion visit to have safety assessments performed as described in Appendix 3. In the event that an infusion is delayed, additional tests or assessments, such as routine safety laboratory tests, may be performed by the Treating Investigator as clinically indicated. At infusion visits, patients should remain in observation for at least 1 hour after the completion of the infusion.

Additional unscheduled visits for the assessment of potential disease progression or MS relapses, new neurological symptoms, or safety events may occur at any time. Assessments performed at unscheduled (non-dosing) visits will be as clinically indicated.

Patients with new neurological symptoms suggestive of MS relapse or MS worsening should have an EDSS and 9-HPT performed by the Examining Investigator (within 7 days from the onset of the new neurological symptoms). Other tests/assessments may be performed as appropriate.

3.1.1.6 Follow-Up 2 Phase

The following patients will move into the FU2 phase (see Figure 2):

- Patients who are ongoing in the FU1 *phase at 144 weeks from randomization for each patient*
- Patients who *have completed 144 weeks of* the double-blind treatment phase and *will* not enter the OLE phase
- Patients who *have* complete*d* or withdraw*n* from the OLE phase *or from PDP OCR treatment phase*

Laboratory and safety assessments for *the* FU2 *phase* will be performed during the clinic visits that occur every 24 weeks (see Appendix 4). All patients will continue in the FU2 *phase* until the end of the phase. The end of *the* FU2 *phase* is defined as 48 weeks after the last patient to enter the OLE *phase* has had his or her last OLE visit.

3.1.1.7 B-Cell Monitoring Phase

At the end of the FU2 *phase*, all patients will move into BCM phase until the end of the study. This study will end when all patients who are not being treated with an alternative B cell-depleting therapy have repleted his or her B cells. A patient's B cells will be considered to be repleted once B-cell levels have returned to baseline value or the lower limit of normal (whichever is lower).

Visits will be performed every 24 weeks and will include laboratory and safety assessments only (see Appendix 4).

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study will occur when all patients who are not being treated with an alternative B cell-depleting therapy have repleted his or her B cells (i.e., B-cell level of the patient has returned to the baseline value or the lower limit of normal, whichever is lower).

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately *9*.5 years (assuming that the last patient randomized after 3 years from the *start of the* study *has* receive*d* blinded treatment *for 144* weeks, followed by OLE *phase for at least 2 years (at least 4 doses of ocrelizumab) for each patient*, 48 weeks of FU2 phase, and [variable] BCM phase).

In addition, the Sponsor may decide to terminate the study at any time.

3.3 RATIONALE FOR STUDY DESIGN

This study (WA40404) is a pivotal Phase III clinical trial composed of the following phases: screening, double-blind treatment, *an optional PDP OCR treatment,* FU1, OLE, FU2, and BCM. The double-blind treatment phase is designed to demonstrate the efficacy on upper limb function and safety of ocrelizumab in patients with PPMS,

including those later in their disease course, in comparison with placebo. The OLE phase serves to further evaluate long-term safety, tolerability, and efficacy of ocrelizumab treatment in patients with PPMS.

3.3.1 Rationale for Ocrelizumab Dose and Schedule

The dose level of ocrelizumab administered in this study is 600 mg every 24 weeks.

Ocrelizumab will be administered intravenously as dual infusions (300 mg on Days 1 [Dose 1 Infusion 1] and 15 [Dose 1 Infusion 2]) for the first dose and subsequently as a single IV infusion (600 mg) every 24 weeks in 500 mL 0.9% sodium chloride. This dosing regimen is consistent with the dosing regimen used in ocrelizumab Phase III/IV studies, as well as with the summary of product characteristics (SmPC) and the U.S. prescribing information (USPI).

In the double-blind treatment phase, study drug for patients randomized to the placebo group will be administered analogously to those receiving ocrelizumab.

3.3.2 Rationale for Patient Population

In comparison with the previous ocrelizumab PPMS study (WA25046), this study will evaluate the efficacy of ocrelizumab compared with placebo on the preservation of upper limb function in a population that also includes patients with more advanced PPMS who acquired significant lower extremity impairment. This study will enroll patients with PPMS with an EDSS score of 3.0-8.0 and duration of disease less than 10 years if EDSS score $\leq$5.0 or less than 15 years if EDSS score 5.5–6.5 or less than 20 years if EDSS score 7.0–8.0 with an age range up to $\leq$65 years. These criteria will be implemented to recruit patients with PPMS later in their disease course and with a higher severity of disability. The study will evaluate upper limb function using the 9-HPT measure as a primary objective, and the treatment effect of ocrelizumab will be explored according to the presence of inflammatory activity on MRI at baseline.

3.3.3 Rationale for Control Group

In this study, the control group treatment is placebo.

PPMS is a neurologically disabling condition, without a disease-modifying treatment until recently. Ocrelizumab is the first and currently the only MS treatment approved for the PPMS indication, and its label differs depending on the region. Ocrelizumab was approved by the European Commission on 8 January 2018 for patients with early PPMS in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity. Additional evidence was requested by the EMA Committee for Medicinal Products to further elaborate the effect of ocrelizumab on the patient population with PPMS later in their disease course (EDSS score $>$6.5), in patients aged 55–65 years, and in patients with different inflammatory profiles.

Pursuant to the Helsinki Declaration, when standard treatment of a disease exists, placebo should generally not be used in clinical trials (WMA 1964). The benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists, or
- Where, for compelling and scientifically sound methodological reasons, the use of placebo is necessary to determine the efficacy or safety of an intervention and the subjects who receive placebo, or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

To better contextualize the efficacy of the various PPMS subgroups, a broader population needs to be investigated in a controlled trial. Given that no standard therapy exists in the European Union and some other parts of the world for the treatment of patients with PPMS later in their disease course/without imaging features characteristic of inflammatory activity, a placebo-controlled trial is acceptable provided that appropriate patient consent and safeguards are instituted to minimize the risk of serious or irreversible harm resulting from exposure to placebo. In this study, patients randomized to placebo who experience a DPE during the double-blind treatment phase will be given the option to switch to ocrelizumab (see Section 3.1.1.3).

The Sponsor recognizes that a treatment period lasting $144\ weeks$ poses risks to patients randomized to placebo. For this reason, several study elements will be employed to protect the well-being of study participants:

- The Informed Consent Form clearly defines the duration of the study including the double-blind treatment phase, OLE phase, and follow-up phases. The probabilities of assignment to placebo and ocrelizumab are indicated in easily understood terms in multiple sections of the Informed Consent Form.
- Patients who experience a DPE during the double-blind treatment phase will be given the option to switch to PDP OCR after they have completed at least 120 weeks of double-blind treatment (see Section 3.1.1.3 for definition of DPE). Patients will have to provide their informed consent prior to switching to PDP OCR.
- A thorough medical monitoring plan will be implemented by the study Sponsor to ensure the safety of all study participants. Moreover, an iDMC will be instituted to further protect the wellbeing of patients in the study.
- Upon withdrawal from study treatment for any reason, patients will be recommended to stay in the study for follow-up but may be eligible for treatment with some alternative therapies at the discretion of and in consultation with their Treating Investigator.

3.3.4 Rationale for the Use of Premedications (Methylprednisolone and Antihistamines)

To reduce the frequency and severity of infusion-related reactions (IRRs), patients will be premedicated with 100 mg methylprednisolone IV and an antihistamine approximately 30 minutes prior to administration of ocrelizumab (see Section 4.3.2.2). An integrated analysis of patients with MS who were treated with ocrelizumab revealed that the addition of antihistamines to the pretreatment with methylprednisolone decreased the incidence of IRRs by 2-fold (OCREVUS® U.S. Package Insert). Administered infrequently at a low dose, methylprednisolone is not anticipated to affect the efficacy or safety outcomes of the study. Methylprednisolone (or an alternative steroid in patients where methylprednisolone is contraindicated) will be administered to patients in both treatment groups during the treatment period to maintain the treatment blind.

3.3.5 Rationale for Biomarker Assessments

A blood protein biomarker sample (plasma and serum) will be taken. Assessment of the sample may include, but will not be limited to, NfL, a marker of neuronal injury and/or other neurodegeneration/inflammatory markers. *Biomarkers of neuroinflammation, including NfL, 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 PPMS and RMS (Gunnarsson et al. 2011; Axelsson et al. 2014, Kuhle et al. 2019). NfL can be detected in the blood, and blood levels are correlated with CSF levels, 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 et al. 2019; Kuhle et al. 2019).* If the patient requires a CSF sample to screen for IgG index or the presence of oligoclonal bands at screening, the leftover CSF will be stored and the assessment of the sample may include, but will not be limited to, NfL. Patients for whom screening CSF was collected will have the option to participate in a collection of CSF at Week 48; this sample will be used for exploratory biomarker determination that may include, but may not be limited to, NfL. NfL, in addition to other possible markers, may be used to assess the patient's disease activity, and/or as a pharmacodynamic, prognostic, or predictive biomarker(s) for disease progression and/or to assess drug activity, efficacy, safety, or MS pathogenesis.

Exploratory research on safety biomarkers may be conducted to support future drug development. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation. Adverse event reports will not be derived from exploratory safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 1000 patients will be enrolled in this study, of which at least 350 patients are planned to be in the MRI-active subgroup.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Ability to provide written informed consent and be compliant with the study protocol
- Diagnosis of PPMS in accordance with the McDonald criteria (Thompson et al. 2017)
- Age 18–65 years at time of signing Informed Consent Form
- EDSS score at screening and baseline ≥ 3.0 to 8.0, inclusive
- Disease duration from the onset of MS symptoms relative to randomization date:

  Less than 20 years in patients with an EDSS score at screening 7.0–8.0

  Less than 15 years in patients with an EDSS score at screening 5.5–6.5

  Less than 10 years in patients with an EDSS score at screening ≤ 5.0
- Documented history or presence at screening of at least one of the following laboratory findings in a CSF specimen (source documentation of laboratory results and method must be verified)

  Elevated IgG index

  One or more IgG oligoclonal bands detected by isoelectric focusing
- Screening and baseline 9-HPT completed in > 25 seconds (average of the two hands)
- Ability to complete the 9-HPT within 240 seconds with each hand at screening and baseline
- Neurological stability for ≥ 30 days prior to baseline
- Patients previously treated with immunosuppressants, immunomodulators, or other immunomodulatory therapies must undergo an appropriate washout period according to the local label of the immunosuppressant/immunomodulatory drug used

  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 before deciding to enter the study of their treatment options and, that by participating in this study, they may be randomized to placebo for a period of 120 weeks or greater.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use adequate contraceptive methods during the

treatment period and for 6 or 12 months (as applicable by the Ocrevus local label) after the final dose of ocrelizumab.

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

The following contraceptive methods *are considered acceptable (failure rate >1% [Clinical Trial Facilitation Group (CTFG)]): (1) progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action; (2) male or female condom with or without spermicide; (3) cap, diaphragm, or sponge with spermicide; (4) combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier method).*

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

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 *individual*. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not *adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.*

- For female patients without reproductive potential:

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

4.1.2 Exclusion Criteria

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

- History of relapsing-remitting or secondary progressive MS at screening

- Confirmed serious opportunistic infection including: active bacterial, viral, fungal, mycobacterial infection or other infection, including tuberculosis or atypical mycobacterial disease
- Patients who have or have had confirmed or a high degree of suspicion of progressive multifocal leukoencephalopathy (PML)
- Known active malignancy or are being actively monitored for recurrence of malignancy
- Immunocompromised state, defined as one or more of the following:

  CD4 count $< 250/\mu L$

  Absolute neutrophil count $< 1.5 \times 10^3/\mu L$

  Serum IgG < 4.6 g/L
- Receipt of a live-attenuated vaccine within 6 weeks prior to randomization
- Inability to complete an MRI (contraindications for MRI, including but not restricted to, pacemaker, cochlear implants, intracranial vascular clips, surgery within 6 weeks of entry in the study, coronary stent implanted within 8 weeks prior to the time of the intended MRI, etc.) or contraindication to Gd administration
- Patients requiring symptomatic treatment of MS (e.g., fampridine) and/or physiotherapy who are not on a stable regimen. Patients must not initiate symptomatic treatment of MS or physiotherapy within 4 weeks of randomization.
- Contraindications to mandatory premedications (i.e., corticosteroids and antihistamines) for IRRs, including:

  Uncontrolled psychosis for corticosteroids

  Closed-angle glaucoma for antihistamines
- Known presence of other neurologic disorders *that could interfere with the diagnosis of MS or assessments of efficacy and/or safety during the study,* including, but not limited to, the following:

  History of *hemorrhagic or* ischemic cerebrovascular disorders (e.g., stroke, transient ischemic attack) or *hemorrhage or* ischemia of the spinal cord

  History or known presence of CNS or spinal cord tumor (e.g., meningioma, glioma)

  History of metabolic myelopathy or known presence of untreated causes of metabolic myelopathy (e.g., untreated vitamin B12 deficiency)

  History or known presence of infectious myelopathy (e.g., due to syphilis, Lyme disease, HTLV-1, herpes zoster)

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

  Neuromyelitis optica

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

History or known presence of sarcoidosis

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

- Pregnant or breastfeeding, or intending to become pregnant during the study and for 6 or 12 months (as applicable by the Ocrevus local label) after last infusion of the study drug
- Lack of peripheral venous access
- Significant, uncontrolled disease, such as cardiovascular (including cardiac arrhythmia), pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine or gastrointestinal, or any other significant disease that may preclude patient from participating in the study
- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study
- History of alcohol or other drug abuse
- History of primary or secondary (non–drug-related) immunodeficiency
- Treatment with any investigational agent within 24 weeks prior to screening (Visit 1) or 5 half-lives of the investigational drug (whichever is longer), or treatment with any experimental procedure for MS (e.g., treatment for chronic cerebrospinal venous insufficiency)
- Previous treatment with B cell–targeting therapies (e.g., rituximab, ocrelizumab, atacicept, belimumab, ofatumumab, and alemtuzumab)
- Any previous treatment with bone marrow transplantation and hematopoietic stem cell transplantation
- Any previous history of transplantation or anti-rejection therapy
- Treatment with IV Ig or plasmapheresis within 12 weeks prior to randomization
- Systemic corticosteroid therapy within 4 weeks prior to screening

  The screening period may be extended for patients who have used systemic corticosteroids for MS before screening. For a patient to be eligible, systemic corticosteroids should also not have been administered between screening and baseline.
- Positive serum β-hCG measured at screening or positive urine β-hCG at baseline
- 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 PCR)
- Any additional exclusionary criterion as per ocrelizumab (Ocrevus®) local label, if more stringent than the above

- Lack of MRI activity at screening/baseline if more than 650 patients without MRI activity have already been enrolled, as defined by T1 Gd+ lesion(s) and/or new and/or enlarged T2 lesion(s) in the screening, to ensure that at least 350 patients with MRI activity will be randomized

Re-testing before baseline: In rare cases in which the screening laboratory samples are rejected by the central laboratory (e.g., hemolyzed sample) or the result is not assessable (e.g., indeterminate) or abnormal, the tests need to be repeated within 4 weeks. Any abnormal screening laboratory value that is clinically relevant should be retested to rule out any progressive or uncontrolled underlying condition. The last value before randomization must meet study criteria.

4.1.3 Eligibility Criteria for Open-Label Extension Phase

Patients who meet the following entry criteria may participate in the OLE phase:

- Completed the double-blind treatment phase of the trial and who, in the opinion of the investigator, may benefit from treatment with ocrelizumab

  Patients who withdrew from study treatment and received another disease-modifying therapy (DMT) or commercial ocrelizumab will not be allowed to enter in the OLE phase.

- Able and willing to provide written informed consent to participate in the OLE phase and to comply with the study protocol
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use adequate contraceptive methods during the treatment period and for 6 or 12 months (as applicable by the Ocrevus local label) after the final dose of ocrelizumab.

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

  The following contraceptive methods *are considered acceptable (failure rate >1% [CTFG]): (1) progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action; (2) male or female condom with or without spermicide; (3) cap, diaphragm, or sponge with spermicide; (4) combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier method).*

  Birth control methods that are highly effective (i.e. failure rate <1% [CTFG]) may also be used but are not required, and include: (1) oral, intravaginal or transdermal combined hormonal contraception associated with inhibition of

ovulation; (2) oral, injectable or implantable progestogen-only hormonal contraception associated with inhibition of ovulation; (3) intrauterine device; (4) intrauterine hormone-releasing system; (5) bilateral tubal occlusion; (6) vasectomised partner; (7) sexual abstinence.

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 *individual*. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not *adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.*

For female patients without reproductive potential:

Women may be enrolled if surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy) or post-menopausal (i.e., spontaneous amenorrhea for the past year confirmed by a FSH level>40 mIU/mL), unless the patient is receiving a hormonal therapy for her menopause.

4.2 METHODS OF TREATMENT ASSIGNMENT AND BLINDING

Randomization and blinding will be employed to minimize bias in treatment assignment and to provide the basis for valid statistical inference. Eligible patients must be randomized through IxRS prior to receiving any study drug. Patients who discontinue treatment for any reason will not be replaced. Under no circumstances are patients who enroll in this study and who have completed treatment as specified, permitted to be re-randomized to this study.

The randomization list will not be available to the study centers, monitors, project statisticians, or to the Sponsor project team. All individuals directly involved in the study will remain blinded to the treatment assignment until the primary analysis.

To maintain integrity of the trial results and to prevent potential unblinding of the assigned arm during the double-blind treatment phase as a result of adverse events or changes to laboratory results, the following additional measures will be implemented until the time of the primary analysis:

- To prevent potential unblinding as a result of adverse events or laboratory changes, a **"dual assessor"** approach will be used to evaluate efficacy and safety**. Each site will have two blinded investigators: a principal or Treating Investigator and a rating or Examining Investigator.**

  The Treating Investigator will be the safety assessor and should be a neurologist with experience in the care of patients with MS. The Treating Investigator will have access to safety data only and will make all treatment decisions based on the patient's clinical response and laboratory findings.

  The Examining Investigator will be the efficacy assessor and should be a neurologist or other qualified health care practitioner trained and certified in

administering and scoring the 9-HPT, Functional System Scores (FSS) and EDSS, and SDMT. **The Examining Investigator (or her/his certified designee) will assess the 9-HPT, EDSS scores (including dysphagia/bladder dysfunction assessments), and SDMT**. *Until the primary analysis*, the Examining Investigator and their qualified designees (if applicable) will not be involved with any aspect of medical management of the patient and will not be allowed access to patient data.

The Treating Investigator and the Examining Investigator will not be allowed to switch roles. *Until the primary analysis*, an investigator/site staff at a single site may not be a treating investigator for some patients and an examining investigator for others.

- Patient education: During the double-blind treatment phase, prior to being examined by the Examining Investigator, patients should be instructed not to discuss with the Examining Investigator what (if any) adverse effects they may be experiencing.
- Blinded, central MRI assessments: During the double-blind treatment phase, a blinded, central MRI reader will assess all MRI scans performed during the study. Of note, screening and baseline scans will be used for the assessment of patient eligibility, and therefore they will not be blinded.
- Blinding of laboratory parameters: Selected laboratory parameters that may lead to unblinding of the treatment assignment, such as flow cytometry assessment of cell counts including CD19+ cells, lymphocyte count, and Ig levels will be blinded in all patients until the *primary analysis*. To ensure patient safety during the study and to allow for assessments of the re-treatment criteria, a central laboratory will provide study investigators and the Medical Monitor(s) with reflex messages triggered by abnormal blinded laboratory results and will be instructed to suspend further treatment with study drug until the patient becomes eligible for ocrelizumab re-treatment. Investigators will be notified of their patient's abnormal laboratory test results. Consult the laboratory manual for additional information.
- Ocrelizumab and placebo treatment allocation will remain blinded until the primary database lock for the primary analysis.

To facilitate analysis of the biological samples collected in this study, the treatment code will be released to the responsible analytical person when the samples have been received at the analytical site and are ready for assay. The result of the analysis must not be released with individual identification of the patient until after the unblinding for the primary analysis.

Study site personnel and patients will be blinded to treatment assignment until after the primary analysis. 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, sample handling staff, IxRS service provider, and iDMC members.

While PK and ADA samples must 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. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to patients' treatment assignments to identify appropriate samples to be analyzed. PK samples from patients assigned to the comparator arm will not be analyzed for study drug PK concentration except at baseline or by request (e.g., to evaluate a possible error in dosing). ADA samples will be analyzed for all patients treated with study drug.

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.

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 a justification for any non-emergency 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, 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.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is ocrelizumab and matching placebo used to maintain the blind.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Ocrelizumab and Placebo

Ocrelizumab will be supplied by the Sponsor in 15 cc Type I glass vials as a sterile, single-use solution for IV infusion and contains no preservatives. Each vial contains 300 mg of ocrelizumab, at a nominal fill volume of 10 mL. The drug product is formulated as 30 mg/mL ocrelizumab in 20 mM sodium acetate at pH 5.3, with 106 mM trehalose dihydrate and 0.02% polysorbate 20. Ocrelizumab may contain fine translucent and/or reflective particles associated with enhanced opalescence. Do not

use the solution if discolored or if the solution contains discrete foreign particulate matter. The infusion solution must be administered using an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 0.2 micrometer or less). For information on the formulation and handling of ocrelizumab, see the Ocrelizumab Investigator's Brochure, local prescribing information, and Drug Preparation Guidelines.

In this study, ocrelizumab-matching placebo will be supplied by the Sponsor. The placebo will have the same composition and configuration as the drug product but will not contain ocrelizumab. Ocrelizumab placebo solutions for IV administration will be prepared by dilution of the ocrelizumab placebo into infusion bags containing 0.9% sodium chloride, using an identical procedure as for the active product.

4.3.1.2 NonInvestigational Medicinal Products

In this study, non-investigational medicinal products will include premedication to the ocrelizumab infusion. The following premedication will be used:

- Mandatory methylprednisolone (or an equivalent)
- Mandatory antihistaminic drug (e.g., diphenhydramine)
- Recommended oral analgesic/antipyretic (e.g., acetaminophen 1 g)

Refer to Section 4.3.2.2 for further details on premedication administration.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1. Any dose modification should be noted on the Study Drug Administration Electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.4.4.

Guidelines for treatment modification, interruption, or discontinuation for patients who experience adverse events are provided in Section 5.1.4.3.

4.3.2.1 Ocrelizumab and Placebo

The ocrelizumab dose administered will be 600 mg every 24 weeks. The first dose of ocrelizumab will be administered as two 300 mg IV infusions given 14 days apart. For the subsequent doses, ocrelizumab will be administered as a single 600-mg IV infusion every 24 weeks. A minimum interval of 20 weeks must be kept between the ocrelizumab second infusion during the double-blind treatment phase (Dose 1) and the next infusion at double-blind treatment phase (Dose 2). A minimum interval of 22 weeks must be maintained between each dose of ocrelizumab. This dosing regimen is consistent with the dosing regimen used in the ocrelizumab Phase III/IV studies, as well as with the SmPC and the USPI (see Table 4).

Patients who experience a DPE during the double-blind treatment phase will be given the option to switch to PDP OCR after they completed at least 120 weeks of double-blind treatment (see Section *3.1.1.3* for details). To maintain the original blind, PDP OCR will

be offered to all patients who qualify, regardless of their original treatment assignment. The first dose of the PDP OCR will be administered as two 300 mg IV infusions (given 14 days apart) 24 weeks after the last dose of blinded study drug. A minimum interval of 20 weeks must be kept between the ocrelizumab second infusion during the PDP OCR (Dose 1) and the next infusion at PDP OCR (Dose 2). A minimum interval of 22 weeks must be maintained between each dose of ocrelizumab.

Patients who are eligible (see Section 3.1.1.5) and wish to enter the OLE phase will receive two 300 mg IV infusions given 14 days apart for the first OLE dose (OLE Dose 1). For subsequent doses, patients will continue open-label treatment with a single IV infusion of 600 mg ocrelizumab every 24 weeks (OLE Doses 2–N; see Appendix 3 for more details).

Ocrelizumab infusions should be initiated and supervised by an experienced professional with access to appropriate medical support to manage severe reactions such as serious IRRs. It is anticipated that the patient will need to stay at the hospital or clinical site for a full day at an infusion visit. Each ocrelizumab 300 mg dose should be administered as a slow IV infusion over approximately 2.5 hours. Each ocrelizumab 600 mg dose should be administered as a slow IV infusion over approximately 3.5 hours.

Table 4 Overview of Ocrelizumab or Placebo Dosing and Schedule

	Amount of Ocrelizumab (or Placebo) to Be Administered		Infusion Instructions
Initial dose (600 mg), divided into two infusions [a]	Infusion 1	300 mg IV in 250 mL 0.9% sodium chloride	• Initiate the infusion at a rate of 30 mL/hr for 30 minutes. • The rate can be increased in 30 mL/hr increments every 30 minutes to a maximum of 180 mL/hr. • Each infusion should be given over approximately 2.5 hours.
	Infusion 2 (2 weeks later) [b]	300 mg IV in 250 mL 0.9% sodium chloride	
Subsequent doses (600 mg), [b] once every 24 weeks	Single infusion [b]	600 mg IV in 500 mL 0.9% sodium chloride	• Initiate the infusion at a rate of 40 mL/hr for 30 minutes. • 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.

[a] For patients who receive ocrelizumab at study start of the double-blind phase, start PDP OCR, or *start* OLE.

[b] Prior to the next infusion, a clinical evaluation will be performed to ensure that the patient remains eligible for re-treatment.

Note: Before each infusion of ocrelizumab, 100 mg of methylprednisolone IV and an antihistaminic drug will be administered to reduce the potential for infusion-related reactions.

Alternative Shorter Infusion of Subsequent 600 mg Ocrelizumab Doses

If patient did not experience a serious IRR with any previous ocrelizumab infusion, a shorter (2 hour) infusion of 600 mg can be administered for subsequent doses during any treatment phase. This does not apply for any initial dose (i.e., for patients who receive ocrelizumab at study start of the double-blind phase, start PDP OCR, or *start* OLE). The shorter infusion should be started at a rate of 100 mL/h. This should be escalated at the rates shown in Table 5.

Table 5 Alternative Shorter Infusions of Ocrelizumab 600 mg

Time (minutes)	Infusion Rate (mL/hr)	Maximum Dose per Interval [a] (mg)	Cumulative Dose (mg)
0–15	100	30	30
15–30	200	60	90
30–60	250	150	240
60–120 [b]	300	360	600

[a] Assumes that the infusion bag contains 600 mg ocrelizumab in 500 mL 0.9% sodium chloride. Refer to Dose Preparation Guidelines for more information.

[b] The shorter infusion of 600 mg ocrelizumab should be completed in approximately 120 minutes (2 hours).

Refer to Section 5.1.1.1 of this protocol and to current version of the IB for further details on the alternative shorter infusion option, including safety information.

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

The patient will need to remain at the clinic at every visit for at least 1 hour after the completion of the infusion for observation. After completion of the infusion, the IV cannula should remain in situ for at least 1 hour to allow for administration of drugs intravenously, if necessary, in the event of a delayed reaction. If no adverse events occur during this period of time, the IV cannula may be removed, and the patient may be discharged.

4.3.2.2 Premedications

Methylprednisolone has been shown to decrease the incidence and the severity of infusion reactions. An integrated analysis of patients with MS treated with ocrelizumab revealed that the addition of antihistamines pretreatment with methylprednisolone decreased the incidence of IRRs by 2-fold.

To reduce potential IRRs, all patients must receive mandatory prophylactic treatment with 100 mg of methylprednisolone administered by slow IV infusion, to be completed

approximately 30 minutes before the start of each ocrelizumab (or placebo) infusion. In the rare case when the use of methylprednisolone is contraindicated for the patient, use of an equivalent dose of an alternative steroid should be used as premedication prior to the infusion.

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

Analgesic/antipyretic such as acetaminophen/paracetamol (1 g) can also be considered.

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

4.3.2.3 ReTreatment Criteria for Ocrelizumab

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

- Absence of severe allergic or anaphylactic reaction to a previous ocrelizumab infusion
- Absence of any significant or uncontrolled medical condition or treatment-emergent, clinically significant laboratory abnormality
- Absence of active infection
- ANC $\geq 1.5 \times 10^3/\mu L$
- CD4 cell count $\geq 250/\mu L$
- IgG ≥ 3.3 g/L
- Negative pregnancy test

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

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

4.3.3 Investigational Medicinal Product Accountability

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

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

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

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

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

Refer to the pharmacy manual and the effective ocrelizumab for information on IMP handling, including preparation and storage, and accountability.

4.3.4 Continued Access to Ocrelizumab

Patients may be eligible to receive ocrelizumab as part of the OLE phase of this study, as described in Section 3.1.1.5.

The Sponsor will offer continued access to Roche IMP ocrelizumab free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

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

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

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

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

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

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

4.4 CONCOMITANT THERAPY

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

4.4.1 Treatment for Symptoms of Multiple Sclerosis

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

4.4.2 Treatment of Relapses

Patients who experience a relapse during study may receive treatment with IV or oral corticosteroids, if judged to be clinically appropriate by the investigator. The following standardized treatment regimen may be used as warranted: 1 g/day IV methylprednisolone for a maximum of 5 consecutive days. 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 patient or investigator feels he or she has met the criteria for withdrawal (see Section 4.7.1).

4.4.3 Prohibited Therapy and Alternative Treatment PostOcrelizumab

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

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

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

4.4.4 Immunizations

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

Immunization with any live or live-attenuated vaccine (i.e., measles, mumps, rubella, oral polio vaccine, Bacille Calmette-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 ocrelizumab treatment and for as long as the patient is B-cell depleted.

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

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

4.5 STUDY ASSESSMENTS

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

4.5.1 Informed Consent Forms and Screen *Failures*

All patients must sign and date the most current Institutional Review Board/Ethics Committee (IRB/EC) approved Informed Consent Form before any study specific assessments or procedures (including screening evaluations) are performed. 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 *detailed* record of all patients screened and *document* eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including, but not limited to, clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), general cancer risk factors, breast cancer-specific risk factors, reproductive status, smoking history and smoking status, will be recorded at baseline.

In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment and ongoing therapies (e.g., physiotherapy including its indication) will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained, and any changes in medications and allergies should be recorded.

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

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

4.5.3 Physical Examinations

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

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. 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.

4.5.4 Vital Signs

Vital signs will include measurements of systolic and diastolic blood pressure while the patient is in a seated position, pulse rate, and temperature.

On the infusion days, blood pressure, pulse rate, and temperature should be taken within 45 minutes prior to the premedication (methylprednisolone) infusion. In addition, blood pressure and pulse rate should be obtained prior to start of infusion, every hour during the infusion, at the end of infusion, and 1 hour after the end of the infusion. On non-infusion days, the vital signs may be taken at any time during the visit. Blood pressure and pulse rate will be recorded on the appropriate eCRF. Temperature should be measured and recorded in patient's notes only. Clinically significant abnormalities should be recorded on the Adverse Event or Infusion-Related Reaction/Cytokine-Release Syndrome eCRF. In the event of an IRR or if clinically indicated, additional vital signs readings (e.g., blood pressure and pulse rate) should be taken during and post-infusion at the discretion of the investigator and should be recorded on a dedicated Vital Sign eCRF.

4.5.5 Neurological Examination

A neurological examination will be performed by the Treating Investigator at every planned visit. During an unscheduled visit, the neurological examination will be performed only if deemed necessary.

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

Study investigators will screen patients for signs and symptoms of PML through evaluation of neurological 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). A mandatory MRI scan and CSF analysis may be warranted to assist in the diagnosis of PML. Refer to Appendix 5 for guidance on the diagnosis of PML.

Patients with suspected PML, defined as a new or worsening neurological symptom that necessitates MRI and/or lumbar puncture and CSF analyses to rule out PML, should be withheld from study treatment until PML is ruled out by complete serial clinical evaluations and appropriate diagnostic testing (see Appendix 5). The Medical Monitor should be contacted by email and should be immediately contacted by telephone.

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

4.5.6 9-Hole Peg Test

The 9-HPT is a quantitative measure of upper extremity (arm and hand) function (Goodkin et al. 1988; Fischer et al. 1999b). The test device consists of a container containing nine pegs and a wood or plastic block containing nine empty holes. The patient is to pick up each of the nine pegs one at a time and as quickly as possible place them in the nine holes. Once all the pegs are in the holes, the patient is to remove them again one at a time as quickly as possible and replace them into the container. The total time to complete the task is recorded. Both the dominant and non-dominant hands are tested twice (two consecutive trials of the dominant hand, followed immediately by two consecutive trials of the non-dominant hand).

The 9-HPT will be administered by the Examining Investigator or a qualified designee at the timepoints indicated in the schedule of activities (see Appendix 1, Appendix 2, Appendix 3, and Appendix 4).

4.5.7 Assessment of Disability: Expanded Disability Status Scale

Disability in MS is commonly measured by the EDSS. EDSS will be administered by the Examining Investigator at the timepoints indicated in the schedule of activities (see Appendix 1, Appendix 2, Appendix 3 and Appendix 4). The EDSS will be assessed in all patients by the Examining Investigator at screening, baseline, and every 12 weeks (regularly scheduled visit) during the double-blind treatment and FU1 phases; every 24 weeks during the OLE phase; at any unscheduled visit; and at treatment discontinuation, end of observation, or withdrawal from follow-up visit. Additional EDSS assessments for individual patients may be requested between visits (i.e., during an MS relapse, neurological worsening, etc.). All FSS and total EDSS scores will be captured electronically.

EDSS CDP is defined as an increase of ≥ 1.0 point from the baseline EDSS score that is not attributable to another etiology (e.g., fever, concurrent illness, or concomitant medication) when the baseline score is ≤ 5.5 and ≥ 0.5 point when the baseline score is > 5.5. Disability progression is considered confirmed when the increase in the EDSS score is confirmed at a regularly scheduled visit at least 12 weeks after the initial documentation of the progression. A 24-week CDP requires that the increase in EDSS score be confirmed at least 24 weeks after the initial documentation of the progression.

The EDSS is based on a standard neurological examination, incorporating functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral [or mental]) and ambulation rated and scored as FSS. Each FSS is an ordinal clinical rating scale ranging from 0 to 5 or 6. These ratings are then used in conjunction with observations and information concerning ambulation and use of assistive devices to determine the EDSS score. The EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10.0 (death) (Kurtzke 1983; Kappos 2011). Note that the following items need not be scored: sexual dysfunction and fatigue and consequently should not contribute to the Cerebral FS score nor EDSS step.

4.5.8 Assessment of Relapse

Although relapses are anticipated to be rare in the PPMS population, patients will be evaluated for relapse by the Treating Investigator at each visit throughout the study and, if necessary, at unscheduled visits to confirm relapse occurring between the visits.

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

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

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

The change must affect the following selected FSS: pyramidal, ambulation, cerebellar, brainstem, sensory, or visual. Episodic spasms, sexual dysfunction, fatigue, mood

change, or bladder or bowel urgency or incontinence will not suffice to establish a relapse. Note that the following items need not be scored: sexual dysfunction and fatigue.

It should be noted that all patients with new neurological symptoms defined at a visit or over the telephone should be referred to the Examining Investigator unless the Treating Investigator considers the symptoms consistent with an intensification of neurological symptoms from a transient systemic infection.

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

4.5.9 Symbol Digit Modalities Test

The SDMT (Smith 1982) 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 recognized as being particularly sensitive to slowed processing of information that is commonly seen in MS (Benedict et al. 2017). The SDMT is brief, is 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 collected orally, 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 schedules of activities (see Appendix 1, Appendix 2, Appendix 3, and Appendix 4).

4.5.10 Mandatory and Optional MRI Sequences

MRI will be used to monitor CNS lesions in patients with MS and potentially other pathophysiology, such as inflammation and neurodegeneration. Mandatory MRI scans (formally known as 'brain MRI') will be obtained in all patients at study visits as indicated in Appendix 1, Appendix 2, Appendix 3, and Appendix 4.

During the screening phase, two mandatory MRI scans (performed at least 6 weeks apart, but not more than 24 weeks apart) or one MRI with the mandatory sequences that can be compared with a historical MRI acquired in the previous 1 year will be performed to assess the patient's MRI activity level. MRI activity is defined as the presence of any T1 Gd+ lesion(s) and/or new and/or enlarging T2 lesion(s) during the screening period (see also Section 3.1). If the presence of new or enlarging lesions is ascertained, the patient will be stratified to the MRI-active subgroup. The MRI performed closer to randomization (i.e., either the second MRI scan at screening or the [only] screening MRI scan in the case where a historical scan was used for the assessment of MRI activity) will be considered as baseline MRI for the study analyses and will be captured under the baseline visit in the eCRF. Note that this baseline scan should be obtained maximum

6 weeks before but at least 10 days prior to performing the baseline visit to allow time for the centralized reading center to assess its quality and for potential re-scans if needed.

Postbaseline, the mandatory MRI scans will be obtained in all patients at Weeks 24, 48, and 72. From Week 72 onward, MRI scans will be performed every 48 weeks (i.e., at Week 120, 168, etc.). In addition, mandatory MRI scans will be obtained in patients who withdraw from study treatment (at withdrawal visit) if one was not performed during the prior 4 weeks. Mandatory MRI scans should occur within a window of ±4 weeks of the scheduled visit, as per the schedules of activities (see Appendix 1, Appendix 2, Appendix 3, and Appendix 4). *At the Week 120 visit for patients switching to PDP OCR treatment, mandatory MRI scans should be obtained within 4 weeks before the Week 120 visit.*

The mandatory MRI sequences are comprised of both brain and *axial* cervical spinal sequences if site technology is available, and data from these scans will contribute measurements for the key MRI secondary endpoints as well as novel exploratory endpoints. For details of the mandatory MRI sequences, refer to the MRI Acquisition Procedures Manuals. *Axial c*ervical spin*e* sequences are not required for the first mandatory MRI at screening MRI nor are expected to be included in a historical MRI used for screening (if applicable), but these *axial cervical spine* sequences should be included in second mandatory MRI scan (considered the baseline MRI).

If site technology is available, in addition to the mandatory MRI sequences, optional, additional *sagittal* cervical spinal cord MRI sequences may be acquired for baseline, Weeks 24 and 120, at treatment discontinuation, and every 48 weeks in the OLE (according to the yearly schedule as carried over from the double-blind treatment phase). These *sagittal cervical spine* sequences provide further information on cervical spinal cord lesions and atrophy. Additional optional *sagittal* cervical spinal cord MRI sequences are not required to accompany the first mandatory MRI at screening MRI nor are expected to be included in a historical MRI used at screening, but these sequences should be included in the second mandatory MRI (considered the baseline MRI) scan. *Subjects who choose to participate, an additional signed Informed Consent Form (ICF – denoted as 'Consent for optional cervical spinal cord MRI scans' in the master ICF), dedicated to the sagittal cervical spine is required.* For details of the additional optional *sagittal* cervical spine MRI sequences, refer to the MRI Acquisition Procedures Manuals.

During the OLE, MRI mandatory and additional optional *sagittal* cervical spinal cord scans will be performed every 48 weeks (according to the yearly schedule as carried over from the double-blind treatment phase).

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

MRI scans will be read by a centralized reading center for efficacy endpoints. The centralized reading center will be blinded to treatment assignment, and the reading will be performed in the absence of clinical information.

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 will be described in a separate MRI Acquisition Procedures Manual.

All MRI scans will also be reviewed locally by a radiologist for safety, and the MRI scan report containing only non-MS pathology will be provided to the Treating Investigator. During the double-blind treatment phase, only the local radiologist/technician at the investigational site who is assigned to this study may have access to the MRI scans, except at screening and baseline when the Treating Investigator may view the MRI scan. To protect the blind, the Treating Investigator must not review the MRI scans (including additional optional cervical MRIs) obtained after randomization unless a safety concern arises. In the event that the Treating Investigator becomes aware of these MRI results, this should be documented in the eCRF, indicating the reason.

Note: The Treating Investigator may have access to MRI scans performed during the OLE phase *after the primary analysis*.

If patients receive corticosteroids for an MS relapse, every effort should be made to obtain an MRI scan prior to the first corticosteroid dose if the pre-corticosteroid 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 MRI scan.

4.5.11 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the central laboratory for analysis unless otherwise indicated (further details will be provided in the laboratory manual).

- Hematology: hemoglobin, hematocrit, RBC, WBC (absolute and differential: neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells), and quantitative platelet count
- Blood chemistry: AST, ALT, gamma-glutamyl transferase, total bilirubin, creatinine, amylase, potassium, sodium
- Flow cytometry: Analysis will include, but is not limited to, the determination of the duration of B-cell depletion and recovery (CD19+), B-cell subsets (e.g., CD19, CD27, IgD, CD38 markers to assess naive, memory, plasmablasts and/or other populations), and T-cell counts (CD3+, CD4+, CD8+).
- Quantitative Ig: Ig levels (IgG, IgM, and IgA)

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. Refer to Appendix 1, Appendix 2, Appendix 3, and Appendix 4 for details.

- Urinalysis**:** A urine dipstick will be performed at the site (pH, specific gravity, glucose, protein, ketones, blood), and a microscopic examination if abnormal and clinically significant will be performed at the site (local laboratory).
- Pregnancy test: All women of childbearing potential will have a serum pregnancy test at screening.

All women of childbearing potential must have regular pregnancy tests. A urine pregnancy test (sensitivity of at least 25 mU/mL β-hCG) will be performed locally at the timepoints shown in Appendix 1, Appendix 2, Appendix 3, and Appendix 4. On infusion visits, the urine pregnancy test should be performed prior to the methylprednisolone infusion. A positive urine pregnancy test should be confirmed with a serum test through the central laboratory prior to any further dosing with study drug. If a urine pregnancy test is positive, the patient will not receive the scheduled dose, and a confirmatory serum pregnancy test will be performed by the central laboratory.

- Viral serology and detection: All patients must have negative HBsAg test result at screening prior to enrollment. If total HBcAb is positive at screening, hepatitis B virus (HBV) DNA measured by PCR must be negative to be eligible.

  For patients enrolled with negative HBsAg and positive total HBcAb, HBV DNA (PCR) must be repeated every 12 weeks during the double-blind phase. Retests will continue in OLE phase on a 24-week basis as per the scheduled visits. Patients in whom the viral DNA becomes positive but in whom the quantity is at the lower limit of detection of the assay should have the test repeated as soon as possible. Patients found to have a confirmed viral DNA-positive test should be referred to a hepatologist for immediate assessment. These patients will not receive further infusions of study drug and will enter the follow-up phase.

  Liver function (i.e., ALT/SGPT, AST/SGOT, gamma-glutamyl transferase, total bilirubin) should be reviewed throughout the study. Patients who develop evidence of liver dysfunction should be assessed for viral hepatitis and, if necessary, referred to a hepatologist or other appropriately qualified expert. Study drug should be withheld until the diagnosis of viral hepatitis has been excluded. Patients who develop hepatitis B should be withdrawn from the treatment and should enter the follow-up phase. Should treatment be prescribed, this will be recorded in the eCRF. Patients with viral hepatitis due to other agents, such as hepatitis A, may resume treatment after recovery.
- Biomarker sample: A plasma and a serum sample will be collected, and analysis may include, but will not be limited to, NfL. The sample may be shipped to the Sponsor, or one or more laboratories designated by the Sponsor for analysis.

- CSF: If the patient does not have documented history or presence at screening of at least one laboratory finding of either elevated IgG index or one or more IgG oligoclonal bands detected by isoelectric focusing *on* a prior CSF specimen, a CSF specimen will be collected to test for these parameters during the screening phase. The remainder of this CSF sample will be retained as a biomarker sample, and analysis may include, but will not be limited to, NfL. The sample may be shipped to the Sponsor, or one or more laboratories designated by the Sponsor for these analyses. Patients for whom screening CSF was collected will have the option to participate in a collection of CSF at Week 48; this sample will be used for exploratory biomarker determination that may include, but may not be limited to, NfL.

All laboratory samples collected during the study will be shipped to a central laboratory, with the exception of urine dipsticks/urine probes, which will be analyzed locally unless otherwise indicated.

Laboratory samples will be taken at the study visit as described in the schedules of activities (see Appendix 1, Appendix 2, Appendix 3, and Appendix 4).

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

At participating sites, screening blood and CSF samples collected from patients who do not enroll in the study (screen-fail samples) may be used for research related to the disease under study and the development of disease-related tests or tools.

Biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Plasma and/or serum samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed
- Any leftover CSF samples that were collected for IgG index/OCB analysis to determine eligibility for patients who did not have historical data and the optional Week 48 CSF sample will be destroyed no later than 5 years after the final Clinical Study Report has been completed or until exhausted, or earlier depending on local regulations.

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

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

4.5.12 Patient-Reported Outcomes

Patient-reported outcome (PRO) data will be collected via questionnaires to characterize the treatment benefit of ocrelizumab. The questionnaires, translated and culturally validated into the local language as appropriate, will be completed in their entirety at specified timepoints during the study. To ensure instrument validity and that data standards meet health authority requirements, questionnaires will be self-administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, 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 dexterity), appropriate site personnel (except the Examining Investigator) may administer the PRO to the patient; however, staff should not influence responses in any way and questions and response options should be read out verbatim.

Patients will use an electronic device to capture PRO data. The electronic device and/or instructions for completing the questionnaires electronically will be provided by site staff. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

4.5.12.1 *EQ5D5L*

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 (see Appendix 6). Published weighting systems allow for creation of a single composite score of the patient's health status. The EQ-5D-5L takes approximately 5 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations.

4.5.12.2 Multiple Sclerosis Impact Scale, Version 2

The MSIS, v2 is a 29-item patient-reported measure of the physical and psychological impacts of MS (Hobart et al. 2001). Patients are asked to rate how much their functioning and well-being has been impacted over the past 14 days on a 4-point scale, from “Not at all” (1) to “Extremely” (4) (see Appendix 7). The physical score is the sum of items 1–20, which is then transformed onto a 0–100 scale. The psychological score is the sum of items 21–29, transformed onto a 0–100 scale. Higher scores indicate a greater impact of MS. A change of 7.5 points on the physical scale is considered to be clinically meaningful.

4.5.12.3 Modified Fatigue Impact Scale

The MFIS is a 21-item instrument that asks patients to rate the impact of fatigue over the past 4 weeks on a 5-point Likert scale, from “Never” (0) to “Almost always” (4) (Fischer

et al. 1999a) (see Appendix 8). The total score is the sum of all items from 0 to 84, with higher scores indicating greater impacts of fatigue. Physical, cognitive, and psychosocial domain scores can also be calculated.

4.5.12.4 ABILHAND

The ABILHAND measures the ability to measure everyday activities that use upper limbs. It was originally developed for rheumatoid arthritis (Penta et al. 1998) and has since been used in MS (Cano et al. 2015; Mikol et al. 2015; see Appendix 9). Each item is scored on a 4-point scale, using "Impossible" (0), "Very Difficult" (1), "Difficult" (2), and "Easy" (3).

4.5.12.5 Quality of Life in Neurological DisordersUpper Extremity Function

The Neuro-QoL-UE (fine motor, activities of daily living [ADL]) domain is a 20-item questionnaire used to assess upper limb function, which involves people with MS through each stage of its development (Gershon et al. 2012; see Appendix 10). Items include assessments of dressing, cooking, eating, cleaning, and writing from which the patient uses a 5-point Likert scale to rate his or her performance ranging from “without any difficulty” (5) to “unable to do” (1). Item scores are summed, multiplied by 100, and divided by 80; a higher score (range: 0−100) indicates better health reported function.

4.5.12.6 Patient Global Impression of Change for Fatigue

The Patient Global Impression of Change for Fatigue is a single item completed by the patient to assess changes in fatigue over the last 6 months (see Appendix 11). Patients will be asked to respond on a 7-point Likert scale from “very much better” (1) to “very much worse” (7).

4.5.12.7 Patient Global Impression of Change for Upper Limb Function

The PGIC-UL is a single item questionnaire completed by the patient to assess upper limb function compared with the function over the last 6 months (see Appendix 12). The patient will be asked to rate their upper limb function using a 7-point Likert scale ranging from “very much better” (1) to “very much worse” (7). The PGIC-UL is used as an anchor to determine what is a clinically meaningful change in ABILHAND and the Neuro-QoL-UE.

4.5.13 Samples for Whole Genome Sequencing

At participating sites, blood samples will be collected for DNA extraction to enable whole genome sequencing (WGS) or other genotype analysis to assess the patient’s germline genotype for allelic variations or mutations that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, or can increase the knowledge and understanding of disease biology. The blood samples may be sent to one or more laboratories for analysis.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and whole exome sequencing (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. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

Collection and submission of WGS samples is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS sampling, this section of the protocol (Section 4.5.13) will not be applicable at that site.

Candidate genes of MS susceptibility or progression that have been identified will be assessed in DNA from the study patients and may include, but will not be limited to, those in the human leukocyte antigen locus (IMSGC and WTCCC 2011; IMSGC 2013; Patsopoulos et al. 2013; Didonna and Oksenberg 2015). The genotype will also be assessed to identify potential new markers that may be prognostic of MS progression or disease worsening or to assess predictive value of markers for enhanced ocrelizumab response. The DNA genotype may be assessed for genes that have been associated with increased risk for MS or otherwise used to further understand the pathogenesis of MS (IMSGC and WTCCC 2011; IMSGC 2013).

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

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

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

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

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

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

4.5.14 Optional Samples for Research Biosample Repository

4.5.14.1 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 biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens 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.

Specimens for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.14.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.14) will not be applicable at that site.

4.5.14.3 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 or diseases:

- A single sample for DNA collected as indicated in the schedule of activities
- Plasma samples collected over time as indicated in the schedule of activities
- RNA samples collected over time as indicated in the schedule of activities
- *Leftover samples from the main trial*

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES), next-generation sequencing, or other genomic analysis methods.

Genomics is increasingly informing researchers 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. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

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

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

4.5.14.4 Confidentiality

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

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

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

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

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

4.5.14.5 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 the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be

required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

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

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

4.5.14.6 Withdrawal from the Research Biosample Repository

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

If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

A patient's withdrawal from Study WA40404 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study WA40404.

4.5.14.7 Monitoring and Oversight

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

4.5.15 Optional Smartphone-Based Digital Outcome Assessment

Floodlight RPM digital outcome data collection encompasses active tests that have been developed to be self-administered by patients via smartphone devices. The Floodlight RPM assessment in this study may include, but may not be limited to, the following tests: information processing speed test; active gait and posture tests (only for patients with a baseline EDSS score $<$7.0), including a static balance test, a U-turn test, and a 2-minute walk test; hand motor function tests, including the "Draw a Shape" and "Pinching" test; daily mood questions; a MS symptom tracker; and the continuous analysis of mobility through passive monitoring. Patient participation in this data collection is optional. Only patients, who consent to Floodlight RPM self-assessments at screening will be asked to begin performing the digital assessment. The patient adherence data from the 4 weeks prior to baseline will be used to determine if the patient can continue to use Floodlight RPM *for 144 weeks from randomization. Screening for Floodlight RPM participation will close in November 2022 in order for the last Floodlight RPM patient enrollment to occur by the end of December 2022.*

4.5.16 Optional CSF Collection

Patients for whom screening CSF was collected will have the option to participate in a collection of CSF at Week 48 of the double-blind treatment phase; this sample will be used for exploratory biomarker determination that may include, but may not be limited to, NfL (see Section 3.3.5). The CSF sample should be collected prior to the ocrelizumab (or placebo) infusion at Week 48 (within a window of 14 days prior to the actual scheduled visit Week 48; see Appendix 1).

4.6 OVERVIEW OF CLINICAL VISITS

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

Visits should be scheduled with reference to the date of the baseline visit (Day 1). A minimum interval of 20 or 22 weeks, depending if the previous dose was administered in one or two infusions as per Section 3.1.1.2, Section *3.1.1.3*, and Section 3.1.1.5, respectively, should be maintained between each infusion.

At infusion visits, it is anticipated that the patients will have to stay at the hospital or clinic for a full day. Patients treated with ocrelizumab should remain in observation for at least 1 hour after the completion of the infusion. If for logistical reasons the infusion cannot be administered on the same study visit day, the infusion should be given within the next 24 hours provided that the patient still meets re-treatment criteria.

Patients who cannot receive their infusion at the scheduled visit or within 24 hours of the visit should be rescheduled for a delayed dosing visit (see Section 4.6.1). Additional

unscheduled visits for the assessment of disease worsening, new neurological symptoms, or safety events may occur at any time.

Patients who are pregnant and breastfeeding should continue to follow the schedule of activities; however, no infusions will occur. If there is a concern with the ability of a pregnant or breastfeeding patient to complete all scheduled assessments, or if assessments are contraindicated with pregnancy, the investigator must contact the Medical Monitor for further discussion.

4.6.1 Delayed Dosing Visit

Delayed dosing visits may be scheduled only if the infusion cannot be administered at the timepoints defined in the schedules of activities (see Appendix 1, Appendix 2, Appendix 3, and Appendix 4). Thus, a patient who had all assessments of a dosing visit performed, but could not receive the 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.

4.6.2 Unscheduled Visits

Patients who develop new or worsening neurological symptoms should be seen at the investigational site as soon as possible, regardless of the dates of their pre-planned, scheduled study visits and regardless of the study period. The EDSS assessment should be performed for any suspected neurological worsening. If an MS relapse is diagnosed or suspected, EDSS assessment should be performed within 7 days, in addition to completing the appropriate eCRF.

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

4.7 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.7.1 Study Treatment Discontinuation

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

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determines it is in the best interest of the patient

Additionally, patients must be withdrawn from treatment under the following circumstances:

- Life-threatening (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Grade 4) infusion-related event that occurred during a previous ocrelizumab infusion

- Demonstrate active hepatitis B infection, either new onset or reactivation
- PML
- Patients who decide to discontinue the treatment

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

An excessive rate of treatment withdrawals can render the study non-interpretable; therefore, unnecessary treatment withdrawal of patients should be avoided.

If a patient meets any of the treatment withdrawal criteria (see above), the patient must be withdrawn from treatment. Patients who prematurely withdraw from study drug treatment will need to return to the clinic for a treatment discontinuation visit (see Appendix 1, Appendix 2, and Appendix 3 for additional details). After treatment discontinuation, every effort should be made to have the patient enter the follow-up phase of the study (FU1 or FU2).

For patients who have withdrawn from study drug treatment, the investigator should decide as to further treatment of the underlying disease (see Section 4.4.3 for recommendations on alternative treatments for MS post-ocrelizumab).

4.7.2 Patient Discontinuation from Study

Patients will return to the clinic for an end of observation or withdrawal from follow-up visit.

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure

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

Patients who withdraw from study drug treatment during any study period, for any reason, are encouraged to enter and complete the applicable follow-up phase (see Section 4.7.1). Patients who withdraw from FU1 or FU2 will return to the clinic for a withdrawal from follow-up visit (see Appendix 2 and Appendix 4 for additional details). If a patient discontinues from the study, the patient should be asked if he or she can still

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

When applicable, patients should be informed of circumstances under which their participation may be terminated at the medical discretion of the investigator without their consent. Any administrative or other reasons for withdrawal must be documented and explained to the patient.

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

4.7.3 Study Discontinuation

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

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

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

4.7.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with ocrelizumab in completed and ongoing studies. The anticipated important safety risks for

ocrelizumab are outlined below. Refer to the ocrelizumab local labels and the Ocrelizumab Investigator's Brochure for a complete summary of safety information.

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

5.1.1 Risks Associated with Ocrelizumab

Important, identified, and potential risks associated with ocrelizumab are described in the approved risk management plan and provided below. Refer to the most recent version of the Ocrelizumab Investigator's Brochure for updates on risks associated with ocrelizumab treatment.

5.1.1.1 Identified Risks and Adverse Drug Reactions

Infusion-Related Reactions

All CD20-depleting agents administered via the intravenous route, including ocrelizumab, have been associated with acute IRRs. Following the approved administration regimen (which includes the use of premedication prior to treatment with ocrelizumab to reduce frequency and severity of IRRs), symptoms of IRRs may occur during any ocrelizumab infusion, but have been more frequently reported during the first infusion. Physicians should alert patients that IRRs can occur within 24 hours of the infusion. Across the RMS and PPMS trials, symptoms associated with IRRs included, but are not limited to the following: pruritus, rash, urticaria, erythema, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, tachycardia and anaphylaxis.

Patients should be observed for at least 1 hour after the completion of the infusion for any symptom of IRR. Patients will be informed about delayed post-infusion symptoms and instructed to contact the study physician if he or she develops such symptoms.

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

For further guidance on how to manage IRRs refer to the current Ocrelizumab Investigator's Brochure.

Alternative Shorter Infusion of Subsequent Doses

In a study (MA30143, ENSEMBLE Plus) designed to characterize the safety profile of shorter ocrelizumab infusions in patients with RRMS, no differences were found in the frequency and severity of IRRs associated with shorter (2 hour) infusions compared with

conventional infusions (3.5 hours). For further details, refer to the current version of the I*nvestigator's* B*rochure*.

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 it had been reported in 1 patient with rheumatoid arthritis treated with ocrelizumab. HBV screening should be performed in all patients before initiation of treatment with ocrelizumab as per local guidelines. Patients with active 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 below.

Impaired Response to Vaccination

After treatment with ocrelizumab for 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 raised 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.

Investigators 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 who are on ocrelizumab. Vaccination with live or live-attenuated vaccines are not recommended during the treatment with ocrelizumab and until B cells have returned to normal levels.

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

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

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.

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

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

Delayed Return of Peripheral B Cells

Treatment with ocrelizumab leads to rapid depletion of CD19+ B cells in blood by 14 days posttreatment (first timepoint of assessment) as an expected pharmacologic effect. This was sustained throughout the treatment period. The longest follow-up duration after the last ocrelizumab infusion from Phase II Study WA21493 in 51 patients

indicates that the median time to repletion (returned to baseline/LLN, whichever occurred first) of B cells was 72 weeks (range 27–175 weeks). Patients with prolonged B-cell depletion should be monitored until his or her B cells have repleted.

5.1.1.2 Potential Risks

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 none of 668 females treated with interferon β-1A or placebo. Patients should follow standard breast cancer screening guidelines.

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

If a malignant event is reported, key available information on cancer will be collected for this study and reported as a serious adverse event on the eCRF. Further explorations and detailed cancer information will be solicited via a questionnaire (e.g., further details on tumor diagnostics, grade/staging, and available histopathologic and genetic testing results).

Progressive Multifocal Leukoencephalopathy

*John Cunningham (JC) virus infection resulting in PML has been reported very rarely 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 the risk of PML cannot be ruled out, p*hysicians 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 *scans preferably with contrast (compared with pretreatment MRI scans),* confirmatory CSF testing for JC viral DNA, and repeat neurological assessments should be considered. If PML is confirmed, ocrelizumab must be discontinued permanently.

Refer to Appendix 5 for diagnosis guidance of PML. See the Ocrelizumab Investigator's Brochure for more details.

Hypersensitivity Reactions

Hypersensitivity may be difficult to distinguish from IRRs in terms of symptoms. A hypersensitivity reaction may present during any infusion, although typically would not present during the first infusion. For subsequent infusions, more severe symptoms than previously experienced, or new severe symptoms, should prompt consideration of a potential hypersensitivity reaction. If a hypersensitivity reaction is suspected during

infusion, the infusion must be stopped immediately and permanently. Patients with known IgE-mediated hypersensitivity to ocrelizumab must not be treated.

Neutropenia

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

5.1.2 Risks Associated with Corticosteroids

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

5.1.3 Risks Associated with Antihistamines

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

5.1.4 Management of Patients Who Experience Adverse Events

5.1.4.1 Dose Modifications

Study drug dose modifications are not foreseen.

5.1.4.2 Treatment Interruption

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 4.3.2.3 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).

5.1.4.3 Management Guidelines

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. Follow ocrelizumab local label for further guidelines.

Handling of IRRs will depend on the intensity of symptoms (see also Table 6 for grading of intensity of IRRs).

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

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

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

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.

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 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

Clinical relapses will be recorded only on the appropriate eCRF. IRRs will be recorded only on a pre-specified Infusion-Related Reaction/Cytokine-Release Syndrome eCRF.

B-cell depletion is the expected outcome of ocrelizumab treatment and is not an adverse event. However, patients may be at risk for infections and particular attention should be directed toward early identification and treatment of infections. During the study, investigators are requested to promptly investigate patients reporting signs or symptoms of infection, to take appropriate specimens for identification of the pathogen, and to treat infections aggressively. Prior to enrollment in the study, it is recommended that the investigator review and, if warranted, update each patient's immunizations in accordance with country medical immunization guidelines (see Section 4.4.4).

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

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

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

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

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

If the MS relapse results in hospitalization for any reason other than for routine treatment of the relapse (e.g., for a treatment course beyond the standard treatment; see Section 5.3.5.11) or when hospitalization is prolonged, the MS relapse should be considered a serious adverse event.

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 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below:

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

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4.1–5.6.

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

5.3.1 Adverse Event Reporting Period

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

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported throughout the study duration.

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 6 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 6 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 7):

- 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 7 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/Cytokine-Release Syndrome 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/Cytokine-Release Syndrome eCRF. Report a local IRR for any symptoms affecting only the skin and localized to only one place.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than IRRs (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.

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.4 Persistent or Recurrent Adverse Events

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

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

5.3.5.5 Abnormal Laboratory Values

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

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

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

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

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

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

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.7 Abnormal Liver Function Tests

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

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

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

5.3.5.8 Deaths

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

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

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

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

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of MS

Events that are clearly consistent with expected pattern of progression of the underlying disease should not be recorded as adverse events; however, clinical MS relapses will be recorded on eCRF. These data will be captured as effectiveness assessment data only. In most cases, the expected pattern of progression will be based on EDSS scores and/or 9-HPT times. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

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

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

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

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

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

5.3.5.12 Patient-Reported Outcome Data

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

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)
- Accidental overdoses or medication errors see Section 5.4.4 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

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

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

5.4.1 Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be provided separately. To ensure the

safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

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

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 48 weeks after the last dose of study drug but may be extended in patients whose B cells take longer to replete. 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.

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

Instructions for reporting post-study adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed *through the Informed Consent Form* to immediately inform the investigator if they become pregnant during the study. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be

recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. Information regarding child health up to 1 year should be collected on the infant health questionnaire (see Appendix 13).

5.4.3.2 Abortions

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

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

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

5.4.3.3 Congenital Anomalies/Birth Defects

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

5.4.4 Reporting Requirements for Cases of Accidental Overdose or Medication Error

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

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

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

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

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

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

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

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

5.5 FOLLOWUP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator FollowUp

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to

follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

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

All pregnancies reported during the study should be followed with a Pregnancy Outcome and Infant Health Information on First Year of Life questionnaire provided by the Sponsor.

5.5.2 Sponsor FollowUp

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, 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.

Related serious adverse events must be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed.

All adverse events must be collected and reported during the study through the end of the FU2 phase, which is at least 48 weeks after the last infusion, but may be extended in patients whose B cells take longer to replete.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

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

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

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

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Ocrelizumab Investigator's Brochure

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

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

For a list of serious adverse drug reactions that are considered expected, refer to the current Ocrelizumab Investigator's Brochure.

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

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

6.1 DETERMINATION OF SAMPLE SIZE

The primary objective for this study is to evaluate the efficacy of ocrelizumab compared with placebo on time to 20% worsening from baseline in 9-HPT time confirmed for at least 12 weeks in all randomized patients and in patients with MRI activity. The sample size was estimated on the basis of data from Study WA25046 (ORATORIO).

A two-group test of equal exponential survival is used to determine the sample size for the time to 12-week confirmed 20% worsening in the 9-HPT. With a sample size of 1000 patients (of which at least 350 patients are expected in the MRI-active population), a double-blind treatment phase of 144 weeks, an annual dropout rate of 10%, and a randomization ratio of 1:1, it is expected that approximately 355 events will be observed in all randomized patients (placebo progression rate: 40%), which will provide approximately 82.1% power to detect a hazard ratio of 0.70 at a type I error rate of 0.0146 and approximately 77.3% power to detect a hazard ratio of 0.75 at a type I error rate of 0.05. Likewise, it is expected that approximately 134 events will be observed in the MRI-active subgroup (placebo progression rate: 44%), which will provide approximately 81.5% power to detect a hazard ratio of 0.60 at a type I error rate of 0.04.

Operating characteristics (power and expected total number of events) for true underlying hazard ratio values of 0.60, 0.70, and 0.75 are provided in Table 8 for all randomized patients and the MRI-active subgroup.

Table 8 Operating Characteristics for Proposed Study Design for Possible True Underlying Hazard Ratio Values

	MRI-Active Subgroup	All Patients Randomized	All Patients Randomized
Expected number of events	134	355	355
Expected proportion of placebo patients with 9-HPT events at Week 120	44%	40%	40%
2-sided alpha for the log-rank test	0.04	0.0146	0.05
Power	*81.5%*	*82.1%*	*77.3%*
Detectable hazard ratio	0.60	0.70	0.75

9-HPT = 9-Hole Peg Test; MRI = magnetic resonance imaging.

Note: Operating characteristics are based on the following assumptions: event times are exponentially distributed, and patients are followed for 144 weeks.

It should be noted that the type I error rate to be used for the testing in all randomized patients will be adjusted depending of the proportion of events in the MRI-active subgroup (see Section 6.4.1.3 for control of type I error).

6.2 SUMMARIES OF CONDUCT OF STUDY

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

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, 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, for the MRI-active subgroup and all randomized patients as allocated.

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 Analysis

The primary analysis will compare the time from randomization to 20% increase from baseline in the 9-HPT time that is sustained for at least 12 weeks between ocrelizumab and placebo in all randomized patients and in the MRI-active subgroup. If at least one of the two co-primary analyses is statistically significant, then the trial is considered positive. Type I error will be controlled using a fallback and loop-back procedure (see Section 6.4.1.3).

There are two co-primary analyses:

- In all randomized patients
- In the MRI-active subgroup

The MRI-active subgroup is defined as patients with any T1 Gd lesion and/or new and/or enlarging T2 lesion during the screening period or at baseline.

The 9-HPT time is the reciprocal of the score for the 9-HPT as described in the MS functional composite guide (National Multiple Sclerosis Society 2001). The score for the 9-HPT is an average of the four trials (2 for the dominant hand and 2 for the non-dominant hand), calculated as follows: the two trials for each hand are averaged, converted to the reciprocals of the mean times for each hand, and then the two reciprocals are averaged. The most recent 9-HPT measured before first dose administration *(or randomization for non-treated patients)* will be considered baseline.

The p-value will be calculated from a log-rank test, stratified by the randomization stratification factors.

The hazard ratio will be estimated from a Cox regression, stratified by the randomization factors. In addition, a sensitivity analysis that adjusts for sex and continuous baseline 9-HPT will be performed to assess the impact of these prognostic factors.

The handling of intercurrent events and missing data is described in Section 6.4.1.1.

6.4.1.1 Estimands for the Primary Analysis

The primary analysis has two co-primary estimands (see ICH E9 [R1] addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials; EMA 2017).

Co-primary estimand 1 follows a combination of treatment-policy and hypothetical strategies and estimates the treatment effect in the MRI-active subgroup of ocrelizumab versus placebo, regardless of adherence to the randomized treatment had the patients not initiated another MS DMT or commercial ocrelizumab on the basis of the following attributes:

a) Population: The population will be MRI-active patients as allocated.

b) Variable: The variable will be time from randomization to 12-week sustained 20% increase from baseline in 9-HPT time. The 9-HPT time will be the reciprocal of the score for the 9-HPT as described in the MS functional composite guide (National Multiple Sclerosis Society 2001) and Section 6.4.1.

Time to 12-week sustained 20% increase from baseline in 9-HPT is defined as the time from randomization to the first disease progression, which is confirmed at the next regularly scheduled visit at least 12 weeks after the initial disease progression. Assessments occurring within 30 days after a protocol-defined relapse will not be used for confirmation of a 9-HPT disability progression. The non-confirmatory 9-HPT assessments (if any) should be at least equal to the minimum change required for progression. Disease progression is defined as a 20% increase of 9-HPT time from baseline.

c) Intercurrent events will be handled as follows:

- Withdrawal from treatment: Patient will be followed *for 144 weeks from randomization* regardless of adherence to study treatment or reason for withdrawal, and data will be collected and included in the analysis, following a treatment-policy strategy.
- Initiation of another MS *DMT* or commercial ocrelizumab *prior to or at Week 144 from randomization*: Future disease progression in the hypothetical scenario as if no other therapy had been initiated is predicted on the basis of previously observed data and the preceding reason for withdrawal from study treatment. The following strategies will be used:
  - If the patient withdraws from study treatment due to lack of efficacy, a disability progression event will be imputed at the time of initiation of another treatment.
  - Withdrawal from study treatment due to another reason will be:

    Imputed as a disability progression event if the patient had an initial increase of 20% in 9-HPT time at his or her last 9-HPT measurement prior to the initiation of another treatment

    Censored at the last 9-HPT measurement prior to the initiation of another treatment in all other cases
- Withdrawal from study (missing data) *prior to or at Week 144 from randomization*:
  - If the patient withdraws from study treatment due to lack of efficacy, a disability progression event will be imputed at the time of withdrawal from the study.
  - Withdrawal from study treatment due to another reason will be:

    Imputed as a disability progression event if the patient had an initial increase of 20% in 9-HPT time at his or her last 9-HPT measurement

    Censored at the last 9-HPT measurement in all other cases

- Patients without prior event at *Week 144 from randomization* will be censored at the date of the last 9-HPT assessment.
- The switch to PDP OCR has no impact on this efficacy endpoint because it can only occur after a confirmed disability progression in 9-HPT and EDSS (see Section 3.1.1.3). Patients who experience a DPE during the double-blind treatment phase will be given the option to switch to PDP OCR after they completed at least 120 weeks of double-blind treatment.

d) Population-level-summary estimator: The hazard ratio will be calculated from a Cox-regression to estimate the treatment-benefit, and the log-rank p-value will be used to test the statistical significance. Both will be stratified by the stratification factors from the randomization.

e) Handling of missing data:

f) Missing assessments at scheduled visits prior to the last 9-HPT assessment of a patient: intermediate missing data will not be replaced; progression detection or confirmation will be delayed to the next available 9-HPT assessment.

Sensitivity analyses for co-primary estimand 1:

- A tipping-point analysis will be performed to assess the impact of the assumptions for patients who had an initial progression just before initiation of another MS DMT or commercial ocrelizumab, or withdrawal from study. In this analysis, the impact of different disability progression probabilities between 0 and 100% by randomized treatment arm will be assessed.
- Sensitivity analysis will be performed where the observed profile of patients in the placebo group is used to impute time to event for patients experiencing censoring because of the following:
  - Initiation of another MS DMT or commercial ocrelizumab
  - Withdrawal from study (missing data)

Supplementary estimand applying treatment-policy strategy to withdrawal from study treatment and to initiation of other treatments:

This supplementary estimand will use a treatment-policy strategy to estimate the treatment effect of ocrelizumab versus placebo on upper extremity disability progression, on the basis of initial treatment, regardless whether patients adhered to randomized treatment or initiated other treatments (e.g., discontinued treatment or switched to another MS DMT or commercial ocrelizumab).

Supplementary estimand to estimate the treatment effect had the patient not withdrawn from study treatment:

The supplementary estimands will use a hypothetical strategy to estimate the treatment effect of ocrelizumab versus placebo on upper extremity disability progression had the patient not withdrawn from study treatment as follows:

- The same estimand as the primary analysis for the Oratorio study (WA25046):

If the patient withdraws from treatment, an event is imputed as if the patient had an initial increase of 20% in 9-HPT time at his or her last 9-HPT measurement prior to withdrawal from treatment and no follow-up data are available, otherwise the patient is censored at the last 9-HPT measurement prior to withdrawal from treatment in all other cases.

- Estimand counting withdrawal due to lack of efficacy as treatment failure:

  This estimand will estimate the treatment effect measured as time to disease progression or discontinuation from the randomized treatment due to lack of efficacy (composite endpoint). Same as the estimand above (Study WA25046); however, patients who withdrew from treatment due to lack of efficacy will also have an imputed event.

- Estimand counting withdrawal due to lack of efficacy or due to adverse events as treatment failure:

  This estimand will estimate the treatment effect measured as time to disease progression or discontinuation from the randomized treatment due to lack of efficacy or due to an adverse event (composite endpoint). Same as the estimand above (Study WA25046); however, patients who withdrew from treatment due to lack of efficacy or due to an adverse event will also have an imputed event.

Co-primary estimand 2 will be similar to the co-primary estimand 1 except the population will be for all randomized patients as allocated.

6.4.1.2 Estimands for the Secondary Endpoint of Time to Confirmed Disability Progression

The estimand for the secondary endpoint of 12-week CDP follows the same combination of treatment-policy and hypothetical strategies as for the primary endpoint but using the variable time to CDP. This will estimate the treatment effect of ocrelizumab versus placebo, regardless of adherence to the randomized treatment, had the patients not initiated another MS DMT or commercial ocrelizumab on the basis of the following attributes:

a) Population: The population will be all patients randomized as allocated.

b) Variable: The variable will be time to 12-week confirmed CDP.

   Time to CDP (12-week confirmation) is defined as the time from randomization to the first disease progression, which is confirmed at the next regularly scheduled visit at least 12 weeks after the initial disease progression. Disease progression is defined as an increase of ≥ 1.0 point from baseline EDSS score, if the baseline EDSS score is between 3.0 and 5.5 points (inclusive), or an increase of ≥ 0.5 point if the baseline EDSS score is > 5.5 points. The assessments within 30 days after a protocol-defined relapse will not be used for confirmation of a CDP. The non-confirmatory EDSS assessments (if any) between the initial and confirmation of disease progression should be at least as high as the minimum change required for progression.

c) Intercurrent events will be handled as below:

- Withdrawal from treatment: Patients will be followed *for 144 weeks from randomization* regardless of adherence to study treatment or reason for withdrawal, and data will be collected and included in the analysis, following a treatment-policy strategy.
- Initiation of another MS *DMT* or commercial ocrelizumab *prior to or at Week 144 from randomization*: Future disease progression in the hypothetical scenario as if no other therapy had been initiated is predicted on the basis of previously observed data and the preceding reason for withdrawal from study treatment. *The following strategies will be used:*
  - If the patient withdraws from study treatment due to lack of efficacy, a disability progression event will be imputed at the time of initiation of another treatment.
  - Withdrawal from study treatment due to another reason will be:

    Imputed as an event if the patient had an initial increase of EDSS at his or her last EDSS assessment prior to the initiation of another treatment

    Censored at the last EDSS assessment prior to the initiation of another treatment in all other cases
- Withdrawal from study (missing data) *prior to or at Week 144 from randomization*:
  - If the patient withdraws from study treatment due to lack of efficacy, a disability progression event will be imputed at the time of withdrawal from study.
  - Withdrawal from study treatment due to another reason will be:

    Imputed as an event if the patient had an initial increase of EDSS at his or her last EDSS assessment

    Censored at the last EDSS assessment in all other cases
- Patients still ongoing and without prior event at *Week 144 from randomization* will be censored at the date of the last EDSS assessment.
- The switch to PDP OCR has no impact on this efficacy endpoint because it can only occur after a confirmed disability progression in 9-HPT and EDSS (see Section *3.1.1.3*). Patients who experience a DPE during the double-blind treatment phase will be given the option to switch to PDP OCR after they completed at least 120 weeks of double-blind treatment.

d) Population-level-summary estimator: The hazard ratio will be calculated from a Cox-regression to estimate the treatment benefit, and log-rank p-value will be calculated to test the statistical significance. Both will be stratified by the stratification factors from the randomization.

e) Handling of missing data:

Missing assessments at scheduled visits prior to the last EDSS assessment of a patient: intermediate missing data will not be replaced; progression detection or confirmation will be delayed to next available EDSS assessment. The same

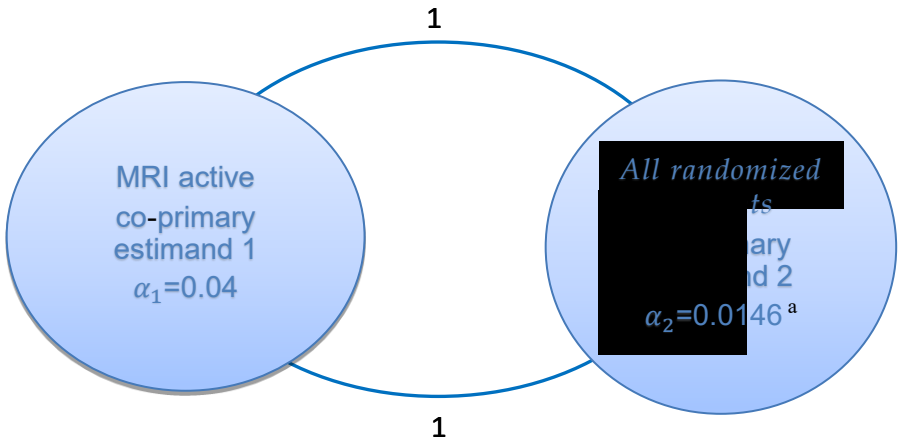
supplementary estimands applied to the primary endpoint will also be applied to the secondary endpoint of 12-week CDP.

6.4.1.3 Control of the Type I Error

The primary analysis will be performed after *the last randomized patient reaches the 144 weeks of double-blind treatment (+ 12 weeks to allow for the confirmation of the latest event).*

The type 1 error will be controlled for the co-primary estimands with a fallback and loopback procedure, with an alpha of 0.04 for the MRI-active subgroup. The alpha for the all randomized population will be calculated according to Spiessens-Debois method (2010), the final proportion of information in the MRI-active subgroup. For example, if 36% (*129* of *355*) of all events in *all randomized patients* have occurred in the MRI-active subgroup, the alpha for the all randomized population will be 0.0146 (see Figure 3).

Figure 3 Graphical Representation of the Control of the Type I Error



MRI = magnetic resonance imaging.

[a] The *a* level indicated for estimand 2 is an example assuming that 36% (*129* of *355*) of all events in *all randomized patients* have occurred in the MRI-active subgroup. The actual alpha level for the primary analysis will be determined based on the actually observed events based on the Spiessens-Debois method.

Calculation of α_1 and α_2 will be as follows:

α_1 is arbitrarily chosen as 0.04, to maximize the power of the analysis for the MRI-active subgroup.

α_2: calculated according to the Spiessens-Debois method (2010). For example of α_2 calculated assuming *129* events in MRI-active subgroup and *355* events in the ITT, α_2 = 0.0146. a_2 will be calculated at the primary analysis, with the proportion of information in the MRI-active subgroup.

Fallback: If the analysis of the co-primary estimand 1 has a p-value < 0.04, then the analysis for the co-primary estimand 2 will be tested with $\alpha = 0.05$.

Loop-back: If the analysis of the co-primary estimand 2 has a p-value < 0.0146, then the co-primary estimand 1 will be tested with $\alpha = 0.05$.

If at least one of the two co-primary estimands is statistically significant, then the trial is positive.

If only one of the co-primary estimands is positive, the secondary endpoints will be tested for *all randomized patients* and the MRI-active subgroup but the p-value will not be formally controlled.

If both co-primary estimands are statistically significant, then the secondary endpoints will be tested with $\alpha = 0.05$.

The secondary endpoints will be tested in a hierarchical gatekeeping procedure for *all randomized patients*, and as exploratory in the MRI-active subgroup.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy objective for this study is to evaluate the efficacy of ocrelizumab compared with placebo for all randomized patients on the basis of the following endpoints, in hierarchical order:

- Upper limb disability progression, defined as time to 20% increase from baseline in 9-HPT confirmed for at least 24 weeks
- Time to 12-week CDP in EDSS, defined as an increase in EDSS score that is confirmed for at least 12 weeks (an increase of ≥ 1.0 point from baseline EDSS score in patients with a baseline EDSS score ≤ 5.5 or an increase of ≥ 0.5 point in patients with a baseline EDSS score of > 5.5)
- Time to 24-week CDP in EDSS, defined as an increase in EDSS score that is confirmed for at least 24 weeks (an increase of ≥ 1.0 point from baseline EDSS score in patients with a baseline EDSS score ≤ 5.5 or an increase of ≥ 0.5 point in patients with a baseline EDSS score of > 5.5)
- Differences in the percent change in total volume of T2 lesions on MRI from baseline up to Week 120 will be analyzed using analysis of covariance and mixed effect model repeat measurement (MMRM) analyses
- Differences in the mean percentage change in total brain volume on MRI scans from Week 24 to Week 120 will be analyzed using an MMRM analysis

The estimand for the secondary endpoint of 12-week CDP in EDSS is described in Section 6.4.1.2.

6.4.3 Exploratory Efficacy Endpoints

The secondary efficacy endpoints will also be evaluated as exploratory analyses for the MRI-active subgroup.

An exploratory efficacy objective for this study is to evaluate the efficacy of ocrelizumab compared with placebo on the primary and secondary endpoints in the subgroup of patients ages >55 versus ≤ 55, patients with EDSS score ≤ 6.5 versus >6.5, *males and females (all randomized patients, MRI-active subgroup and MRI-inactive subgroup),* and in the MRI-inactive subgroup *versus MRI-active subgroup*. Because the above subgroups of patients ages >55 and with EDSS score >6.5 were not enrolled in the previous PPMS study (WA25046), there is a special interest in analyzing these subgroups. An MRI-active subgroup is a co-primary endpoint; therefore, the complementary MRI-inactive subgroup will also be analyzed.

Other exploratory analyses for *all randomized patients* and MRI-active subgroup are on the basis of the following endpoints:

- Proportion of patients free of disability progression on upper limbs by 9-HPT at Week 120 and at time of clinical cutoff of primary analysis
- Change from baseline to Week 120 in fatigue as measured by MFIS
- Change from baseline to Week 120 and from Week 24 to Week 120 in cervical spinal cord volume on MRI scans
- Change from baseline to Week 120 in ABILHAND
- Change from baseline to Week 120 in the upper limb domain of a life quality measure for patients with neurological disorders (Neuro-QoL-UE)
- Change from baseline to Week 120 in the PGIC-UL function
- Change from baseline to Week 120 in the PGIC-F
- Change from baseline to Week 120 in the MSIS-29 physical score
- Proportion of patients at Week 120 with a pre-specified, clinically meaningful decline on the MSIS-29
- Change from baseline to Week 120 in the SDMT
- Rate of decline in fine motor skills of upper extremities and manual/finger dexterity as measured by smartphone-based digital outcome assessment (Floodlight RPM)
- The number of Gd-enhancing T1 lesions and number of new or enlarging T2 hyperintense lesions as detected by mandatory MRI
- The change from baseline in total non-enhancing T1 lesion volume on MRI scan of the brain.

6.5 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received at least one infusion (partial or complete) of study drug (ocrelizumab or placebo), with patients grouped according to treatment received

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.

The main safety objective for this study is to evaluate the safety of ocrelizumab compared with placebo until when patients receive any PDP OCR, commercial ocrelizumab treatment, or other *MS DMT* in all patients who receive at least one infusion (partial or complete) of study drug (ocrelizumab or placebo).

The safety endpoints considered are as follows:

- Adverse events leading to study treatment withdrawal
- Adverse events in patients previously treated with an *another DMT for MS*
- Proportion of patients with adverse events and serious adverse events
- Incidence rates per 100 PY for infections, serious infections, death, and malignancies, including breast cancer
- *Vital signs (blood pressure and pulse rate) during and 1 hour after infusion*
- Change from baseline in laboratory test results for hematology and chemistry
- Change from baseline in laboratory test results for immunoglobulins (IgA, IgM, IgG) and T-cell subtype (CD3, CD4, CD8): MMRM analyses will be performed. Fixed effects in the model will include treatment arm, visit, treatment by visit interaction, stratification factors, baseline value of the immunoglobulin or T-cell, and baseline by visit interaction. Visits will be treated as a repeated variable within a patient. Patient, treatment, and visit will be treated as factor variables. An unstructured variance-covariance structure will be applied to model the within-patient errors. Appropriate variance stabilizing transformations of the laboratory measurements (e.g., log-transformation) may be applied.
- Association of decrease in each immunoglobulin (IgA, IgM, IgG) and serious infections: incidence rate of serious infections per 100 PY during the episodes of confirmed drop of immunoglobulin levels below LLN versus the incidence rate of serious infections per 100 PY in the remaining exposure (before or after a confirmed drop, and during the overall exposure for the patients without any confirmed drop of immunoglobulin) for each treatment arm. The exposure of a confirmed episode is counted from the day the immunoglobulin first decreased below LLN until the day it is normalized above LLN, and the serious infections with onset date in between are counted. The 95% confidence interval will be calculated using Poisson distribution methods.
- Association of decrease in each T-cell subtype (CD3, CD4, CD8) and serious infections will be analyzed as for the immunoglobulin described above.

Additional safety objectives for this study will include evaluation of the following:

- Subgroup analyses: patients with MRI-active versus MRI-inactive, patients aged ≤ 55 versus > 55 years, patients with a baseline EDSS score of ≤ 6.5 versus > 6.5, females and males, and patients previously treated (prior to randomization) with $another\ DMT\ for\ MS$
- Incidence rates per 100 PY for infections, serious infections, death, and malignancies, including breast cancer
- Pharmacodynamics, as measured by B-cell levels in blood

The ocrelizumab pool for long-term safety analysis will consist of all randomized patients who received at least one infusion (partial or complete) of ocrelizumab (study drug, PDP OCR, or commercial ocrelizumab) until when patients receive any other $MS\ DMT$ as follows:

- Adverse events leading to withdrawal of ocrelizumab treatment
- Adverse events in patients previously treated with $another\ DMT\ for\ MS$
- Proportion of patients with adverse events and serious adverse events
- Incidence rates per 100 PY for infections, serious infections, death, and malignancies, including breast cancer
- Change from first administration of ocrelizumab in laboratory test results for hematology and chemistry
- Change from first dose of ocrelizumab in immunoglobulins (IgA, IgM, IgG) and T-cell subtype (CD3, CD4, CD8)
- Associations of decrease in each immunoglobulin (IgA, IgM, IgG) and serious infections
- Associations of decrease in each T-cell subtype (CD3, CD4, CD8) and serious infections

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

6.6 PHARMACOKINETIC ANALYSES

PK analysis of ocrelizumab serum concentration versus time data will be conducted using a population PK approach. Nonlinear mixed effects modeling (with software NONMEM) will be used to analyze the sparse sampling dose-concentration-time data of ocrelizumab. 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 that would interfere with PK evaluation. The PK data of this study may be pooled with data from other studies. Population PK parameters (e.g., clearances and volumes) will be estimated and the influence of covariates, such as sex, body weight, and baseline CD19 lymphocytes, on these parameters will be investigated. Exposure (area under the concentration–time

curve) to ocrelizumab will be estimated. The selection of other parameters will depend on the final PK model used for this analysis. Additional PK analyses will be conducted as appropriate.

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 will be analyzed and reported via descriptive statistics.

6.8 BIOMARKER ANALYSES

Biomarkers will be assessed at baseline and subsequent timepoints following administration of ocrelizumab. Pharmacodynamic biomarkers will be presented as absolute value over time and/or percent change relative to baseline over time *and/or proportion of participants with biomarker levels within a defined threshold 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.

NfL analysis: High versus low NfL subgroups will be defined using 1) baseline median of all randomized patients, and 2) two fixed thresholds based on the current assay technology (Quanterix Simoa) for serum NfL (a =8.0 pg/mL, b =10.6 pg/mL) or plasma NfL (a =7.5 pg/mL, b =9.8 pg/mL), or equivalent thresholds to be determined and pre-specified based on future available clinical NfL assay(s). NfL levels (actual value and percentage change from baseline) at each visit up to time of clinical cutoff of primary analysis will be assessed.

NfL treatment response will be presented as absolute values over time, percent change relative to baseline over time, and/or proportion of participants with NfL levels below the defined thresholds defined over time.

The prognostic or predictive relationship between baseline NfL and the study primary endpoint (20% worsening from baseline in 9-HPT confirmed for at least 12 weeks) and key secondary endpoints (20% worsening from baseline in 9-HPT confirmed for at least 24 weeks, 12-week CDP on EDSS, and 24-week CDP on EDSS) will be analyzed using cox-proportional hazards model using the subgroup variable as a covariate within each treatment arm, and in the combined arms (allowing for the effect of NfL subgroup to vary across treatment arms). This univariate model is compared to a model adjusted for the following covariates: age, sex, body mass index, region (United States vs. rest of world) and baseline clinical measure corresponding to the outcome (9-HPT or EDSS).

The prognostic relationship between on-treatment NfL (measured at Weeks 24 or 48) and subsequent disability progression on the same clinical outcomes listed above (re-baselined from the time of NfL measurement) will be analyzed within each treatment arm using cox-proportional hazards model using the NfL subgroup variable as a covariate.

6.9 INTERIM ANALYSIS

6.9.1 Planned Interim Analysis

There is no planned interim analysis.

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, central imaging, electronic PRO, and IxRS data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

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

PRO data will be collected 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 PATIENTREPORTED OUTCOME DATA

Patients will use an electronic device to capture PRO data. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

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

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

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, PROs, 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 at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

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

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

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

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

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, unless permitted or required by law.

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

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

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

Study data, which may include data on germline mutations, 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.

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 prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits 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 will provide clinical operations management, data management, and medical monitoring.

At least 220 sites globally are estimated to participate to enroll approximately 1000 patients, of which at least 350 patients are planned to be in the MRI-active subgroup. 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.

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.

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 external Steering Committee will stay blinded to all data until the primary analysis.

9.6 PUBLICATION 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 provided upon request.* For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

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

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

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

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

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

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

9.7 PROTOCOL AMENDMENTS

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

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

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Appendix 1
Schedule of Activities: Double-Blind Treatment

	Screen.	Double-Blind Treatment											Delayed Dosing Visit[a]	Unschd. Visit[b]	Tx Discon. Visit[c]
Dose		1			2		3		4		N[d]				
Visit	1	2	3	4	5	6	7	8	9	10	n	N			
Study week		0	2	12	24	36	48	60	72	84	n	n + 12 wks			
(Window in days)	–168 to –1		±2	±7	±5	±7	±5	±7	±5	±7	±5	±7			
Informed consent[e]	x														
Review of eligibility criteria	x	x													
Demographic data	x														
Medical history and baseline conditions	x														
PROs (ABILHAND, Neuro-QoL-UE, MFIS, MSIS-29)[f]	x	x			x		x		x		x				x
PGIC-F, PGIC-UL[f]					x		x		x		x				x
EQ-5D-5L[f]		x			x		x		x		x				x
Vital signs[g]	x	x	x	x	x		x		x		x		x		
Weight, height		x													
Physical examination[h]	x	x			x		x		x		x		x		x
Neurological examination[i]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
9-HPT[j]	x	x		x	x	x	x	x	x	x	x	x		x	x
EDSS[k]	x	x		x	x	x	x	x	x	x	x	x		x	x
SDMT		x			x		x		x		x				x
Hematology, chemistry, urinalysis[l]	x	x		x	x	x	x	x	x	x	x	x			x
Flow cytometry (including CD3/4/8/19 count)[m]	x	x	x		x		x		x		x		x		x

Appendix 1: Schedule of Activities: Double-Blind Treatment (cont.)

	Screen.	Double-Blind Treatment											Delayed Dosing Visit[a]	Unschd. Visit[b]	Tx Discon. Visit[c]
Dose		1			2		3		4		N[d]				
Visit	1	2	3	4	5	6	7	8	9	10	n	N			
Study week		0	2	12	24	36	48	60	72	84	n	n + 12 wks			
(Window in days)	–168 to –1		±2	±7	±5	±7	±5	±7	±5	±7	±5	±7			
CD4				x		x		x		x		x			
IgG, IgA, IgM	x	x		x		x		x		x		x			x
CSF sample (if required; Week 48 optional)[n]	x						x[n]								
Pregnancy test (if applicable)[o]	x	x	x		x		x		x		x		x		
FSH level (if applicable)[p]	x														
Review of re-treatment criteria			x		x		x		x		x		x		
Pretreatment with IV methylprednisolone and antihistaminic[q]		x	x		x		x		x		x		x		
Administration (infusion) of ocrelizumab/placebo[r]		x	x		x		x		x		x		x		
Concomitant medications[s]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events[t]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Mandatory MRI[u]	x				x		x		x		(x)				x
Optional additional cervical spinal cord MRI[u]	x				x										x
ADA sample (serum)[v]		x			x		x		x		x				x
PK sample (serum)[w]		x	x	x	x		x	x	x		x				x
Biomarker plasma and serum samples[x]		x	x	x	x		x		x		x				x
DNA genotyping sample[y]		x													

Appendix 1: Schedule of Activities: Double-Blind Treatment (cont.)

	Screen.	Double-Blind Treatment											Delayed Dosing Visit[a]	Unschd. Visit[b]	Tx Discon. Visit[c]
Dose		1			2		3		4		N[d]				
Visit	1	2	3	4	5	6	7	8	9	10	n	N			
Study week		0	2	12	24	36	48	60	72	84	n	n + 12 wks			
(Window in days)	–168 to –1		±2	±7	±5	±7	±5	±7	±5	±7	±5	±7			
RBR RNA and RBR plasma samples (optional)[z]		x	x	x	x		x		x		x	x			
RBR DNA sample (optional)[z]		x													
Digital outcome assessments (Floodlight RPM) (optional)[aa]	x	x	– – –	– – –	– – –	– – –	– – –	– – –	– – –	– – –	– – –	– – –	– – –	– – –	– – – ▶
Hepatitis B screening[bb]	x														
Hepatitis B virus DNA[bb] (if required)				x	x	x	x	x	x	x	x	x			x

9-HPT = 9-Hole Peg Test; ADA = anti-drug antibody; CSF = cerebrospinal fluid; Discon. = discontinuation; EC = Ethics Committee; eCRF = electronic Case Report Form; EDSS = Expanded Disability Status Scale; FSH = follicle-stimulating hormone; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; IRB = Institutional Review Board; MFIS = Modified Fatigue Impact Scale; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSIS-29 = Multiple Sclerosis Impact Scale–29; Neuro-QoL-UE = Quality of Life in Neurological Disorders-Upper Extremity Function; PDP OCR = post–double-progression ocrelizumab; PGIC-F = Patient Global Impression of Change for Fatigue; PGIC-UL = Patient Global Impression of Change for Upper Limb Function; PK = pharmacokinetic; PML = progressive multifocal leukoencephalopathy; PRO = patient-reported outcome; RBR = Research Biosample Repository; RPM = remote patient monitoring; Screen. = screening; SDMT = Symbol Digit Modalities Test; Tx = treatment; Unschd. = unscheduled; WGS = whole genome sequencing; (x) = every 48 weeks.

Note: All assessments should be performed on the day of the scheduled visit, unless otherwise specified. On infusion days, all assessments should be performed prior to dosing, unless otherwise specified. For more information regarding the double-blind treatment phase, see Section 3.1.1.2. See Figure 2 for information regarding how a patient proceeds through the different study phases.

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

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

[c] Patients who discontinue study drug prematurely from the double-blind treatment phase will return to the clinic for a treatment discontinuation visit.

Appendix 1: Schedule of Activities: Double-Blind Treatment (cont.)

[d] The assessments required for N represent the typical schedule of assessments for the double-blind treatment phase *with Week 144 being the last visit*. If the study ends for any reason or the patient must be withdrawn from treatment, a treatment discontinuation visit should be performed.

[e] Must be obtained and documented in written form before any study-specific screening procedure and initiation of study treatment and PDP OCR (if applicable).

[f] Questionnaires will be self-administered prior to the administration of study treatment. The questionnaires should be completed before the patient receives any information on disease status, prior to the administration of non-PRO assessments, and in the following order each time, whenever possible: ABILHAND, Neuro-QoL-UE, PGIC-UL, MFIS, PGIC-F, MSIS-29, and EQ-5D-5L. Questionnaires will be completed every 6 months during the double-blind treatment phase. EQ-5D-5L will not be completed at screening. PGIC-UL and PGIC-F will not be completed at screening and baseline.

[g] Includes pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Temperature should be measured and recorded in patient's notes only. Blood pressure and pulse rate will be recorded on the appropriate eCRF. On ocrelizumab (or placebo) infusion visits, vital signs should be taken within 45 minutes prior to the methylprednisolone infusion. In addition, blood pressure and pulse rate should be obtained prior to start of infusion, every hour during the infusion, at the end of infusion and 1 hour after the end of the infusion. On non-infusion days, the vital signs may be taken at any time during the visit. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF page. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

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

[i] Neurological examinations will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Potential relapses should be recorded throughout the treatment period. All patients with new neurological symptoms suggestive of MS worsening should have EDSS assessment performed by Examining Investigator. Investigators will also screen patients for signs and symptoms of PML by evaluating neurological deficits localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, hemiparesis, cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination). Patients with suspected PML should be withheld from ocrelizumab treatment until PML is ruled out by complete clinical evaluation and appropriate diagnostic testing. A patient with confirmed PML should be withdrawn from the study treatment permanently.

[j] Both the dominant and non-dominant hands are tested twice (two consecutive trials of the dominant hand, followed immediately by two consecutive trials of the non-dominant hand) (National Multiple Sclerosis Society 2001).

[k] EDSS including functional system scores will be assessed and collected.

Appendix 1: Schedule of Activities: Double-Blind Treatment (cont.)

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

[m] B cells and other cell types and/or B-cell subsets will be assessed in fresh whole blood using flow cytometry.

[n] CSF sample will only be required at screening for patients who do not have documented history of elevated IgG index and/or one or more IgG oligoclonal bands detected by isoelectric focusing. The CSF specimen will be sent out to the central laboratory to verify presence of elevated IgG index and IgG oligoclonal bands. Leftover CSF will be stored by the central laboratory for biomarker use. Patients for whom screening CSF was collected will have the option to participate in a collection of CSF at Week 48. The CSF sample should be collected prior to the ocrelizumab (or placebo) infusion at Week 48 (within a window of 14 days prior to the actual scheduled visit Week 48). This sample will be used for exploratory biomarker determination.

[o] All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, the patient will not receive the scheduled dose, and a confirmatory serum pregnancy test will be performed. Urine β-hCG (sensitivity of at least 25 mU/mL) will be performed locally.

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

[q] Patients will receive prophylactic treatment with 100 mg of methylprednisolone IV and an oral or IV antihistamine (e.g., IV diphenhydramine 50 mg or an equivalent dose of an alternative) prior to infusion of ocrelizumab. The methylprednisolone administration is to be completed approximately 30 minutes before the start of each ocrelizumab (or placebo) infusion; antihistamines should be administered 30–60 minutes prior to the start of an infusion. In the rare case when the use of methylprednisolone is contraindicated for the patient, use of an equivalent dose of an alternative steroid should be used as premedication prior to the infusion. It is also recommended that patients receive an analgesic/antipyretic such as acetaminophen/paracetamol (1 g) 30–60 minutes prior to ocrelizumab (or placebo) infusion.

[r] The investigator must review the clinical and laboratory re-treatment criteria prior to subsequent infusion of ocrelizumab. The patient will need to remain under observation at the clinical site for at least 1 hour after infusion. At infusion visits, it is anticipated that the patient will need to stay at the hospital or clinical site for a full day.

[s] 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.

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

Appendix 1: Schedule of Activities: Double-Blind Treatment (cont.)

[u] At screening, two mandatory MRI scans will be performed at least 6 weeks apart or one mandatory MRI that can be compared with a historical MRI performed in the previous 1 year to be used for eligibility determination. The mandatory MRI performed closer to randomization will be considered the baseline MRI for the study analyses and should be obtained from 6 weeks up to 10 days prior to randomization. During the study conduct, mandatory MRI scans should occur within ± 4 weeks of the scheduled visit. In addition, mandatory MRI scans will be obtained in patients who withdraw from study treatment (at treatment discontinuation visit) if one was not performed during the prior 4 weeks. From Week 72 onward, mandatory MRI scans will be performed every 48 weeks. The mandatory MRI sequences are comprised of both brain and upper cervical spinal sequences if site technology is available. Cervical spinal sequences are not required for the first mandatory MRI at screening MRI nor are expected to be included in a historical MRI used for screening (if applicable), but these sequences should be included in second mandatory MRI scan (considered the baseline MRI). Additional optional, cervical spinal cord MRI sequences may be acquired for baseline, Weeks 24 and 120, and at treatment discontinuation. Additional optional MRI sequences are not required to accompany the first mandatory MRI at screening MRI, nor are expected to be included in a historical MRI used at screening (if applicable), but these sequences should be included in the second mandatory MRI (considered the baseline MRI) scan. *At the Week 120 visit for patients switching to PDP OCR treatment, mandatory MRI scans should be obtained within 4 weeks before the Week 120 visit.*

[v] Serum sample, to be taken prior to the IV methylprednisolone infusion.

[w] On study drug infusion days, two serum samples (one prior to the IV methylprednisolone infusion and one within 30 minutes after completion of study drug infusion) will be collected. On visits without study drug infusion, PK sample may be collected at any time. At study drug infusion visits, PK samples will be collected from the arm opposite to the infusion.

[x] Plasma and serum samples will be collected before the initial study drug dose at Visit 2 as well as Visits 3, 4, and 5; and every 6 months following for biomarkers during double-blind treatment, as indicated.

[y] A single mandatory DNA sample will be collected for patient genotyping at the baseline visit. If the DNA sample is not collected at the baseline visit, it may be collected at any subsequent visit. Collection and submission of this sample is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS sampling (see Section 4.5.13), collection of this sample will not be applicable at that site.

[z] These sample types to be collected for research purposes if patient agrees to separate optional RBR consent—a single RBR DNA sample at baseline visit (or any subsequent visit if missed), and an RBR RNA and a RBR plasma sample collected at all indicated visits.

[aa] Digital outcome assessments are optional only. Patients who choose to and consent to the optional digital outcome assessments at screening will be asked to begin performing digital assessments 4 weeks prior to baseline (i.e., Days –28 to 1; see Section 4.5.15).

[bb] All patients must have negative HBsAg test result at screening prior to enrollment. If total HBcAb is positive at screening, HB virus DNA measured by PCR must be negative to be eligible. For those patients enrolled with negative HBsAg and positive total HBcAb, HB virus DNA (PCR) must be repeated every 12 weeks during double-blind treatment phase.

Appendix 2
Schedule of Activities: Follow-Up 1 (and PDP OCR)

	FU1 [a]						Delayed Dosing Visit [b]	Unschd. Visit [c]	Tx Discon. Visit [d]	EOO or WD from FU
	Follow-up	PDP OCR								
Dose	Visits every 12 wk (± 7 d)	1			N [e]					
Visit		1	2	3	n	n				
Study week		0	2	12	n	n+ 12wk				
(Window in days)			±2	±7	±5	±7				
Informed consent [f]		x								
PROs (ABILHAND, Neuro-QoL-UE, MFIS, MSIS-29) (every 48 weeks) [g]	(x)	x			(x)				x	
PGIC-F, PGIC-UL (every 48 weeks) [g]	(x)	x			(x)				x	
EQ-5D-5L (every 48 weeks) [g]		x			(x)				x	
Vital signs [h]		x	x	x	x		x			
Physical examination [i]	x	x			x		x		x	x
Neurological examination [j]	x	x	x	x	x	x	x	x	x	x
9-HPT [k]	x	x		x	x	x		x	x	x
EDSS [l]	x	x		x	x	x		x	x	x
SDMT	x	x			x			x	x	x
Hematology, chemistry, urinalysis [m]	x	x		x	x	x			x	x
Flow cytometry (including CD3/4/8/19 count) [n]	x	x	x		x		x		x	x
CD4				x		x				
IgG, IgA, IgM	x	x		x		x			x	
Pregnancy test (if applicable) [o]		x	x		x		x			
Review of re-treatment criteria		x	x		x		x			
Pretreatment with IV methylprednisolone and antihistaminic [p]		x	x		x		x			
Administration (infusion) of ocrelizumab [q]		x	x		x		x			

Appendix 2: Schedule of Activities: Follow-Up 1 (and PDP OCR) (cont.)

	FU1 [a]						Delayed Dosing Visit [b]	Unschd. Visit [c]	Tx Discon. Visit [d]	EOO or WD from FU
	Follow-up	PDP OCR								
Dose	Visits every 12 wk (± 7 d)	1			N [e]					
Visit		1	2	3	n	n				
Study week		0	2	12	n	n+ 12wk				
(Window in days)			±2	±7	±5	±7				
Concomitant medications [r]	x	x	x	x	x	x	x	x	x	x
Adverse events [s]	x	x	x	x	x	x	x	x	x	x
Mandatory MRI (every 48 weeks) [t]	(x)	(x)			(x)				x	x
ADA sample (serum) [u]	x	x			x				x	
PK sample (serum) [v]	x	x	x	x	x				x	
Biomarker plasma and serum samples [w]		x	x	x	x					x
RBR RNA and RBR plasma samples (optional) [x]		x	x	x	x					x
Digital outcome assessments (Floodlight RPM) (optional) [y]	x	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - - →
Hepatitis B virus DNA [z] (if required)	x	x		x	x	x			x	x

9-HPT = 9-Hole Peg Test; ADA = anti-drug antibody; Discon. = discontinuation; eCRF = electronic Case Report Form; EDSS = Expanded Disability Status Scale; EOO = end of observation; FU = follow up; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; MFIS = Modified Fatigue Impact Scale; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSIS-29 = Multiple Sclerosis Impact Scale–29; Neuro-QoL-UE = Quality of Life in Neurological Disorders-Upper Extremity Function; OLE = open-label extension; PDP OCR = post–double-progression ocrelizumab; PGIC-F = Patient Global Impression of Change for Fatigue; PGIC-UL = Patient Global Impression of Change for Upper Limb Function; PK = pharmacokinetic; PML = progressive multifocal leukoencephalopathy; PRO = patient-reported outcome; RBR = Research Biosample Repository; SDMT = Symbol Digit Modalities Test; Tx = treatment; Unschd. = unscheduled; WD = withdrawal; Wk = week; (x) = every 48 weeks.

Note: All assessments should be performed on the day of the scheduled visit, unless otherwise specified. On infusion days, all assessments should be performed prior to dosing, unless otherwise specified. For more information regarding eligibility for and duration of PDP OCR and FU1, see Sections *3.1.1.3* and 3.1.1.4, respectively. See Figure 2 for information regarding how a patient proceeds through the different study phases (including FU1 and PDP OCR).

Appendix 2: Schedule of Activities: Follow-Up 1 (and PDP OCR) (cont.)

[a] The FU1 phase will run in parallel *with* the double-blind treatment phase until *144 weeks from randomization for each patient* . Scheduled visits will be performed every 12 weeks and will include both efficacy and safety assessments. For patients receiving PDP OCR, patients must sign the optional PDP OCR informed consent *form*. Patients who experience a double-progression event during the double-blind treatment phase will be given the option to switch to PDP OCR after they have completed at least 120 weeks of double-blind treatment. *PDP OCR treatment phase will continue until the end of the OLE phase.* Assessments in FU1 *and PDP OCR* phases that only need to be performed annually are marked in brackets (x).

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

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

[d] Patients who discontinue study drug prematurely from the PDP OCR treatment phase will return to the clinic for a treatment discontinuation visit.

[e] The PDP OCR can be terminated at any time up to the date at which the last data point is collected for the primary analysis (see Section *3.1.1.3*). The assessments required for N represent the typical schedule of assessments for the PDP OCR phase. If the study ends for any reason or the patient must be withdrawn from treatment, a treatment discontinuation visit should be performed.

[f] Must be obtained and documented in written form before any study-specific screening procedure and initiation of study treatment and PDP OCR (if applicable).

[g] Questionnaires will be self-administered prior to the administration of study treatment. The questionnaires should be completed before the patient receives any information on disease status, prior to the administration of non-PRO assessments, and in the following order each time, whenever possible: ABILHAND, Neuro-QoL-UE, PGIC-UL, MFIS, PGIC-F, MSIS-29, and EQ-5D-5L. During FU1 and PDP OCR they will be completed every 48 weeks, starting Week 0 of FU1. EQ-5D-5L will only be completed during PDP OCR.

[h] Includes pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Temperature should be measured and recorded in patient's notes only. Blood pressure and pulse rate will be recorded on the appropriate eCRF. On ocrelizumab infusion visits, vital signs should be taken within 45 minutes prior to the methylprednisolone infusion. In addition, blood pressure and pulse rate should be obtained prior to start of infusion, every hour during the infusion, at the end of infusion and 1 hour after the end of the infusion. On non-infusion days, the vital signs may be taken at any time during the visit. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF page. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

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

Appendix 2: Schedule of Activities: Follow-Up 1 (and PDP OCR) (cont.)

[j] Neurological examinations will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Potential relapses should be recorded throughout the treatment period. All patients with new neurological symptoms suggestive of MS worsening should have EDSS assessment performed by Examining Investigator. Investigators will also screen patients for signs and symptoms of PML by evaluating neurological deficits localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, hemiparesis, cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination). Patients with suspected PML should be withheld from ocrelizumab treatment until PML is ruled out by complete clinical evaluation and appropriate diagnostic testing. A patient with confirmed PML should be withdrawn from the study treatment permanently.

[k] Both the dominant and non-dominant hands are tested twice (two consecutive trials of the dominant hand, followed immediately by two consecutive trials of the non-dominant hand) (National Multiple Sclerosis Society 2001).

[l] EDSS including functional system scores will be assessed and collected.

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

[n] B cells and other cell types and/or B-cell subsets will be assessed in fresh whole blood using flow cytometry.

[o] Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, the patient will not receive the scheduled dose, and a confirmatory serum pregnancy test will be performed. Urine β-hCG (sensitivity of at least 25 mU/mL) will be performed locally.

[p] Patients will receive prophylactic treatment with 100 mg of methylprednisolone IV and an oral or IV antihistamine (e.g., IV diphenhydramine 50 mg or an equivalent dose of an alternative) prior to infusion of ocrelizumab. The methylprednisolone administration is to be completed approximately 30 minutes before the start of each ocrelizumab infusion; antihistamines should be administered 30–60 minutes prior to the start of an infusion. In the rare case when the use of methylprednisolone is contraindicated for the patient, use of an equivalent dose of an alternative steroid should be used as premedication prior to the infusion. It is also recommended that patients receive an analgesic/antipyretic such as acetaminophen/paracetamol (1 g) 30–60 minutes prior to ocrelizumab (or placebo) infusion.

[q] The investigator must review the clinical and laboratory re-treatment criteria prior to subsequent infusion of ocrelizumab. The patient will need to remain under observation at the clinical site for at least 1 hour after infusion. At infusion visits, it is anticipated that the patient will need to stay at the hospital or clinical site for a full day.

[r] 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.

Appendix 2: Schedule of Activities: Follow-Up 1 (and PDP OCR) (cont.)

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

[t] During the study conduct, mandatory MRI scans should occur within ± 4 weeks of the scheduled visit and will be performed every 48 weeks. In addition, mandatory MRI scans will be obtained in patients who withdraw from study treatment (at Tx Discon, WD from FU or EOO visit) if one was not performed during the prior 4 weeks.

[u] Serum sample, to be taken prior to the IV methylprednisolone infusion.

[v] On study drug infusion days, two serum samples (one prior to the IV methylprednisolone infusion and one within 30 minutes after completion of study drug infusion) will be collected. On visits without study drug infusion, PK sample may be collected at any time. At study drug infusion visits, PK samples will be collected from the arm opposite to the infusion.

[w] Plasma and serum samples will be collected as indicated. Only to be collected for WD from FU visits performed before start of OLE.

[x] These sample types to be collected for research purposes if patient agrees to separate optional RBR consent—a single RBR DNA sample at baseline visit (or any subsequent visit if missed), and an RBR RNA and a RBR plasma sample collected at all indicated visits. Only to be collected for WD from FU visits performed before start of OLE.

[y] Digital outcome assessments are optional only.

[z] For those patients enrolled with negative HBsAg and positive total HBcAb, HB virus DNA (PCR) must be repeated every 12 weeks during FU1 and PDP OCR.

Appendix 3
Schedule of Activities: Open-Label Extension

	OLE Screening	OLE									Delayed Dosing Visit [a]	Unschd. Visit [b]	Tx Discon. Visit [c]
Dose		1			2		3		N [d]				
Visit		1	(2)	3	4	5	6	7	n	n			
Study week		Wk 0	Wk 2	Wk 22	Wk 24	Wk 46	Wk 48	Wk 70	n	$n + 22$ wk			
(Window in days)	–30 to –1		(±2)	(±7)	(±5)	(±7)	(±5)	(±7)	(±5)	(±7)			
Informed consent [e]	x												
Review of eligibility criteria	x												
PROs (ABILHAND, Neuro-QoL-UE, PGIC-UL, MFIS, PGIC-F, MSIS-29, EQ-5D-5L) [f]		x					x		x				x
Vital signs [g]		x	x		x		x		x		x		
Physical examination [h]		x			x		x		x		x		x
Neurological examination [i]		x	x	x	x	x	x	x	x	x	x	x	x
9-HPT [j]		x			x		x		x			x	x
EDSS [k]		x			x		x		x			x	x
SDMT		x			x		x		x				x
Hematology, chemistry, urinalysis [l]	x	x		x		x		x		x			x
Flow cytometry (including CD3/4/8/19 count) [m]		x		x		x		x		x	x		x
CD4	x			x		x		x		x			
IgG, IgA, IgM	x			x		x		x		x			x
Pregnancy test (if applicable) [n]	x	x	x		x		x		x		x		
Review of re-treatment criteria		x	x		x		x		x		x		
Pretreatment with IV methylprednisolone and antihistaminic [o]		x	x		x		x		x		x		

Appendix 3: Schedule of Activities: Open-Label Extension (cont.)

	OLE Screening	OLE									Delayed Dosing Visit [a]	Unschd. Visit [b]	Tx Discon. Visit [c]
Dose		1			2		3		N [d]				
Visit		1	(2)	3	4	5	6	7	n	n			
Study week		Wk 0	Wk 2	Wk 22	Wk 24	Wk 46	Wk 48	Wk 70	n	$n + 22$ wk			
(Window in days)	–30 to –1		(±2)	(±7)	(±5)	(±7)	(±5)	(±7)	(±5)	(±7)			
Administration (infusion) of ocrelizumab [p]		x	x		x		x		x		x		
Concomitant medications [q]	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [r]	x	x	x	x	x	x	x	x	x	x	x	x	x
Mandatory MRI (every 48 weeks) [s]		(x)			(x)		(x)		(x)				x
Additional optional cervical spinal cord MRI (every 48 weeks) [s]		x					x		(x)				x
ADA sample (serum) [t]		x					x		x				x
PK sample (serum) [u]		x					x		x				x
Hepatitis B virus DNA (if required) [v]	x	x		x		x		x		x			x

9-HPT = 9-Hole Peg Test; ADA = anti-drug antibody; Discon. = discontinuation; eCRF = electronic Case Report Form; EDSS = Expanded Disability Status Scale; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; MFIS = Modified Fatigue Impact Scale; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSIS-29 = Multiple Sclerosis Impact Scale–29; Neuro-QoL-UE = Quality of Life in Neurological Disorders-Upper Extremity Function; OLE = open-label extension; PGIC-F = Patient Global Impression of Change for Fatigue; PGIC-UL = Patient Global Impression of Change for Upper Limb Function; PK = pharmacokinetic; PML = progressive multifocal leukoencephalopathy; PRO = patient-reported outcome; SDMT = Symbol Digit Modalities Test; Tx = treatment; Unschd. = unscheduled; Wk = week; (x) = every 48 weeks.

Notes: All assessments should be performed on the day of the scheduled visit, unless otherwise specified. On infusion days, all assessments should be performed prior to dosing, unless otherwise specified. For more information regarding eligibility for and duration of the OLE, see Section 3.1.1.5. See Figure 2 for information regarding how a patient proceeds through the different study phases (including OLE).

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

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

[c] Patients who discontinue study drug prematurely will return to the clinic for a treatment discontinuation visit.

Appendix 3: Schedule of Activities: Open-Label Extension (cont.)

[d] *Patients will remain in the OLE phase for at least 2 years (at least 4 doses of ocrelizumab) for each patient. The assessments required for N represent the typical schedule of assessments for the OLE phase. If the study ends for any reason or the patient must be withdrawn from treatment, a treatment discontinuation visit should be performed.*

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

[f] Questionnaires will be self-administered prior to the administration of study treatment. The questionnaires should be completed before the patient receives any information on disease status, prior to the administration of non-PRO assessments, and in the following order each time, whenever possible: ABILHAND, Neuro-QoL-UE, PGIC-UL, MFIS, PGIC-F, MSIS-29, and EQ-5D-5L.

[g] Includes pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Temperature should be measured and recorded in patient's notes only. Blood pressure and pulse rate will be recorded on the appropriate eCRF. On ocrelizumab infusion visits, vital signs should be taken within 45 minutes prior to the methylprednisolone infusion. In addition, blood pressure and pulse rate should be obtained prior to start of infusion, every hour during the infusion, at the end of infusion and 1 hour after the end of the infusion. On non-infusion days, the vital signs may be taken at any time during the visit. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] Neurological examinations will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Potential relapses should be recorded throughout the treatment period. All patients with new neurological symptoms suggestive of MS worsening should have EDSS assessment performed by Examining Investigator. Investigators will also screen patients for signs and symptoms of PML by evaluating neurological deficits localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, hemiparesis, cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination). Patients with suspected PML should be withheld from ocrelizumab treatment until PML is ruled out by complete clinical evaluation and appropriate diagnostic testing. A patient with confirmed PML should be withdrawn from the study treatment permanently.

[j] Both the dominant and non-dominant hands are tested twice (two consecutive trials of the dominant hand, followed immediately by two consecutive trials of the non-dominant hand) (National Multiple Sclerosis Society 2001).

[k] EDSS including functional system scores will be assessed and collected.

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

[m] B cells and other cell types and/or B-cell subsets will be assessed in fresh whole blood using flow cytometry.

[n] Urine pregnancy tests will be performed at specified visits. If a urine pregnancy test is positive, the patient will not receive the scheduled dose, and a confirmatory serum pregnancy test will be performed. Urine β-hCG (sensitivity of at least 25 mU/mL) will be performed locally.

Appendix 3: Schedule of Activities: Open-Label Extension (cont.)

[o] Patients will receive prophylactic treatment with 100 mg of methylprednisolone IV and an oral or IV antihistamine (e.g., IV diphenhydramine 50 mg or an equivalent dose of an alternative) prior to infusion of ocrelizumab. The methylprednisolone administration is to be completed approximately 30 minutes before the start of each ocrelizumab infusion; antihistamines should be administered 30–60 minutes prior to the start of an infusion. In the rare case when the use of methylprednisolone is contraindicated for the patient, use of an equivalent dose of an alternative steroid should be used as premedication prior to the infusion. It is also recommended that patients receive an analgesic/antipyretic such as acetaminophen/paracetamol (1 g) 30–60 minutes prior to ocrelizumab infusion.

[p] The investigator must review the clinical and laboratory re-treatment criteria prior to subsequent infusion of ocrelizumab. The patient will need to remain under observation at the clinical site for at least 1 hour after infusion. At infusion visits, it is anticipated that the patient will need to stay at the hospital or clinical site for a full day.

[q] 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.

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

[s] MRI scans should occur within a window of ±4 weeks of the scheduled visit. In addition, mandatory MRI scans and additional optional cervical spinal MRI scans (if applicable) will be obtained in patients who withdraw from study treatment (at treatment discontinuation visit) if one was not performed during the prior 4 weeks. During the OLE, mandatory MRI scans will be performed every 48 weeks indicated by (x) (according to the yearly schedule as carried over from the double-blind treatment phase). Additional optional cervical spinal scans will be performed every 48 weeks starting from the baseline OLE visit.

[t] Serum sample, to be taken prior to the IV methylprednisolone infusion.

[u] On study drug infusion days, two serum samples (one prior to the IV methylprednisolone infusion, and one within 30 minutes after completion of study drug infusion) will be collected. On visits without study drug infusion, PK sample may be collected at any time. During study drug infusion visits, PK samples will be collected from the arm opposite to the infusion.

[v] For those patients enrolled with negative HBsAg and positive total HBcAb, HB virus DNA (PCR) must be repeated every 24 weeks.

Appendix 4
Schedule of Activities: Follow-Up 2 and BCM

	FU2 [a]	BCM [b]	EOO or WD from FU
Study week	Visits every 24 wk	Visits every 24 wk	
(Window in days)	(±7 d)	(±7 d)	
Physical examination [c]	x	x	x
Neurological examination [d]	x	x	x
Hematology, chemistry, urinalysis [e]	x	x	x
Flow cytometry (including CD3/4/8/19 count) [f]	x	x	x
IgG, IgA, IgM	x		
Concomitant medications [g]	x	x	x
Adverse events [h]	x	x	x
MRI [i]			x
ADA sample (serum) [j]	x		
PK sample (serum) [k]	x		
Hepatitis B virus DNA (if required) [l]	x	x	x

ADA = anti-drug antibody; BCM = B-cell monitoring; eCRF = electronic Case Report Form; EOO = end of observation; FU = follow up; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; MRI = magnetic resonance imaging; MS = multiple sclerosis; PK = pharmacokinetic; PML = progressive multifocal leukoencephalopathy; WD = withdrawal; Wk = week.

Notes: All assessments should be performed on the day of the scheduled visit, unless otherwise specified. For more information regarding FU2 and BCM, see Sections 3.1.1.6 and 3.1.1.7, respectively. See Figure 2 for information regarding how a patient proceeds through the different study phases (including FU2 and BMC).

[a] Laboratory and safety assessments performed during clinical visits every 24 weeks. All patients will continue in the FU2 until the end of the FU2 phase. For information regarding FU2 duration and eligibility, refer to Section 3.1.1.6.

[b] At the end of FU2 *phase*, all patients will move into BCM phase until the end of the study. For more information regarding the end of the study, see Section 3.2.

[c] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[d] Neurological examinations will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Potential relapses should be recorded throughout the treatment period. All patients with new neurological symptoms suggestive of MS worsening should have EDSS assessment performed by Examining Investigator. Investigators will also screen patients for signs and symptoms of PML by evaluating neurological deficits localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, hemiparesis, cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination). Patients with suspected PML should be withheld from ocrelizumab treatment until PML is ruled out by complete clinical evaluation and appropriate diagnostic testing. A patient with confirmed PML should be withdrawn from the study treatment permanently.[e]

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

[f] B cells and other cell types and/or B-cell subsets will be assessed in fresh whole blood using flow cytometry.

[g] 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.

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

[i] Mandatory MRI scans will be obtained in patients who withdraw from study (at WD from FU or EOO visit) if one was not performed during the prior 4 weeks.

[j] Serum samples may be collected at any time.

[k] PK sample may be collected at any time during the visit.

[l] For those patients enrolled with negative HBsAg and positive total HBcAb, HB virus DNA (PCR) must be repeated every 24 weeks.

Appendix 5
Progressive Multifocal Leukoencephalopathy: Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy

ACTION STEPS IF PML IS SUSPECTED

- If the clinical presentation is suggestive of progressive multifocal leukoencephalopathy (PML) (see Table 1), further investigations should include brain magnetic resonance imaging (MRI) evaluation as soon as possible. If MRI evaluation reveals lesions suspicious for PML (Berger et al. 2013; Figure 1) a lumbar puncture with evaluation of the cerebrospinal fluid (CSF) should be undertaken for the detection of JC virus (JCV) DNA by polymerase chain reaction using a validated sensitive assay. For details, refer to the most up to date laboratory manual providing storage conditions and shipment instructions. A diagnosis of PML can potentially be made by evaluating clinical and MRI findings plus the identification of JCV in the CSF. This sample will be stored for 1 year after the last patient, last visit.
- There is no known treatment or cure for PML. Treatment considerations are discussed in the medical literature (Calabrese et al. 2007).

MRI ASSESSMENT

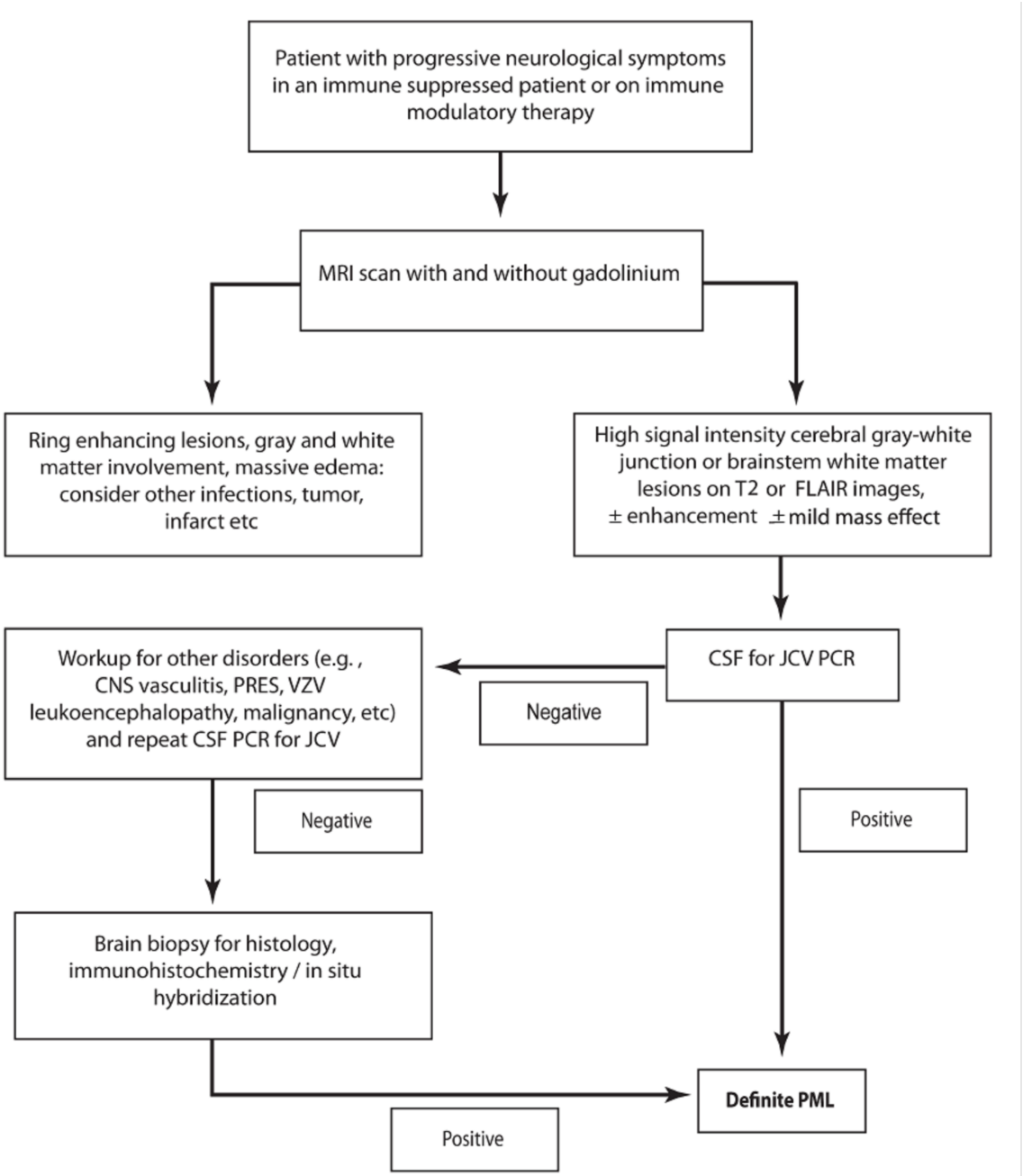
- Although there are no pathognomonic findings that differentiate PML from multiple sclerosis (MS), a mandatory MRI scan that includes fluid-attenuated inversion recovery and T2-weighted and T1-weighted sequences, with and without gadolinium, should be performed to assess patients with neurological changes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

CSF ASSESSMENT

- The detection of JCV DNA in the CSF of a patient with clinical and MRI features suggestive of PML establishes the diagnosis of PML.
- If JCV DNA is not detected in CSF and if clinical suspicion of PML remains high, a repeat lumbar puncture should be performed.
- If diagnosis remains uncertain and suspicion of PML remains high, a brain biopsy may be considered to establish a definitive diagnosis.

Appendix 5: Progressive Multifocal Leukoencephalopathy: Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy (cont.)

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



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

Appendix 5: Progressive Multifocal Leukoencephalopathy: Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy (cont.)

Table 1 Clinical Signs and Symptoms Typical of MS and PML

Clinical Signs and Symptoms Typical of MS and PML*		
Onset	**MS** **Acute**	**PML** **Subacute**
Evolution	➢ Over hours to days ➢ Normally stabilized ➢ Resolve spontaneously even without therapy	➢ Over weeks ➢ Progressive
Clinical presentation	➢ Diplopia ➢ Paresthesia ➢ Paraparesis ➢ Optic neuritis ➢ Myelopathy	➢ Cortical symptoms/signs ➢ Behavioral and neuropsychological alteration ➢ Retrochiasmal visual defects ➢ Hemiparesis ➢ Cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination)

MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy.

Adapted from Kappos et al. 2007.

Appendix 5: Progressive Multifocal Leukoencephalopathy: Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy (cont.)

Table 2 MRI Lesion Characteristics Typical of PML and MS

Feature	Multiple Sclerosis	PML
Location of new lesions	Mostly focal; may affect entire brain and spinal cord, in white and possibly gray matter; posterior cranial fossa lesions are rarely seen	Diffuse lesions, mainly subcortical and rarely periventricular, located almost exclusively in white matter, although occasional extension to gray matter has been seen; posterior fossa frequently involved (cerebellum)
Borders	Sharp edges; mostly round or finger-like in shape (especially periventricular lesions), confluent with other lesions; U-fibers may be involved	Ill-defined edges; infiltrating; irregular in shape; confined to white matter, sparing gray matter; pushing against the cerebral cortex; U-fibers destroyed
Mode of extension	Initially focal, lesions enlarge within days or weeks and later decrease in size within months	Lesions are diffuse and asymmetric, extending homogeneously; no confluence with other lesions; confined to white-matter tracks, sparing the cortex; continuous progression
Mass effect	Acute lesions show some mass effect	No mass effect even in large lesions (but lesion slightly abuts cerebral cortex)
On T_2-weighted sequence	Acute lesions: hyperintense center, isointense ring, discrete hyperintensity outside the ring structure Subacute and chronic lesions: hyperintense, with no ring structure	Diffuse hyperintensity, slightly increased intensity of newly involved areas compared with old areas, little irregular signal intensity of lesions
On T_1-weighted sequence	Acute lesions: densely hypointense (large lesions) or isointense (small lesions); increasing signal intensity over time in 80%; decreasing signal intensity (axonal loss) in about 20%	Slightly hypointense at onset, with signal intensity decreasing over time and along the affected area; no reversion of signal intensity
On FLAIR sequence	Hyperintense, sharply delineated	Hyperintensity more obvious, true extension of abnormality more clearly visible than in T_2-weighted images
With enhancement	Acute lesions: dense homogeneous enhancement, sharp edges Subacute lesions: ring enhancement Chronic lesions: no enhancement	Usually no enhancement even in large lesions; in patients with HIV, some peripheral enhancement is possible, especially under therapy
Atrophy	Focal atrophy possible, due to focal white-matter degeneration; no progression	No focal atrophy

FLAIR = fluid-attenuated inversion recovery; MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy.
Adapted from Yousry et al. 2006.

Appendix 5: Progressive Multifocal Leukoencephalopathy: Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy (cont.)

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

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Appendix 6
EQ-5D-5L

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Health Questionnaire

English version for the USA

Appendix 6: *EQ-5D-5L* (cont.)

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

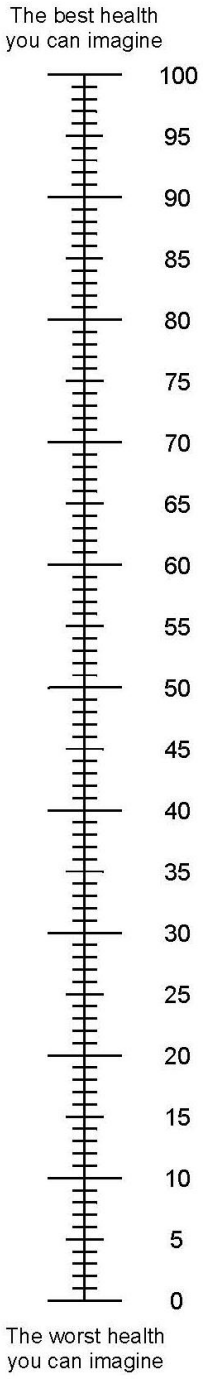
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

Appendix 6: *EQ-5D-5L* (cont.)

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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Appendix 7
Multiple Sclerosis Impact Scale, Version 2

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

- The following questions ask for your views about the impact of MS on your day-to-day life in the **past 14 days**.
- For each statement, please circle the one number that best describes your situation.
- Please answer all questions.

In the past 14 days, how much has your MS limited your ability to …	Not at all	A little	Moderate-ly	Extreme-ly
1. Do physically demanding tasks?	1	2	3	4
2. Grip things tightly (e.g. turning on taps)?	1	2	3	4
3. Carry things?	1	2	3	4

In the past 14 days, how much have you been bothered by …	Not at all	A little	Moderate-ly	Extreme-ly
4. Problems with your balance?	1	2	3	4
5. Difficulties moving around indoors?	1	2	3	4
6. Being clumsy?	1	2	3	4
7. Stiffness?	1	2	3	4
8. Feelings of heaviness in your arms and/or legs?	1	2	3	4
9. Tremors in your arms and/or legs?	1	2	3	4
10. Spasms in your arms and/or legs?	1	2	3	4
11. Your body not doing what you want it to do?	1	2	3	4
12. Having to depend on others to do things for you?	1	2	3	4

Appendix 7: Multiple Sclerosis Impact Scale, Version 2 (cont.)

Multiple Sclerosis Impact Scale Version 2 (MSIS-29v2) continued

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

MSIS-29v2 2005 2

MSIS-29 - United States/English - Version of 22 Feb 13 - MAPI Institute.
ID7215 / MSIS-29_AU2.0_eng-US.doc

Appendix 8
Modified Fatigue Impact Scale

Patient's Name: _____ **Date:** _____/_____/_____
month day year

ID#: _____ **Test#:** 1 2 3 4

MODIFIED FATIGUE IMPACT SCALE (MFIS)

Following is a list of statements that describe how fatigue may affect a person. Fatigue is a feeling of physical tiredness and lack of energy that many people experience from time to time. In medical conditions like MS, feelings of fatigue can occur more often and have a greater impact than usual. Please read each statement carefully, and then circle the one number that best indicates how often fatigue has affected you in this way during the past 4 weeks. (If you need help in marking your responses, tell the interviewer the number of the best response.) Please answer every question. If you are not sure which answer to select, please choose the one answer that comes closest to describing you. The interviewer can explain any words or phrases that you do not understand.

Because of my fatigue during the past 4 weeks…

		Never	Rarely	Sometimes	Often	Almost always
1.	I have been less alert.	0	1	2	3	4
2.	I have had difficulty paying attention for long periods of time.	0	1	2	3	4
3.	I have been unable to think clearly.	0	1	2	3	4
4.	I have been clumsy and uncoordinated.	0	1	2	3	4
5.	I have been forgetful.	0	1	2	3	4
6.	I have had to pace myself in my physical activities.	0	1	2	3	4
7.	I have been less motivated to do anything that requires physical effort.	0	1	2	3	4

Appendix 8: Modified Fatigue Impact Scale (cont.)

Because of my fatigue during the past 4 weeks…

		Never	Rarely	Sometimes	Often	Almost always
8.	I have been less motivated to participate in social activities.	0	1	2	3	4
9.	I have been limited in my ability to do things away from home.	0	1	2	3	4
10.	I have had trouble maintaining physical effort for long periods.	0	1	2	3	4
11.	I have had difficulty making decisions.	0	1	2	3	4
12.	I have been less motivated to do anything that requires thinking.	0	1	2	3	4
13.	My muscles have felt weak.	0	1	2	3	4
14.	I have been physically uncomfortable.	0	1	2	3	4
15.	I have had trouble finishing tasks that require thinking.	0	1	2	3	4
16.	I have had difficulty organizing my thoughts when doing things at home or at work.	0	1	2	3	4
17.	I have been less able to complete tasks that require physical effort.	0	1	2	3	4
18.	My thinking has been slowed down.	0	1	2	3	4
19.	I have had trouble concentrating.	0	1	2	3	4

Appendix 8: Modified Fatigue Impact Scale (cont.)

Because of my fatigue during the past 4 weeks…

		Never	Rarely	Sometimes	Often	Almost always
20.	**I have limited my physical activities.**	**0**	**1**	**2**	**3**	**4**
21.	**I have needed to rest more often or for longer periods.**	**0**	**1**	**2**	**3**	**4**

Appendix 9
ABILHAND

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ABILHAND – English Version

How DIFFICULT are the following activities?		Impossible	Very Difficult	Difficult	Easy	N/A
1.	Turning over the pages of a book					
2.	Pulling up the zipper of trousers					
3.	Peeling onions					
4.	Sharpening a pencil					
5.	Using a spoon					
6.	Using a screwdriver					
7.	Picking-up a can					
8.	Taking the cap off a bottle					
9.	Filing one's nails					
10.	Grasping a coin on a table					
11.	Closing a door					
12.	Washing one's face					
13.	Peeling potatoes with a knife					
14.	Turning off a tap					
15.	Buttoning up trousers					
16.	Dialling on a keypad phone					
17.	Opening a screw-topped jar					
18.	Cutting one's nails					
19.	Turning on a radio					
20.	Tearing open a pack of chips					
21.	Turning on a lamp					
22.	Combing one's hair					
23.	Unwrapping a chocolate bar					
24.	Hammering a nail					
25.	Replacing a light bulb					
26.	Inserting a diskette into a drive					
27.	Making pancake batter					
28.	Spreading butter on a slice of bread					
29.	Counting bank notes					
30.	Washing one's hands					
31.	Handling a stapler					

Please turn over

Page 1 of 2

Appendix 9: ABILHAND (cont.)

	How DIFFICULT are the following activities?	Impossible	Very Difficult	Difficult	Easy	N/A
32.	Winding up a wrist watch					
33.	Turning a key in a keyhole					
34.	Turning on a television set					
35.	Brushing one's hair					
36.	Drawing					
37.	Ringing a door bell					
38.	Placing a glass of water on a table					
39.	Drinking a glass of water					
40.	Buttoning up a shirt					
41.	Threading a needle					
42.	Cutting meat					
43.	Eating a sandwich					
44.	Handling a 4 colour ballpoint pen with one hand					
45.	Blowing one's nose					
46.	Wrapping up gifts					
47.	Fastening the zipper of a jacket					
48.	Fastening a snap (jacket, bag, ...)					
49.	Writing a sentence					
50.	Shelling hazelnuts					
51.	Screwing a nut on					
52.	Opening mail					
53.	Typewriting					
54.	Squeezing toothpaste on a toothbrush					
55.	Taking a coin out of the pocket					
56.	Brushing one's teeth					

Appendix 10
Quality of Life in Neurological Disorders-Upper Extremity Function (Fine Motor, ADL)

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

Upper Extremity Function (Fine Motor, ADL)

Please respond to each question or statement by marking one box per row.

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA40	Are you able to turn a key in a lock?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA50	Are you able to brush your teeth?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQUEX44	Are you able to make a phone call using a touch tone key-pad?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB21	Are you able to pick up coins from a table top?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA43	Are you able to write with a pen or pencil?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA35	Are you able to open and close a zipper?...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA55	Are you able to wash and dry your body?..	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB26	Are you able to shampoo your hair?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA22	Are you able to open previously opened jars?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB22	Are you able to hold a plate full of food?..	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA47	Are you able to pull on trousers?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA54	Are you able to button your shirt?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB41	Are you able to trim your fingernails?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQUEX39	Are you able to cut your toe nails?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PAF9	Are you able to bend down and pick up clothing from the floor?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

English
June 18, 2018

Appendix 10: Quality of Life in Neurological Disorders-Upper Extremity Function (Fine Motor, ADL) (cont.)

Neuro-QoL Item Bank v1.0 – Upper Extremity Function (Fine Motor, ADL)

		No difficulty	A little difficulty	Some difficulty	A lot of difficulty	Can't do
NQUEX03	How much DIFFICULTY do you currently have using a spoon to eat a meal?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQUEX04	How much DIFFICULTY do you currently have putting on a pullover shirt?.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQUEX05	How much DIFFICULTY do you currently have taking off a pullover shirt?.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQUEX06	How much DIFFICULTY do you currently have removing wrappings from small objects?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQUEX15	How much DIFFICULTY do you currently have opening medications or vitamin containers (e.g., childproof containers, small bottles)?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

English
June 18, 2018

Page **2** of **2**

Appendix 11
Patient Global Impression of Change for Fatigue

Over the last 6 months, my fatigue is (please tick one box):

☐ Very much better

☐ Much better

☐ A little better

☐ The same

☐ A little worse

☐ Much worse

☐ Very much worse

Appendix 12
Patient Global Impression of Change for Upper Limb Function

Some people with MS have problems with their hands and arms (e.g., weakness, stiffness, or numbness in fingers). These problems can make it difficult to do everyday tasks (e.g., doing up buttons, using cutlery, carrying a heavy box, or taking a book off a high shelf).

Over the last 6 months, how has your ability to do tasks involving your arms/hands changed? (please tick a box):

☐ Very much better

☐ Much better

☐ A little better

☐ The same

☐ A little worse

☐ Much worse

☐ Very much worse

Appendix 13
Pregnancy Outcome and Infant Health Information on First Year of Life

Pregnancy Outcome and Infant Health Information on First Year of Life

If twin or multi-gestational pregnancy, this questionnaire has to be filled out separately for each baby born in the multi-gestational pregnancy.

Please check all that apply and provide detailed information on complications in infant on last page.

Table 1: Parent's (or person with parental responsibility in law) consent to data collection

Has parent's (or person's with parental responsibility in law) data authorization form been signed?	☐Yes ☐No	Date signed _____	Other – comment _____
	Date consent withdrawn: (if applicable)		

Table 2: Information on birth

Mode of birth	☐Vaginal delivery Forceps / vacuum: - Yes ☐ - No ☐ ☐Cesarean section (CS) - scheduled CS ☐ - emergency CS ☐	Reason for assisted delivery/Cesarean section_____
Gestational age at birth	_____ weeks - since conception ☐ - since LMP ☐	Induced labor - Yes ☐ - No ☐

Appendix 13: Pregnancy Outcome and Infant Health Information on First Year of Life (cont.)

Table 3: Growth alteration, congenital anomalies and functional deficits

Date of Assessment			
Growth alteration - Yes ☐ - No ☐	☐Small for gestational age (SGA) ☐Low birth weight ☐Short birth length	If Growth alteration present: Specify weight:_____ Specify length: _____	Contributing factors:
Congenital anomalies - Yes ☐ - No ☐	☐ Major structural malformation A defect that has either cosmetic or functional significance to the child	Specify: _____ _____	Contributing factors:
	☐ Minor structural malformation A defect that occurs infrequently but has neither cosmetic nor functional significance to the child	Specify: _____ _____	
	☐ Deformation A defect attributable to deformation of a structure, which had previously formed normally (usually due to mechanical force)	Specify: _____ _____	
	☐ Disruption A defect due to destruction of a structure, which has previously formed normally (may be of vascular, infectious, or mechanical origin)	Specify: _____ _____	
Functional deficit (except for infections, which should be described in separate table below) - Yes ☐ - No ☐	☐Functional deficit	Specify: _____ _____ _____	Contributing factors: _____ _____

Appendix 13: Pregnancy Outcome and Infant Health Information on First Year of Life (cont.)

Status of infant at the time of latest follow-up (at birth, 3 months, 6 months, 12 months)

Table 4: Status of infant

Date of Assessment		Contributing factors/ Comments
Status of infant	☐Normal ☐Abnormal, specify abnormality: _____ ☐Neonatal/infant death, specify cause and date of death: _____	_____ _____
Nursing status	☐Exclusive breastfeeding ☐Mixed feeding (partial breastfeeding along with infant formula and/or baby food), specify date since when: _____ ☐Fully weaned, specify date since when: _____	_____

Infections in neonate and infant during first year of life

Any infection detected at birth?

☐ Yes
☐ No
☐ Unknown

If infection detected at birth then Tables 5 and 6 should to be filled out and additional detailed information may be provided on last page.

If no infection detected at birth, however an infection developed later during the first year of live, please move directly to Table 7.

If no infection detected at birth, and if also no infection developed during the first 12 months then move directly to Table 8.

Table 5: Information on infection in neonate at birth

Specify the event term:	**Event number**		
Location of infection present in neonate at birth? Site of infection (specify):		**Outcome of infection?**	**Duration of infection?**
		☐Resolved ☐Improving ☐Fatal ☐Persisting ☐Unknown	**Duration**:_____

Appendix 13: Pregnancy Outcome and Infant Health Information on First Year of Life (cont.)

Intensity of infection (Grade 1-5 NCI CTCAE)?	**Seriousness of infection?**	**Treatment with anti-infective?**	**Pathogen causing infection known?**
Severity: ☐Mild (Grade 1) ☐Moderate (Grade 2) ☐Severe (Grade 3)	Serious: ☐Yes ☐No	☐Yes, specify: _____ ☐No	☐Yes, specify: _____ ☐No
☐Life-threatening (Grade 4) ☐Death (Grade 5)		☐Unknown	☐Unknown
Relevant laboratory test results (in newborn infant):			
CD19 count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
IgG levels	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
White blood cell count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Neutrophil count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Lymphocyte count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Other, specify:	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____

Appendix 13: Pregnancy Outcome and Infant Health Information on First Year of Life (cont.)

Table 6: Maternal risk factors for neonatal infection (during most recent pregnancy, if infant developed neonatal infection at birth)

Maternal risk factors for neonatal infection	**Date of diagnosis**	If **diagnosed, was pregnant mother treated with anti-infective prior to delivery?**
☐Maternal intrapartum colonization or infection with group B streptococcus (GBS) ☐Maternal listeriosis ☐Premature rupture of membranes (PROM) ☐Meconium in amniotic fluid (meconium-stained liquid) ☐Active genital herpes infection ☐CMV ☐HPV (papilloma virus) Other, specify	_____ _____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____ _____

Relevant laboratory test results in pregnant mother:			
CD19 count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
IgG levels	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
White blood cell count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Neutrophil count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Lymphocyte count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Other, specify: (e.g., any specific antibodies and their titers)	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____

Any infection detected during first year of infant's life?

☐ Yes
☐ No
☐ Unknown

If infection detected during first year of infant's life, then Table 7 should be filled out and additional detailed information may be provided on last page. If no infection developed during first 12 months of life, then please move directly to Table 8.

Table 7: Information on infection detected during first year of infant's life

Specify the event term:	**Event number (automatically populated by the system?)**		
Location of infection?	**Infant's age on day of onset of infection?**	**Outcome of infection?**	**Duration of infection?**
Site of infection (specify): _____ _____	**Age:** _____	☐Resolved ☐Improving ☐Fatal ☐Persisting ☐Unknown	**Duration:**_____
Intensity of infection (Grade 1-5 NCI CTCAE)?	**Seriousness of infection?**	**Treatment with anti- infective?**	**Pathogen causing infection known?**
Severity: ☐Mild (Grade 1) ☐Moderate (Grade 2) ☐Severe (Grade 3) ☐Life-threatening (Grade 4) ☐Death (Grade 5)	Serious: ☐Yes ☐No	☐Yes, specify: _____ ☐No ☐Unknown	☐Yes (specify): _____ ☐No ☐Unknown
Relevant laboratory test results (in infant):			
CD19 count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
IgG levels	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
White blood cell count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Neutrophil count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Lymphocyte count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Other, specify:	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____

Appendix 13: Pregnancy Outcome and Infant Health Information on First Year of Life (cont.)

Table 8: Vaccinations administered to infant at birth and during first year of age

Vaccinations administered at birth and during first year of age	Date administered	Infant's age on day of vaccination	Comments (abnormal outcome, reason for postponing vaccination, etc.)
☐Hepatitis B			
☐Rotavirus			
☐Diphtheria, tetanus, and pertussis			
☐Hemophilus influenza type b			
☐Pneumococcal			
☐Poliovirus ☐Attenuated oral polio vaccine ☐Inactivated polio vaccine			
☐Meningococcal group B bacteria			
☐Tuberculosis (Bacille Calmette Guérin, BCG) bacteria			
☐Other vaccination, specify: _____			

Table 9: Fetal/neonatal abnormalities in previous pregnancies

Fetal/neonatal abnormalities (in previous pregnancies)			Please, provide specifics including contributing factors
None ☐	Yes ☐	Unknown ☐	
Infection; if yes, specify			
Death in utero; if yes, specify reason			
Birth defects; if yes, specify			
Family history of birth defects; if yes, specify			
Small for gestational age at birth (or Intrauterine growth retardation)			
Premature delivery (before 37 weeks)			
Other; specify			

Detailed information on health-related findings in infant during first year of life

Please enter text in the free text box below.

Signature Page for Protocol - WA40404 - OCREVUS - Published
System identifier: RIM-CLIN-452662

Approval Task	Hans-Martin Schneble (schneblh) Country Medical Director 13-Oct-2022 16:19:15 GMT+0000

Approval Task	Yusuf Tanrikulu (tanrikuy) Deputy EU QPPV 13-Oct-2022 17:49:31 GMT+0000

ANNEX 4:

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Questionnaire
Infant's first year of life follow-up

AER:	
Site No:	
Local Case ID:	
Pregnancy Reporting Form:	☐ Form sent out, ☐ Form returned
Type of ocrelizumab exposure:	☐ In utero exposure ☐ Exposure via breastfeeding

Patient* ID/Initials:	
Patient* Date of Birth (DD-MMM-YYYY) / Age:	
Patient* ocrelizumab route of administration	☐ IV infusion ☐ SC injection

* Patient = pregnant mother (not her child)

Following the recent report to Roche regarding the birth of a baby to a woman with MS who had received OCREVUS in the 6 months prior to conception or during the pregnancy, we would like to ask you to complete this questionnaire (in addition to the company's global pregnancy reporting form). It is not known whether OCREVUS can impact pregnancy outcome or infant outcomes in humans. It is unknown whether OCREVUS is excreted in human breast milk or has any effect on the breastfed child and on milk production. OCREVUS is a recombinant humanized monoclonal antibody that selectively targets CD20-expressing B-lymphocytes. B-cell levels in human neonates following maternal exposure to OCREVUS have not been studied in clinical trials; however transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. In this questionnaire, we are seeking information on the health of the infant during his/her first year of life, focusing on B cells, infections and vaccination response because of the immunomodulatory effects of ocrelizumab. This will help us to have a better understanding of any potential adverse infant health complications that should be communicated to health authorities, healthcare professionals and patients.

If twin/multi-gestational pregnancy, this questionnaire must be filled out separately for each infant born in the multi-gestational pregnancy.

For each of the four predefined assessment time points of the infant's first year of life (at birth, at 3, 6, and 12 months of age), a separate form needs to be filled out.

Reporter information

1. Reporter information *(table 1 to be filled out at each assessment)*		
First name and surname of reporter completing this form (*if other than addressee, please provide contact information below*) _____		
Health care provider? ☐ Yes ☐ No – Please specify:		
Phone number:	Fax number:	Email address:
Address:		Country:

Status of neonate/infant during his/her first year of life, focus: infections

2. Status of neonate/infant during his/her first year of life *(table 2 to be filled out at each assessment)*	
Date of Assessment (DD-MMM-YYYY): _____ **At birth ☐, age 3 months ☐, age 6 months ☐, age 12 months**	**Comments**

2. Status of neonate/infant during his/her first year of life *(table 2 to be filled out at each assessment)*		
☐		
Overall status of neonate / infant	☐ Normal ☐ Abnormal; specify abnormality: _____ ☐ Neonatal/infant death; specify cause and date of death: _____	
Nursing status	☐ Exclusive breastfeeding ☐ Mixed feeding (partial breastfeeding along with infant formula and / or baby food); specify date since when (DD-MMM-YYYY): _____ ☐ Exclusive infant formula feeding; specify date since when: _____ ☐ Fully weaned; specify date since when: _____	
B cell levels (CD19) in the newborn/infant (to be filled out also in the absence of infections)	☐ Normal, ☐ abnormal, ☐ unknown ***If abnormal, specify test result, normal range and test date (DD-MM-YYYY):*** Test result: _____ Normal range: _____ Test date: _____	
Infection	Any infection detected? ☐ Yes, ☐ No, ☐ Unknown *- If infection detected at birth: please fill out Table 3,* *- If no infection detected at birth, however an infection developed later during the first year of life, please move directly to Table 4,* *- If no infection detected at birth, and if also no infection developed during the first 12 months then move directly to Table 5.*	

3. Information on infection in neonate <u>at birth</u> *(table 3 only to be filled out if infection at birth present)*			
Location of infection present in neonate at birth: Site of infection (specify): _____	**Hospitalisation prolonged because of infection?** ☐ Yes ☐ No	**Outcome of infection:** ☐ Resolved ☐ Improving ☐ Persisting ☐ Fatal ☐ Unknown	**Duration of infection:** _____Days
Intensity of infection (Grade 1-5 NCI CTCAE): Severity: ☐ Mild (Grade 1) ☐ Moderate (Grade 2) ☐ Severe (Grade 3) ☐ Life-threatening (Grade 4) ☐ Death (Grade 5)	**Seriousness of infection?** Serious: ☐ Yes ☐ No	**Treatment with anti-infective?** ☐ Yes, specify: _____ ☐ No ☐ Unknown	**Pathogen causing infection known?** ☐ Yes (specify): _____ ☐ No ☐ Unknown

Relevant laboratory test results, if available (in newborn infant):

Type of laboratory test	***Test result***	***If abnormal, specify test result and normal range***	***If abnormal, test date (DD-MMM-YYYY):***
CD19 count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date: _____
IgG levels	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date: _____

3. Information on infection in neonate <u>at birth</u> *(table 3 only to be filled out if infection at birth present)*			
White blood cell count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date: _____
Neutrophil count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date: _____
Lymphocyte count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date: _____
Other, specify: _____	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date: _____

Maternal risk factors for neonatal infection, if infant developed neonatal infection <u>at birth</u>

Type of maternal risk factor	***Risk factor present?***	***Date of diagnosis: (DD-MMM-YYYY):***	***If diagnosed, was the pregnant mother treated with an anti-infective prior to the delivery?***
Maternal intrapartum colonisation or infection with group B streptococcus	☐ Yes, ☐ no, ☐ unknown	Date: _____	☐ Yes, ☐ no, ☐ unknown
Maternal listeriosis	☐ Yes, ☐ no, ☐ unknown	Date: _____	☐ Yes, ☐ no, ☐ unknown
Active genital herpes infection	☐ Yes, ☐ no, ☐ unknown	Date: _____	☐ yes, ☐ no, ☐ unknown
Premature rupture of membranes	☐ Yes, ☐ no, ☐ unknown	Date: _____	☐ yes, ☐ no, ☐ unknown
Meconium in amniotic fluid (meconium- stained liquid)	☐ Yes, ☐ no, ☐ unknown	Date: _____	☐ yes, ☐ no, ☐ unknown
Other, specify: _____	☐ Yes, ☐ no, ☐ unknown	Date: _____	☐ yes, ☐ no, ☐ unknown

3. Information on infection in neonate <u>at birth</u> *(table 3 only to be filled out if infection at birth present)*			
Relevant laboratory test results in pregnant mother at the time of delivery *(or if not available for time of delivery, laboratory test done during pregnancy):*			
Type of laboratory test	***Test result***	***If abnormal, specify test result and normal range***	***If abnormal, test date (DD-MMM-YYYY):***
CD19 count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date: _____
IgG levels	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:
White blood cell count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:
Neutrophil count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:
Lymphocyte count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:
Other (e.g. any specific antibodies and their titers), specify: _____	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:

4. Information on infection detected during first year of infant's life (*table 4 only to be filled out if an infection developed during the first 12 months of life; for infection present at birth please see table 3)*

Assessment: **at age 3 months ☐,** **at age 6 months ☐,** **at age 12 months ☐**

Location of infection? Site of infection (specify): _____	**Hospitalisation required or prolonged because of infection?** ☐ Yes ☐ No	**Infant's age on day of onset of infection?** _____ Weeks	**Outcome of infection?** ☐ Resolved ☐ Improving ☐ Fatal ☐ Persisting ☐ Unknown	**Duration of infection?** _____Days
Intensity of infection (Grade 1-5 NCI CTCAE): Severity: ☐ Mild (Grade 1) ☐ Moderate (Grade 2) ☐ Severe (Grade 3) ☐ Life-threatening (Grade 4) ☐ Death (Grade 5)		**Seriousness of infection?** Serious: ☐ Yes ☐ No	**Treatment with anti-infective?** ☐ Yes, specify: _____ ☐ No ☐ Unknown	**Pathogen causing infection known?** ☐ Yes (specify): _____ ☐ No ☐ Unknown

Relevant laboratory test results if available (in infant):

Type of laboratory test	***Test result***	***If abnormal, specify test result and normal range***	***If abnormal, test date (DD-MMM-YYYY)***
CD19 count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:
IgG levels	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:
White blood cell count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:
Neutrophil count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:
Lymphocyte count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:
Other, specify: _____ _	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:

5. Vaccinations administered to infant at birth and during first year of life (*table 5 to be filled out at each assessment)*

Vaccinations administered at birth and during first year of life	**Date administered** (DD-MMM-YYYY):	**Infant's age on day of vaccination** (weeks)	**Initial vaccination or booster dose**	**Vaccination postponed to later date than scheduled**	**Comments (abnormal outcome, reason for postponing vaccination, etc.)**
☐ Hepatitis B			☐ Initial ☐ Booster	☐ Yes, ☐ No	
☐ Rotavirus			☐ Initial ☐ Booster	☐ Yes, ☐ No	
☐ Diphtheria, tetanus, and pertussis			☐ Initial ☐ Booster	☐ Yes, ☐ No	
☐ Haemophilus influenzae type b			☐ Initial ☐ Booster	☐ Yes, ☐ No	
☐ Pneumococcal			☐ Initial ☐ Booster	☐ Yes, ☐ No	

5. Vaccinations administered to infant at birth and during first year of life (*table 5 to be filled out at each assessment)*					
Vaccinations administered at birth and during first year of life	**Date administered** (DD-MMM-YYYY):	**Infant's age on day of vaccination** (weeks)	**Initial vaccination or booster dose**	**Vaccination postponed to later date than scheduled**	**Comments (abnormal outcome, reason for postponing vaccination, etc.)**
☐ Poliovirus ☐ Attenuated oral Polio vaccine ☐ Inactivated Polio vaccine			☐ Initial ☐ Booster	☐ Yes, ☐ No	
☐ Meningococcal group B bacteria			☐ Initial ☐ Booster	☐ Yes, ☐ No	
☐ Tuberculosis (Bacille Calmette Guérin, BCG) bacteria			☐ Initial ☐ Booster	☐ Yes, ☐ No	
☐ Other vaccination, specify: _____			☐ Initial ☐ Booster	☐ Yes, ☐ No	

Completed by:

Name: ..... Position: .....

Signature: ..... Date: .....

E-mail: .....

Contact name for further information on the first year of the infant's life:

Function: ..... Tel. No.: .....

E-mail: ..... Fax No.: .....

Contact Address: .....

Detailed information on abnormal health related findings in neonate/infant during first year of life

Please enter text in box below:

Genentech
A Member of the Roche Group

Questionnaire
Infant's first year of life follow-up

AER:	
Site No:	
Local Case ID:	
Pregnancy Reporting Form:	☐ Form sent out, ☐ Form returned
Type of ocrelizumab exposure:	☐ In utero exposure ☐ Exposure via breastfeeding

Patient* ID/Initials:	
Patient* Date of Birth (DD-MMM-YYYY) / Age:	
Patient* ocrelizumab route of administration	☐ IV infusion ☐ SC injection

* Patient = pregnant mother (not her child)

Following the recent report to Genentech regarding the birth of a baby to a woman with MS who had received OCREVUS in the 6 months prior to conception or during the pregnancy, we would like to ask you to complete this questionnaire (in addition to the company's global pregnancy reporting form). It is not known whether OCREVUS can impact pregnancy outcome or infant outcomes in humans. It is unknown whether OCREVUS is excreted in human breast milk or has any effect on the breastfed child and on milk production. OCREVUS is a recombinant humanized monoclonal antibody that selectively targets CD20-expressing B-lymphocytes. B-cell levels in human neonates following maternal exposure to OCREVUS have not been studied in clinical trials; however transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. In this questionnaire, we are seeking information on the health of the infant during his/her first year of life, focusing on B cells, infections and vaccination response because of the immunomodulatory effects of ocrelizumab. This will help us to have a better understanding of any potential adverse infant health complications that should be communicated to health authorities, healthcare professionals and patients.

If twin/multi-gestational pregnancy, this questionnaire must be filled out separately for each infant born in the multi-gestational pregnancy.

For each of the four predefined assessment time points of the infant's first year of life (at birth, at 3, 6, and 12 months of age), a separate form needs to be filled out.

Reporter information

1. Reporter information *(table 1 to be filled out at each assessment)*		
First name and surname of reporter completing this form (*if other than addressee, please provide contact information below*) _____		
Health care provider? ☐ Yes ☐ No – Please specify:		
Phone number:	Fax number:	Email address:
Address:		Country:

Status of neonate/infant during his/her first year of life, focus: infections

2. Status of neonate/infant during his/her first year of life *(table 2 to be filled out at each assessment)*	
Date of Assessment (DD-MMM-YYYY): _____ **At birth ☐, age 3 months ☐, age 6 months ☐, age 12 months ☐**	**Comments**

2. Status of neonate/infant during his/her first year of life *(table 2 to be filled out at each assessment)*		
Overall status of neonate / infant	☐ Normal ☐ Abnormal; specify abnormality: _____ ☐ Neonatal/infant death; specify cause and date of death: _____	
Nursing status	☐ Exclusive breastfeeding ☐ Mixed feeding (partial breastfeeding along with infant formula and / or baby food); specify date since when (DD-MMM-YYYY): _____ ☐ Exclusive infant formula feeding; specify date since when: _____ ☐ Fully weaned; specify date since when: _____	
B cell levels (CD19) in the newborn/infant (to be filled out also in the absence of infections)	☐ Normal, ☐ abnormal, ☐ unknown ***If abnormal, specify test result, normal range and test date (DD-MM-YYYY):*** Test result: _____ Normal range: _____ Test date: _____	
Infection	Any infection detected? ☐ Yes, ☐ No, ☐ Unknown *- If infection detected at birth: please fill out Table 3,* *- If no infection detected at birth, however an infection developed later during the first year of life, please move directly to Table 4,* *- If no infection detected at birth, and if also no infection developed during the first 12 months then move directly to Table 5.*	

3. Information on infection in neonate <u>at birth</u> *(table 3 only to be filled out if infection at birth present)*			
Location of infection present in neonate at birth: Site of infection (specify): _____	**Hospitalisation prolonged because of infection?** ☐ Yes ☐ No	**Outcome of infection:** ☐ Resolved ☐ Improving ☐ Persisting ☐ Fatal ☐ Unknown	**Duration of infection:** _____Days
Intensity of infection (Grade 1-5 NCI CTCAE): Severity: ☐ Mild (Grade 1) ☐ Moderate (Grade 2) ☐ Severe (Grade 3) ☐ Life-threatening (Grade 4) ☐ Death (Grade 5)	**Seriousness of infection?** Serious: ☐ Yes ☐ No	**Treatment with anti-infective?** ☐ Yes, specify: _____ ☐ No ☐ Unknown	**Pathogen causing infection known?** ☐ Yes (specify): _____ ☐ No ☐ Unknown

Relevant laboratory test results, if available (in newborn infant):

Type of laboratory test	***Test result***	***If abnormal, specify test result and normal range***	***If abnormal, test date (DD-MMM-YYYY):***
CD19 count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date: _____
IgG levels	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date: _____
White blood cell count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range:	Date: _____

3. Information on infection in neonate <u>at birth</u> *(table 3 only to be filled out if infection at birth present)*			
		_____	
Neutrophil count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date: _____
Lymphocyte count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date: _____
Other, specify: _____	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date: _____

Maternal risk factors for neonatal infection, if infant developed neonatal infection <u>at birth</u>			
Type of maternal risk factor	***Risk factor present?***	***Date of diagnosis: (DD-MMM-YYYY):***	***If diagnosed, was the pregnant mother treated with an anti-infective prior to the delivery?***
Maternal intrapartum colonisation or infection with group B streptococcus	☐ Yes, ☐ no, ☐ unknown	Date: _____	☐ Yes, ☐ no, ☐ unknown
Maternal listeriosis	☐ Yes, ☐ no, ☐ unknown	Date: _____	☐ Yes, ☐ no, ☐ unknown
Active genital herpes infection	☐ Yes, ☐ no, ☐ unknown	Date: _____	☐ yes, ☐ no, ☐ unknown
Premature rupture of membranes	☐ Yes, ☐ no, ☐ unknown	Date: _____	☐ yes, ☐ no, ☐ unknown
Meconium in amniotic fluid (meconium- stained liquid)	☐ Yes, ☐ no, ☐ unknown	Date: _____	☐ yes, ☐ no, ☐ unknown
Other, specify: _____	☐ Yes, ☐ no, ☐ unknown	Date: _____	☐ yes, ☐ no, ☐ unknown

3. Information on infection in neonate <u>at birth</u> *(table 3 only to be filled out if infection at birth present)*			
Relevant laboratory test results in pregnant mother at the time of delivery *(or if not available for time of delivery, laboratory test done during pregnancy):*			
Type of laboratory test	***Test result***	***If abnormal, specify test result and normal range***	***If abnormal, test date (DD-MMM-YYYY):***
CD19 count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date: _____
IgG levels	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:
White blood cell count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:
Neutrophil count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:
Lymphocyte count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:
Other (e.g. any specific antibodies and their titers), specify: _____	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:

4. Information on infection detected during first year of infant's life (*table 4 only to be filled out if an infection developed during the first 12 months of life; for infection present at birth please see table 3)*

Assessment: **at age 3 months ☐,** **at age 6 months ☐,** **at age 12 months ☐**

Location of infection? Site of infection (specify): _____	**Hospitalisation required or prolonged because of infection?** ☐ Yes ☐ No	**Infant's age on day of onset of infection?** _____ Weeks	**Outcome of infection?** ☐ Resolved ☐ Improving ☐ Fatal ☐ Persisting ☐ Unknown	**Duration of infection?** _____Days
Intensity of infection (Grade 1-5 NCI CTCAE): Severity: ☐ Mild (Grade 1) ☐ Moderate (Grade 2) ☐ Severe (Grade 3) ☐ Life-threatening (Grade 4) ☐ Death (Grade 5)		**Seriousness of infection?** Serious: ☐ Yes ☐ No	**Treatment with anti-infective?** ☐ Yes, specify: _____ ☐ No ☐ Unknown	**Pathogen causing infection known?** ☐ Yes (specify): _____ ☐ No ☐ Unknown

Relevant laboratory test results if available (in infant):

Type of laboratory test	***Test result***	***If abnormal, specify test result and normal range***	***If abnormal, test date (DD-MMM-YYYY)***
CD19 count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:
IgG levels	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:
White blood cell count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:
Neutrophil count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:
Lymphocyte count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:
Other, specify: _____ _	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:

5. Vaccinations administered to infant at birth and during first year of life (*table 5 to be filled out at each assessment)*

Vaccinations administered at birth and during first year of life	**Date administered** (DD-MMM-YYYY):	**Infant's age on day of vaccination** (weeks)	**Initial vaccination or booster dose**	**Vaccination postponed to later date than scheduled**	**Comments (abnormal outcome, reason for postponing vaccination, etc.)**
☐ Hepatitis B			☐ Initial ☐ Booster	☐ Yes, ☐ No	
☐ Rotavirus			☐ Initial ☐ Booster	☐ Yes, ☐ No	
☐ Diphtheria, tetanus, and pertussis			☐ Initial ☐ Booster	☐ Yes, ☐ No	
☐ Haemophilus influenzae type b			☐ Initial ☐ Booster	☐ Yes, ☐ No	
☐ Pneumococcal			☐ Initial ☐ Booster	☐ Yes, ☐ No	

5. Vaccinations administered to infant at birth and during first year of life (*table 5 to be filled out at each assessment)*					
Vaccinations administered at birth and during first year of life	**Date administered** (DD-MMM-YYYY):	**Infant's age on day of vaccination** (weeks)	**Initial vaccination or booster dose**	**Vaccination postponed to later date than scheduled**	**Comments (abnormal outcome, reason for postponing vaccination, etc.)**
☐ Poliovirus ☐ Attenuated oral Polio vaccine ☐ Inactivated Polio vaccine			☐ Initial ☐ Booster	☐ Yes, ☐ No	
☐ Meningococcal group B bacteria			☐ Initial ☐ Booster	☐ Yes, ☐ No	
☐ Tuberculosis (Bacille Calmette Guérin, BCG) bacteria			☐ Initial ☐ Booster	☐ Yes, ☐ No	
☐ Other vaccination, specify: _____			☐ Initial ☐ Booster	☐ Yes, ☐ No	

Completed by:

Name: _____ Position: _____

Signature: _____ Date: _____

E-mail: _____

Contact name for further information on the first year of the infant's life:

Function: _____ Tel. No.: _____

E-mail: _____ Fax No.: _____

Contact Address: _____

Detailed information on abnormal health related findings in neonate/infant during first year of life

Please enter text in box below:

Guided Questionnaire: PML

This request for follow up information is being sent to obtain additional details about this adverse event. By filling in this questionnaire, you will help us to understand more fully the risk factors for this condition.

Patient Information

AER:		Gender	
Patient ID/Initials		Country	
Birthday:		Local Case ID:	

Reporter Information

Name of reporter completing this form **(if other than addressee, provide contact information below)**:		
Health Care Provider? ☐ Yes ☐ No - Please specify:		
Phone Number:	Fax Number:	Email Address:

Roche Drug Therapy Details

Roche Drug Therapy Details	
Roche product used by the patient	
Indication for Roche Product and date of diagnosis	
Start Date/Stop Date of Roche product (MM/DD/YYYY)	Date of Start:_____ Date of Stop:_____
Frequency that the Roche product was taken	☐ Daily, if yes, how many times per day: _____ ☐ Weekly ☐ Monthly ☐Other, please specify:_____ ☐ Cycles (please specify):_____
Starting Dose	a Flat dose: _____mg b. _____mg/kg c. _____mg/m^2
Dose used prior to event	Date of last dose:_____ a. Flat dose: _____mg b. _____mg/kg c. _____mg/m^2
Route	☐ Oral ☐ IV Infusion ☐ Injection SC ☐ Injection IM ☐ Other, please specify:_____ ☐ Indicate if route of administration changed during therapy:_____
If route of administration changed during therapy, please specify	Date of change:_____ Type of change:_____ Other information or comments: _____
Additional treatment details	

Adverse Event:

List the signs and symptoms and their dates of occurrence: Please provide final diagnosis:

Relevant Diagnostic Data

Diagnostic	Baseline (pre-event onset)	At/After Event Onset
	Status / Date / Results	**Status / Date/ Results**
Brain MRI	☐ Done, please attach result, Date:___ ☐ Not Done ☐ Unknown	☐ Done, *please attach result,* Date:___ ☐ Not Done ☐ Unknown
JCV DNA in CSF by qPCR	☐ Done, Result:_____, Date:____ ☐ Not Done ☐ Unknown	☐ Done, Result:_____, Date:_____ ☐ Not Done ☐ Unknown
Brain Biopsy		☐ Done, Result:_____,Date:____ ☐ Not Done ☐ Unknown

Outcome of the event

☐ recovered/resolved ☐ resolved with sequalae ☐ recovering/resolving
☐ unresolved ☐ fatal ☐ unknown

If the patient died:
Was an autopsy performed? P*lease attach result.*
☐Yes ☐ No ☐ Unknown

Cause of death: _____

List any immunosuppressant, immunomodulatory, and/or chemotherapy medications the patient has *received in the past* (including chronic steroid use):

Drug Name (generic or trade name)	Indication	Route: specify (iv/sc/other)	Total # of cycles received by time of event onset	Dosing Regimen & Frequency of Dosing	Start Date	Stop Date or Ongoing

List any immunosuppressant, immunomodulatory, and/or chemotherapy medications the patient was receiving *at the time of event onset* (Including chronic steroid use):

Drug Name (generic or trade name)	Indication	Route: specify (iv/sc/other)	Total # of cycles received at time of event onset	Dosing Regimen & Frequency of Dosing	Start Date	Stop Date or Ongoing

Relevant Medical History and/or current Clinical Conditions (Check all that apply)

Immunodeficiency: ☐ Yes ☐ No ☐ Unknown	**If Yes**, specify:
Bone Marrow or Solid Organ Transplant: ☐ Yes ☐ No ☐ Unknown	Specify:
Malignancy (other than indication for Roche drug): ☐ Yes ☐ No ☐ Unknown	Specify:
Autoimmune Disease (other than indication for Roche drug): ☐ Yes ☐ No ☐ Unknown	Specify:
HIV/AIDS: ☐ Yes ☐ No ☐ Unknown	Specify:
Herpes Simplex: ☐ Yes ☐ No ☐ Unknown	Specify:
Herpes Zoster: ☐ Yes ☐ No ☐ Unknown	Specify:
CMV infection: ☐ Yes ☐ No ☐ Unknown	Specify:
Other Chronic Infections: ☐ Yes ☐ No ☐ Unknown	Specify:
Known CNS Pathology (e.g. CNS lupus, CNS lymphoma): ☐ Yes ☐ No ☐ Unknown	Specify:
Other – Specify:	

Other Relevant Laboratory/ Data:

Diagnostic	Baseline (pre-event onset)	At Event Onset	Following Event Resolution
	Date/Results (normal range)	Date/Results (normal range)	Date/Results (normal range)
WBC (White Blood Cell Count)			
ALC (Absolute Lymphocyte Count)			
ANC (Absolute Neutrophil Count)			
CD19			
CD4			
CD8			
IgM			
IgG			
Blood anti-JCV Ab (Ab index)			
JCV DNA in urine			
Other:			
Does the patient have a stored serum sample available that was drawn within the previous 5 years of event onset? ☐ Yes ☐ No ☐Unknown **Specify:**			

Completed by:

Name: ..... Position: .....

Signature: ..... Date: .....

E-mail: .....

Ocrelizumab Specific Additional List of Progressive Multifocal Leukoencephalopathy (PML) Questions

Instructions for the affiliate:

Patient Information (to be consistent with the information entered in the non-ocrelizumab specific PML GQ).

AER:		Gender	
Patient ID/Initials		Country	
Birthday:		Local Case ID:	

Please fill in the unique patient NeuroRX Login Credentials in the section 'Brain magnetic imaging (MRI) scan images' below.

Instructions for the neurologist:

The ocrelizumab specific progressive multifocal leukoencephalopathy (PML) checklist is provided to you in addition to the non-drug specific PML guided questionnaire (GQ) and should be filled out within one week of its receipt.

By completing this ocrelizumab specific PML checklist you will support us to better understand suspected or confirmed reports of PML recently reported in a patient treated with ocrelizumab and contributing factors specifically relevant for ocrelizumab (e.g. including prior administered multiple sclerosis (MS) disease modifying therapies (DMTs).

Please provide all available information from the time period when ocrelizumab was administered and, if applicable, also when any other immunomodulatory/ immunosuppressive therapy/ies, referred as the generic term DMT, was administered for MS prior to the switch to ocrelizumab. For previously administered MS DMTs, please focus on the 3 years prior to commencing therapy with ocrelizumab, but do please also include all DMTs ever administered, including those administered more than 3 years ago. We would like to ask you to provide us with patient's MRI images as we intend to forward any MRI images taken for the patient to an independent radiologist experienced in PML analysis for a second opinion.

Ideally, in order to ensure consistency and avoid duplication, this checklist should be completed by the same person who completed the non ocrelizumab specific PML Guided Questionnaire for the reported patient.

Please complete this checklist starting with information on ocrelizumab and continue with the MS DMT (MS drug # 1) that the patient received most recently before switching to ocrelizumab, followed by the other MS DMTs treatments taken before (MS drug # 2 taken before MS drug # 1) from most recent to less recent MS drug.

Question	Ocrelizumab	MS DMT#1 (administered right before switching to ocrelizumab)	MS DMT#2 (received before MS DMT#1)	MS DMT#3 (received before MS drug#2)	MS DMT#4 (received before MS drug#3) _
Drug name (*please specify DMTs other than ocrelizumab*)	Ocrelizumab	DMT name: _____	DMT name: _____	DMT name: _____	DMT name: _____

Brain magnetic resonance imaging (MRI) scan images

Question	Prior to ocrelizumab start	During ocrelizumab therapy	Prior to MS DMT#1 start	During MS DMT#1 therapy	Prior to MS DMT#2 start	During MS DMT#2 therapy	Prior to MS DMT#3 start	During MS DMT#3 therapy	Prior to MS DMT#4 start	During MS DMT#4 therapy
MRI scan done?	☐Done*, Date:____ ☐Not Done ☐Unknown	☐Done, Date:____ ☐Not Done ☐Unknown	☐Done*, Date:___ ☐Not Done ☐Unknown	☐Done*, Date:____ ☐Not Done ☐Unknown	☐Done*, Date:____ ☐Not Done ☐Unknown	☐Done*, Date:____ ☐Not Done ☐Unknown	☐Done*, Date:____ ☐Not Done ☐Unknown	☐Done*, Date:____ ☐Not Done ☐Unknown	☐Done*, Date:____ ☐Not Done ☐Unknown	☐Done*, Date:____ ☐Not Done ☐Unknown
Institution where MRI was performed (*Please specify*)	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
Could you provide us with the MRI images?	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No
If yes, please upload to the secure link with the following credentials:	AFFILIATE TO ADD NeuroRX Login Credentials: ----------									
Image uploaded?	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No
MRI images provided on a CD (if not uploaded to the secure link)	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No

John Cunningham virus (JCV) detection in cerebrospinal fluid (CSF)										
Question	**Prior to ocrelizumab start:**	**During ocrelizumab therapy**	**Prior to MS DMT#1 start**	**During MS DMT#1 therapy**	**Prior to MS DMT#2 start**	**During MS DMT#2 therapy**	**Prior to MS DMT#3 start**	**During MS DMT#3 therapy**	**Prior to MS DMT#4 start**	**During MS DMT#4 therapy**
JCV CSF test done? ***(if yes, please specify date of test)***	☐Done*, Date:____ ☐Not Done ☐Unknown	☐Done, Date:____ ☐Not Done ☐Unknown	☐Done*, Date:___ ☐Not Done ☐Unknown	☐Done*, Date:____ ☐Not Done ☐Unknown	☐Done*, Date:____ ☐Not Done ☐Unknown	☐Done*, Date:____ ☐Not Done ☐Unknown	☐Done*, Date:____ ☐Not Done ☐Unknown	☐Done*, Date:____ ☐Not Done ☐Unknown	☐Done*, Date:____ ☐Not Done ☐Unknown	☐Done*, Date:____ ☐Not Done ☐Unknown
JCV DNA in CSF:	☐ negative ☐ positive	☐ negative ☐ positive	☐ negative ☐ positive	☐ negative ☐ positive	☐ negative ☐ positive	☐ negative ☐ positive	☐ negative ☐ positive	☐ negative ☐ positive	☐ negative ☐ positive	☐ negative ☐ positive
Assay used: (*Please Specify*)	________	________	________	________	________	________	________	________	________	________
Laboratory performing JCV CSF titer? (*Please specify name and city of the laboratory*):	Lab: ________ City: ________	Lab: ________ City: ________	Lab: ________ City: ________	Lab: ________ City: ________	Lab: ________ City: ________	Lab: ________ City: ________	Lab: ________ City: ________	Lab: ________ City: ________	Lab: ________ City: ________	Lab: ________ City: ________
Lower limit of detection (LLOD) of the JCV SCF assay? *(Please specify):*	________	________	________	________	________	________	________	________	________	________
Other CSF analysis results, e.g. cell count, total protein concentration, glucose concentration *(please specify type of test and result*):	Test(*specify*) ________ ☐ normal ☐ abnormal result: _____ Test(*specify*) ________	Test(*specify*) ________ ☐ normal ☐ abnormal result: _____ Test(*specify*) ________	Test(*specify*) ________ ☐ normal ☐ abnormal result: _____ Test(*specify*) ________	Test(*specify*) ________ ☐ normal ☐ abnormal result: _____ Test(*specify*) ________	Test(*specify*) ________ ☐ normal ☐ abnormal result: _____ Test(*specify*) ________	Test(*specify*) ________ ☐ normal ☐ abnormal result: _____ Test(*specify*) ________	Test(*specify*) ________ ☐ normal ☐ abnormal result: _____ Test(*specify*) ________	Test(*specify*) ________ ☐ normal ☐ abnormal result: _____ Test(*specify*) ________	Test(*specify*) ________ ☐ normal ☐ abnormal result: _____ Test(*specify*) ________	Test(*specify*) ________ ☐ normal ☐ abnormal result: _____ Test(*specify*) ________

	☐ normal ☐ abnormal result: _____ Test(*specify*) __________ ☐ normal ☐ abnormal result: _____	☐ normal ☐ abnormal result: _____ Test(*specify*) __________ ☐ normal ☐ abnormal result: _____	☐ normal ☐ abnormal result: _____ Test(*specify*) __________ ☐ normal ☐ abnormal result: _____	☐ normal ☐ abnormal result: _____ Test(*specify*) __________ ☐ normal ☐ abnormal result: _____	☐ normal ☐ abnormal result: _____ Test(*specify*) __________ ☐ normal ☐ abnormal result: _____	☐ normal ☐ abnormal result: _____ Test(*specify*) __________ ☐ normal ☐ abnormal result: _____	☐ normal ☐ abnormal result: _____ Test(*specify*) __________ ☐ normal ☐ abnormal result: _____	☐ normal ☐ abnormal result: _____ Test(*specify*) __________ ☐ normal ☐ abnormal result: _____	☐ normal ☐ abnormal result: _____ Test(*specify*) __________ ☐ normal ☐ abnormal result: _____	☐ normal ☐ abnormal result: _____ Test(*specify*) __________ ☐ normal ☐ abnormal result: _____
JCV Antibody test <u>in serum/plasma</u>										
Question	**Prior to ocrelizumab start:**	**During ocrelizumab therapy**	**Prior to MS DMT#1 start**	**During MS DMT#1 therapy**	**Prior to MS DMT#2 start**	**During MS DMT#2 therapy**	**Prior to MS DMT#3 start**	**During MS DMT#3 therapy**	**Prior to MS DMT#4 start**	**During MS DMT#4 therapy**
JCV Ab test done in blood?	☐Done*, Date:____ ☐Not Done Unknown	☐Done, Date:____ ☐Not Done Unknown	☐Done*, Date:___ ☐Not Done Unknown	☐Done*, Date:____ ☐Not Done Unknown	☐Done*, Date:____ ☐Not Done Unknown	☐Done*, Date:____ ☐Not Done Unknown	☐Done*, Date:____ ☐Not Done Unknown	☐Done*, Date:____ ☐Not Done Unknown	☐Done*, Date:____ ☐Not Done Unknown	☐Done*, Date:____ ☐Not Done Unknown
Institution where was the JCV blood test done? (*please specify*)	________	________	________	________	________	________	________	________	________	________
Result (negative/positive): Anti-JC virus antibody index Value (*if available*):	☐ negative ☐ positive Index value: _________	☐ negative ☐ positive Index value: _________	☐ negative ☐ positive Index value: _________	☐ negative ☐ positive Index value: _________	☐ negative ☐ positive Index value: _________	☐ negative ☐ positive Index value: _________	☐ negative ☐ positive Index value: _________	☐ negative ☐ positive Index value: _________	☐ negative ☐ positive Index value: _________	☐ negative ☐ positive Index value: _________
Expanded Disability Status Scale (EDSS)										
Question	**Prior to ocrelizumab**	**During ocrelizumab**	**Prior to MS DMT#1**	**During MS DMT#1**	**Prior to MS DMT#2**	**During MS DMT#2**	**Prior to MS DMT#3**	**During MS DMT#3**	**Prior to MS DMT#4**	**During MS DMT#4**

	start:	therapy	start	therapy	start	therapy	start	therapy	start	therapy
EDSS status (*please specify the worst EDSS score recorded per period)*	________	________	________	________	________	________	________	________	________	________
Symptoms suggestive of PML										
Question	**Prior to ocrelizumab start:**	**During ocrelizumab therapy**	**Prior to MS DMT#1 start**	**During MS DMT#1 therapy**	**Prior to MS DMT#2 start**	**During MS DMT#2 therapy**	**Prior to MS DMT#3 start**	**During MS DMT#3 therapy**	**Prior to MS DMT#4 start**	**During MS DMT#4 therapy**
Where there any symptoms possibly suggestive of PML present? *(if yes, specify)*	☐No ☐Unknown ☐Yes: ________ ________ ________ ________	☐No ☐Unknown ☐Yes: ________ ________ ________ ________	☐No ☐Unknown ☐Yes: ________ ________ ________ ________	☐No ☐Unknown ☐Yes: ________ ________ ________ ________	☐No ☐Unknown ☐Yes: ________ ________ ________ ________	☐No ☐Unknown ☐Yes: ________ ________ ________ ________	☐No ☐Unknown ☐Yes: ________ ________ ________ ________	☐No ☐Unknown ☐Yes: ________ ________ ________ ________	☐No ☐Unknown ☐Yes: ________ ________ ________ ________	☐No ☐Unknown ☐Yes: ________ ________ ________ ________

Completed by:

Name:		Position:	
Signature:		Date:	
E-mail:			

ANNEX 5

PROTOCOLS FOR PROPOSED AND ONGOING STUDIES IN RMP PART IV

(NOT APPLICABLE)

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

(NOT APPLICABLE)

ANNEX 7:

OTHER SUPPORTING DATA

(INCLUDING REFERENCED MATERIAL)

ANNEX 7

OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

Referenced Material

Not Applicable

Post-authorization use in populations not studied in clinical trials

Pregnant and Breastfeeding Women

The summary tabulation of prospective and retrospective Individual Case Safety Reports during pregnancy is presented in Appendix 1.

Post-authorization exposure

The summary tabulation of cumulative exposure from marketing experience in the European Economic Area, United States, and rest of world is presented in Appendix 2.

APPENDIX 1: SUMMARY TABULATIONS OF PROSPECTIVE AND RETROSPECTIVE INDIVIDUAL CASE SAFETY REPORTS ON PREGNANCY

Methodology for Summary Tabulations of Prospective and Retrospective Individual Case Safety Reports on Pregnancy

1. OVERVIEW

The summary tabulation of prospective and retrospective Individual Cases Safety Reports (ICSRs) during pregnancy is presented by three sets of outputs (Overall Exposure, Exposure by Parents, and Exposure by Source. For each of these outputs, Period and Cumulative data are presented as separate tables. Exposure by Parents is presented separately for Mother and Father.

2. CASE INCLUSION CRITERIA

An adverse event report (AER) is included in the Period count based on:

- The latest report version in the period
- If it contains the drug of interest and
- There has not been a version containing the drug of interest before the start of the period.
- Additionally, the report has to be flagged as a pregnancy case.

An AER is included in the Cumulative count based on:

- The latest report version cumulative up to the period end date
- If it contains the drug of interest and
- Is flagged as pregnancy case.

Infant cases are excluded from the sets above (Period and Cumulative) if they contain a linked parent case.

3. CALCULATION OF FIELDS DISPLAYED IN OUTPUTS

All summary tables show case (AER) counts by pregnancy outcome, prospective/retrospective, and time of exposure.

Prospecive/Retrospective

This field is directly taken from the pregnancy type field in ARISg. Cases with unknown prospective/retrospective information are treated as retrospective.

Pregnancy outcome

The pregnancy outcome field in the summary table is calculated based on the rules presented in Table 1.

Table 1 Mapping of database values to the pregnancy outcome field

Pregnancy outcome field in table	Pregnancy Outcome value from source data	Further criterion
1. Ectopic pregnancy	"Ectopic pregnancy"	
2. Spontaneous abortion	"Spontaneous abortion"	
3. Elective termination (foetal defects)	"Elective Abortion" or "Therapeutic abortion"	Birth Outcome "Abnormal"
4. Elective termination (no foetal defects or unknown)	"Elective Abortion" or "Therapeutic abortion"	Birth Outcome other than "Abnormal"
5. premature baby	"Premature"	
6. Stillbirth with foetal defects	"Stillbirth" or "Intrauterine Death/Fetal"	Birth Outcome "Abnormal"
7. Stillbirth without foetal defects	"Stillbirth" or "Intrauterine Death/Fetal"	Birth Outcome other than "Abnormal"
8. Live birth with congenital anomaly	"Live birth" or "C-section Delivery"	Linked baby case has an event in congenital SMQ
9. Live birth without congenital anomaly	"Live birth" or "C-section Delivery"	All other cases (no linked congenital AE baby case)
10. Ongoing	"Ongoing"	
11. Unknown	"Not reported" or "Lost to follow-up" or "Unknown"	

Time of exposure

The company Safety Database accounts only for the earliest pregnancy exposure; therefore, exposure during pregnancy by trimester (1st, 2nd or 3rd) is being estimated/ calculated based on the detail in Table 2.

For pregnancies where exposure continued for more than 1 trimester, data are included based on the earliest time of exposure only.

Table 2 Mapping of database values to the time of exposure field

Gestation period	Gestation period unit	Time of exposure value shown in table
Empty		Unknown
0		Before Conception
1	Trimester	1st Trimester
≤ 13	Weeks	1st Trimester
≤ 91	Days	1st Trimester
>3 and ≤6	Months	2nd Trimester
2	Trimester	2nd Trimester
>13 and ≤26	Weeks	2nd Trimester
>91 and ≤182	Days	2nd Trimester
>6 and ≤9	Months	3rd Trimester
> 26	Weeks	3rd Trimester
> 182	Days	3rd Trimester

Mother exposed case

The case is considered a mother exposed case if it is flagged as a pregnancy case as well as either:

- The pregnancy outcome value is not empty, and the pregnancy field is 'Yes'

  OR
- The pregnancy outcome value is empty, and the parent sex is 'Female'

Father exposed case

The case is considered a father exposed case if it is flagged as a pregnancy case as well as either:

- The pregnancy outcome is empty and the parent sex is 'Male'

OR

- The pregnancy outcome is not empty, and the drug of interest is flagged with the biological father exposed to the flagged drug.

Period

	Prospective cases Number					Retrospective cases Number				
	Timing of exposure in pregnancy					Timing of exposure in pregnancy				
Pregnancy Outcome	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**
Ectopic pregnancy	0	0	0	0	2	0	0	0	0	2
Elective termination (foetal defects)	0	0	0	0	1	0	0	0	0	0
Elective termination (no foetal defects or unknown)	0	0	0	0	11	0	0	0	0	4
Live birth with congenital anomaly	0	0	0	0	1	0	0	0	0	4
Live birth without congenital anomaly	0	0	0	0	132	0	1	0	0	159
Ongoing	0	3	0	0	279	0	0	0	0	12
Premature baby	0	1	0	0	8	0	0	0	0	3
Spontaneous abortion	0	1	0	0	22	0	0	0	0	56
Stillbirth without foetal defects	0	0	0	0	2	0	0	0	0	0
Unknown	0	0	0	0	347	0	0	0	0	18
Total	0	5	0	0	805	0	1	0	0	258

Cumulative

	Prospective cases Number					Retrospective cases Number				
	Timing of exposure in pregnancy					Timing of exposure in pregnancy				
Pregnancy Outcome	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**
Ectopic pregnancy	0	0	0	0	13	0	0	0	0	8
Elective termination (foetal defects)	0	0	0	0	7	0	0	0	0	5
Elective termination (no foetal defects or unknown)	1	3	0	0	55	1	1	0	0	34
Live birth with congenital anomaly	0	1	0	0	18	0	0	1	1	14
Live birth without congenital anomaly	2	21	0	2	818	2	5	0	0	560
Ongoing	0	3	0	0	291	0	0	0	0	13
Premature baby	0	1	0	0	15	0	0	0	0	17
Spontaneous abortion	4	2	0	0	98	0	1	0	0	155
Stillbirth with foetal defects	0	0	0	0	0	0	0	0	0	1
Stillbirth without foetal defects	0	0	0	0	6	0	0	0	0	7
Unknown	2	5	1	1	1217	0	1	0	1	105
Total	9	36	1	3	2538	3	8	1	2	919

Period - Mother exposed

	Prospective cases Number					Retrospective cases Number				
	Timing of exposure in pregnancy					Timing of exposure in pregnancy				
Pregnancy Outcome	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**
Ectopic pregnancy	0	0	0	0	2	0	0	0	0	1
Elective termination (foetal defects)	0	0	0	0	1	0	0	0	0	0
Elective termination (no foetal defects or unknown)	0	0	0	0	11	0	0	0	0	4
Live birth with congenital anomaly	0	0	0	0	1	0	0	0	0	3
Live birth without congenital anomaly	0	0	0	0	126	0	1	0	0	148
Ongoing	0	3	0	0	264	0	0	0	0	11
Premature baby	0	1	0	0	8	0	0	0	0	3
Spontaneous abortion	0	1	0	0	21	0	0	0	0	52
Stillbirth without foetal defects	0	0	0	0	2	0	0	0	0	0
Unknown	0	0	0	0	331	0	0	0	0	17
Total	0	5	0	0	767	0	1	0	0	239

Cumulative - Mother exposed

	Prospective cases Number					Retrospective cases Number				
	Timing of exposure in pregnancy					Timing of exposure in pregnancy				
Pregnancy Outcome	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**
Ectopic pregnancy	0	0	0	0	13	0	0	0	0	7
Elective termination (foetal defects)	0	0	0	0	7	0	0	0	0	5
Elective termination (no foetal defects or unknown)	1	3	0	0	54	1	1	0	0	33
Live birth with congenital anomaly	0	1	0	0	18	0	0	1	1	12
Live birth without congenital anomaly	2	20	0	2	755	1	5	0	0	517
Ongoing	0	3	0	0	276	0	0	0	0	12
Premature baby	0	1	0	0	15	0	0	0	0	17
Spontaneous abortion	3	2	0	0	95	0	1	0	0	149
Stillbirth with foetal defects	0	0	0	0	0	0	0	0	0	1
Stillbirth without foetal defects	0	0	0	0	5	0	0	0	0	7
Unknown	2	5	1	1	1161	0	1	0	1	88
Total	8	35	1	3	2399	2	8	1	2	848

Period - Father exposed

	Prospective cases Number					Retrospective cases Number				
	Timing of exposure in pregnancy					Timing of exposure in pregnancy				
Pregnancy Outcome	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**
Ectopic pregnancy	0	0	0	0	0	0	0	0	0	1
Live birth with congenital anomaly	0	0	0	0	0	0	0	0	0	1
Live birth without congenital anomaly	0	0	0	0	6	0	0	0	0	11
Ongoing	0	0	0	0	15	0	0	0	0	1
Spontaneous abortion	0	0	0	0	1	0	0	0	0	4
Unknown	0	0	0	0	16	0	0	0	0	0
Total	0	0	0	0	38	0	0	0	0	18

Cumulative - Father exposed

	Prospective cases Number					Retrospective cases Number				
	Timing of exposure in pregnancy					Timing of exposure in pregnancy				
Pregnancy Outcome	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**
Ectopic pregnancy	0	0	0	0	0	0	0	0	0	1
Elective termination (no foetal defects or unknown)	0	0	0	0	1	0	0	0	0	1
Live birth with congenital anomaly	0	0	0	0	0	0	0	0	0	2
Live birth without congenital anomaly	0	1	0	0	63	0	0	0	0	43
Ongoing	0	0	0	0	15	0	0	0	0	1
Spontaneous abortion	0	0	0	0	2	0	0	0	0	6
Stillbirth without foetal defects	0	0	0	0	1	0	0	0	0	0
Unknown	0	0	0	0	55	0	0	0	0	5
Total	0	1	0	0	137	0	0	0	0	59

Period - Spontaneous

	Prospective cases Number					Retrospective cases Number				
	Timing of exposure in pregnancy					Timing of exposure in pregnancy				
Pregnancy Outcome	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**
Elective termination (no foetal defects or unknown)	0	0	0	0	3	0	0	0	0	0
Live birth with congenital anomaly	0	0	0	0	0	0	0	0	0	1
Live birth without congenital anomaly	0	0	0	0	10	0	1	0	0	34
Ongoing	0	0	0	0	31	0	0	0	0	2
Premature baby	0	0	0	0	1	0	0	0	0	2
Spontaneous abortion	0	0	0	0	3	0	0	0	0	12
Unknown	0	0	0	0	77	0	0	0	0	3
Total	0	0	0	0	125	0	1	0	0	54

Cumulative - Spontaneous

	Prospective cases Number					Retrospective cases Number				
	Timing of exposure in pregnancy					Timing of exposure in pregnancy				
Pregnancy Outcome	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**
Ectopic pregnancy	0	0	0	0	1	0	0	0	0	0
Elective termination (foetal defects)	0	0	0	0	2	0	0	0	0	1
Elective termination (no foetal defects or unknown)	0	2	0	0	16	0	1	0	0	10
Live birth with congenital anomaly	0	0	0	0	0	0	0	1	0	4
Live birth without congenital anomaly	0	5	0	0	56	0	3	0	0	112
Ongoing	0	0	0	0	34	0	0	0	0	2
Premature baby	0	0	0	0	2	0	0	0	0	5
Spontaneous abortion	0	0	0	0	14	0	1	0	0	32
Stillbirth without foetal defects	0	0	0	0	1	0	0	0	0	6
Unknown	0	2	0	0	339	0	1	0	0	23
Total	0	9	0	0	465	0	6	1	0	195

Period - Clinical Study

	Prospective cases Number					Retrospective cases Number				
	Timing of exposure in pregnancy					Timing of exposure in pregnancy				
Pregnancy Outcome	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**
Elective termination (no foetal defects or unknown)	0	0	0	0	0	0	0	0	0	3
Live birth with congenital anomaly	0	0	0	0	0	0	0	0	0	1
Live birth without congenital anomaly	0	0	0	0	6	0	0	0	0	4
Ongoing	0	0	0	0	11	0	0	0	0	0
Spontaneous abortion	0	0	0	0	2	0	0	0	0	1
Unknown	0	0	0	0	6	0	0	0	0	0
Total	0	0	0	0	25	0	0	0	0	9

Cumulative - Clinical Study

	Prospective cases Number					Retrospective cases Number				
	Timing of exposure in pregnancy					Timing of exposure in pregnancy				
Pregnancy Outcome	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**
Ectopic pregnancy	0	0	0	0	3	0	0	0	0	2
Elective termination (foetal defects)	0	0	0	0	3	0	0	0	0	2
Elective termination (no foetal defects or unknown)	1	1	0	0	17	1	0	0	0	14
Live birth with congenital anomaly	0	0	0	0	2	0	0	0	0	1
Live birth without congenital anomaly	2	8	0	1	120	2	0	0	0	23
Ongoing	0	0	0	0	11	0	0	0	0	0
Premature baby	0	0	0	0	3	0	0	0	0	0
Spontaneous abortion	4	0	0	0	16	0	0	0	0	10
Stillbirth with foetal defects	0	0	0	0	0	0	0	0	0	1
Stillbirth without foetal defects	0	0	0	0	1	0	0	0	0	0
Unknown	1	0	0	0	25	0	0	0	0	1
Total	8	9	0	1	201	3	0	0	0	54

Period - Non-Interventional Study/Program

	Prospective cases Number					Retrospective cases Number				
	Timing of exposure in pregnancy					Timing of exposure in pregnancy				
Pregnancy Outcome	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**
Ectopic pregnancy	0	0	0	0	2	0	0	0	0	2
Elective termination (foetal defects)	0	0	0	0	1	0	0	0	0	0
Elective termination (no foetal defects or unknown)	0	0	0	0	8	0	0	0	0	1
Live birth with congenital anomaly	0	0	0	0	1	0	0	0	0	2
Live birth without congenital anomaly	0	0	0	0	115	0	0	0	0	116
Ongoing	0	3	0	0	237	0	0	0	0	10
Premature baby	0	1	0	0	7	0	0	0	0	1
Spontaneous abortion	0	1	0	0	17	0	0	0	0	43
Stillbirth without foetal defects	0	0	0	0	2	0	0	0	0	0
Unknown	0	0	0	0	263	0	0	0	0	10
Total	0	5	0	0	653	0	0	0	0	185

Cumulative - Non-Interventional Study/Program

	Prospective cases Number					Retrospective cases Number				
	Timing of exposure in pregnancy					Timing of exposure in pregnancy				
Pregnancy Outcome	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**
Ectopic pregnancy	0	0	0	0	9	0	0	0	0	4
Elective termination (foetal defects)	0	0	0	0	2	0	0	0	0	2
Elective termination (no foetal defects or unknown)	0	0	0	0	22	0	0	0	0	9
Live birth with congenital anomaly	0	1	0	0	15	0	0	0	1	7
Live birth without congenital anomaly	0	8	0	1	639	0	2	0	0	405
Ongoing	0	3	0	0	246	0	0	0	0	11
Premature baby	0	1	0	0	10	0	0	0	0	11
Spontaneous abortion	0	2	0	0	68	0	0	0	0	113
Stillbirth without foetal defects	0	0	0	0	4	0	0	0	0	1
Unknown	1	3	1	1	849	0	0	0	1	70
Total	1	18	1	2	1864	0	2	0	2	633

Period - Literature - Spontaneous

	Prospective cases Number					Retrospective cases Number				
	Timing of exposure in pregnancy					Timing of exposure in pregnancy				
Pregnancy Outcome	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**
Live birth without congenital anomaly	0	0	0	0	1	0	0	0	0	1
Total	0	0	0	0	1	0	0	0	0	1

Cumulative - Literature - Spontaneous

	Prospective cases Number					Retrospective cases Number				
	Timing of exposure in pregnancy					Timing of exposure in pregnancy				
Pregnancy Outcome	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**
Live birth with congenital anomaly	0	0	0	0	1	0	0	0	0	0
Live birth without congenital anomaly	0	0	0	0	1	0	0	0	0	1
Total	0	0	0	0	2	0	0	0	0	1

Period - Literature - Study

No data

Cumulative - Literature - Study

No data

Period - Literature - Non-Interventional Study/Program

	Prospective cases Number					Retrospective cases Number				
	Timing of exposure in pregnancy					Timing of exposure in pregnancy				
Pregnancy Outcome	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**
Live birth without congenital anomaly	0	0	0	0	0	0	0	0	0	4
Unknown	0	0	0	0	1	0	0	0	0	5
Total	0	0	0	0	1	0	0	0	0	9

Cumulative - Literature - Non-Interventional Study/Program

	Prospective cases Number					Retrospective cases Number				
	Timing of exposure in pregnancy					Timing of exposure in pregnancy				
Pregnancy Outcome	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**	**Before conception**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Unknown**
Ectopic pregnancy	0	0	0	0	0	0	0	0	0	2
Elective termination (no foetal defects or unknown)	0	0	0	0	0	0	0	0	0	1
Live birth with congenital anomaly	0	0	0	0	0	0	0	0	0	2
Live birth without congenital anomaly	0	0	0	0	2	0	0	0	0	19
Premature baby	0	0	0	0	0	0	0	0	0	1
Unknown	0	0	0	0	4	0	0	0	0	11
Total	0	0	0	0	6	0	0	0	0	36

APPENDIX 2: POST-AUTHORIZATION EXPOSURE

Table 1 Cumulative Exposure from Marketing Experience in European Economic Area, Rest of World, and United States (until 31 March 2023)

Region	Indication			Sex			Age (years)				Total	PY
	RMS	PPMS	Unk	M	F	Unk	<18	≥18-65	≥66	Unk		
EEA	58,625	28,875	0	30,625	56,875	0	875	62,125	24,500	0	87,499	198,497
RoW	44,961	22,145	0	23,487	43,619	0	671	47,645	18,790	0	67,106	147,384
USA	98,888	48,706	0	51,658	95,936	0	1,476	104,792	41,326	0	147,594	375,998
Total	**202,473**	**99,726**	**0**	**105,770**	**196,429**	**0**	**3,022**	**214,561**	**84,616**	**0**	**302,199**	**721,879**

EEA=European Economic Area; F=female; M=male; PPMS=Primary progressive multiple sclerosis; PY=patient year; RMS=Relapsing forms of multiple sclerosis, RoW=Rest of world; USA=United States of America, Unk=unknown.

Note: RMS refers to RRMS and all forms of SPMS.

Rounding errors may be introduced in the total figures.

ANNEX 8

SUMMARY OF CHANGES TO THE RISK-MANAGEMENT PLAN OVER TIME

ANNEX 8

SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Version	Approval Date [a]	Change(s)
1.1	Evaluated	**Important identified risks**: Infusion-related reactions Infections **Important potential risks**: Hypersensitivity reactions Malignancies including breast cancer Impaired immunization response **Missing information**: Use in pregnancy and lactation Use in pediatric population Use in patients over 55 years old (including elderly) Long-term safety of Ocrevus treatment Concomitant use of any immunosuppressive/ immunomodulating medication other than steroids for acute relapses Safety of Ocrevus following immunosuppressive/ immunomodulating disease-modifying therapies other than beta interferons and glatiramer acetate Safety of immunosuppressive/ immunomodulating disease-modifying therapies following Ocrevus
1.2	Evaluated	Two new important potential risks of PML and serious infections related to decrease in immunoglobulin (particularly in patients previously exposed to immunosuppressive /immunomodulatory drugs or with pre-existing hypogammaglobinaemia) has been added.
1.3	Evaluated	Removal of studies conducted as PMR for the FDA. Amendment of lay summary as requested in the Day 195 Joint Assessment Report (JAR). Addition of post approval efficacy study to address a question from the CHMP. Updated indication wording for PPMS.
1.4	Approved 5 Jan 2018	Alignment with proposed SPC and addition of PASS.
2.0	Evaluated	Transition to new EU RMP template (in line with revision 2 of GVP Module V): The following important potential risks have been removed from the Ocrevus EU RMP: • Hypersensitivity reactions • Serious Infections related to decrease in immunoglobulins (particularly in patients previously exposed to immunosuppressive/ immunomodulatory drugs or with pre-existing hypogammaglobulinaemia The following important potential risk which was

Version	Approval Date [a]	Change(s)
		previously classified as potential is now considered an important identified risk (on the basis of results from the VELOCE study): Impaired immunization response The following missing information have been removed as there is no scientific evidence to expect any difference from the known safety profile: • Use in pediatric population • Use in elderly patients • Safety of immunosuppressive/ immunomodulating DMTs following ocrelizumab • Off-label use in other neurological indications • Concomitant use of immunosuppressive medication other than steroids for acute relapses The following Category 4 studies were removed and the risks they investigate are already investigated by BA39730 which is Category 3.study Studies: • MN30035 • MA30005 • Open-Label Extensions of Studies WA21092, WA21093, WA21493, and WA25046 WA405404 study was newly added during RMP transition to the new format
2.1	Evaluated	Cumulative post marketing data was added. Important potential risk of serious infections related to decrease in immunoglobulins (particularly in patients previously exposed to immunosuppressive /immunomodulatory drugs or with pre-existing hypogammaglobulinaemia, which had been removed in version 2.0 due to transition to the new RMP template, was added back into the EU RMP as requested in the PRAC assessment report. Safety concerns for study WA40404 (A Phase IIIb Multicenter, Randomised, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Ocrelizumab in Adults with Primary Progressive Multiple Sclerosis) were updated. Missing information for use in pregnancy and lactation has been renamed as safety in pregnancy and lactation.
2.2	Evaluated	The information captured in Part VI: summary of the risk management plan has been written in plain language for better understanding by the general public
2.3	Evaluated	The final list of safety concerns implemented in the

Version	Approval Date [a]	Change(s)
	Approved by CHMP on 31 October 2018	procedure EMEA/H/C/004043/II/0002 is as follows: • Infusion-related reactions • Infections • Impaired immunization response • Malignancies including breast cancer • Progressive multifocal leukoencephalopathy • Serious infections related to decrease in immunoglobulins (particularly in patients previously exposed to immunosuppressive/ immunomodulatory drugs or with pre-existing hypogammaglobulinaemia • Safety in pregnancy and lactation • Long-term safety of ocrelizumab treatment • Safety of ocrelizumab following immunosuppressive/immunomodulating DMTs other than Avonex, Betaferon, Copaxone, or Rebif • Safety in pediatric population
3.0	Evaluated Approved by EMA on 11 February 2020	Version 3.0 of the ocrelizumab EU RMP has been prepared to reflect a new availability date of the final report for Study 17-1133 and to append the outstanding protocol for Study WA40404 Summary of significant changes in this RMP: • Part II: Module SV**:** Updated to include current cumulative exposure from marketing experience • Part III.2: – Study 17-1133: Completion date of the final report and study status have been updated. – Study BA39732: Objectives and study milestones have been updated. – Study BA39730: Objectives and study status have been updated – Study WA40404: Study status has been updated • Part VI: – Link to EPAR has been included – Objectives have been updated for Studies BA39730 and BA39732 • Annex 2: Study details updated for BA39732, BA39730, WA40404, and 17-1133 • Annex 3: – Protocol for Study WA40404 has been appended. – New protocol version for Study BA39732 has been appended – Details and procedure numbers for all relevant protocols have been included • Annex 4: Updated to include current Guided

Version	Approval Date [a]	Change(s)
		Questionnaires for safety concerns
4.0	Evaluated Approved by CHMP on 30 April 2020	Version 4.0 of the ocrelizumab EU RMP has been prepared to support the ocrelizumab shorter infusion filing based on the results from MA30143 Shorter Infusion Substudy primary CSR. The Sponsor is proposing to introduce an alternative shorter (2h) infusion with subsequent ocrelizumab doses as alternative to the conventional (3.5h infusion) regimen. Summary of significant changes in this RMP: • Part I: Product Overview: Inclusion of shorter infusion duration • Part II: Module SIII – Clinical Trial Exposure: Updated to include patient exposure from the MA30143 substudy • Part II: Module SVII - Identified and Potential Risks: Information on the Important Identified Risk, Infusion-Related Reactions, was updated
5.0	Evaluated Approved by CHMP on 26 November 2020	Version 5.0 of the ocrelizumab EU RMP has been prepared to fulfill the PV commitment by the provision of final study report of Study 17-1133 and subsequently remove the Study 17-1133 from the PV plan. This version also consolidates the changes submitted for approved EU RMP Versions 3.0 and 4.0. Summary of significant changes in this RMP: • Part II: Module SII: – Study 15-3109: The study has been completed and the results from the study have been updated. • Part III.2: – Study 17-1133: Updated the completion date of the final report. – Removal of Study 17-1133 from the PV Plan • Annex 3: – Protocol for Study 17-1133 has been removed. – Protocol for Study BA39730 has been appended.
6.0	Evaluated	Version 6.0 of the ocrelizumab EU RMP has been prepared to: • Support the update of Section 4.4 of the EU SmPC to include the term ‘anaphylaxis’ among the possible symptoms of infusion-related reactions. • Re-classify the important potential risk “Serious

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		infections related to decrease in immunoglobulins (particularly in patients previously exposed to immunosuppressive/ immunomodulatory drugs or with pre-existing hypogammaglobulinaemia)'' to non-important identified risk and subsequent removal from the ocrelizumab EU RMP V6.0. Summary of significant changes in this RMP: • The important potential risk ''Serious infections related to decrease in immunoglobulins (particularly in patients previously exposed to immunosuppressive/ immunomodulatory drugs or with pre-existing hypogammaglobulinaemia)'' has been reclassified to a non-important identified risk and removed from the ocrelizumab EU RMP (the rationale for the reclassification and removal is provided in Section SVII.2). This update was reflected in Part II: Module SVII.2, Part II: Module SVII3.1.4, Part II: Module SVIII, Part V, Part V.3, IIA, and IIB. In addition, "Serious infections related to decrease in immunoglobulins (particularly in patients previously exposed to immunosuppressive/ immunomodulatory drugs or with pre-existing hypogammaglobulinaemia)'' have been removed from the 'Safety concerns addressed' in WA40404 study. This update was reflected in Part III.2. • Module SVII 3.1(infusion-related reactions): the term 'anaphylaxis' was introduced (in Section 4.4 of EU SmPC) among the possible symptoms of infusion-related reactions. • Part II: Module SII: The malignancies monitoring plan has been updated to clarify the ongoing assessment process, including removal of the reference to the biannual DSR on malignancies. • Part II: Module SII: – Study 15-3109 is now completed and the results from the study have been updated. – Mechanisms of drug interactions has been updated with findings from Study BN29739. • Part II: Module SV: Post-authorization exposure has been aligned and updated with Periodic Benefit Risk Evaluation Report (PBRER) #1100411

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		(DLP: 27 March 2020). • Part II: Module SVII3.1: – Information has been updated for important identified risk, infections. – Information has been updated and aligned with PBRER #1100411 (DLP: 27 March 2020) for important potential risk, progressive multifocal leukoencephalopathy. • Part II: Module SVII3.1: – Information has been updated and aligned with PBRER #1100411 (DLP: 27 March 2020) for information on missing information, safety in pediatric population. • Parts III.2 and III.3: – Study BA39730 – PV milestone has been updated (Table 45 and Table 50). • Editorial changes have been made to Part II: SI.1, Part II: Module SIV.1 (Table 14), and Module SVII3.2. • Part VI: – Link to EPAR has been included. • Annex 2: – PV milestone has been updated for Study BA39730 • Annex 3: – Protocol for Study BA39730 has been appended.
7.0	Evaluated Approved by CHMP on 21 February 2021	Combines changes as described above for versions 5.0 and 6.0, as well as corrections in response to additional EMA review comments received on 23 November 2020.
8.0	Evaluated	The risk of “Impaired immunization response” was removed from the list of safety concerns in the RMP. This is reflected in Part II, Module II: SVII.2, SVII 3.1.1 and SVIII, Part III and Part V. The missing information of “Safety of ocrelizumab following immunosuppressive/immunomodulating DMTs other than Avonex, Betaferon, Copaxone, or Rebif” was removed from the list of safety concerns in the RMP.

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		This was reflected in Part II, Module II: SVII.2, SVII 3.2 and SVIII, Part III and Part V. Justification for removal of the two safety concerns was included in Part II: Module SVII.2. The completed Study BN29739 was removed from the PV plan. This was reflected in Part III and Annex 2. The requirements of the GVP Guidance: Population-Specific Considerations III: Pregnant and Breastfeeding Women were reflected in the relevant section: additional information pertaining to this patient population was added in Part II: Module SI, SII, SIV.3, and Annex 7; the Roche standard pregnancy follow-up process was described in Part III. The milestones for Study BA39730 were updated in Part III, to reflect the change in PBRER periodicity. Other changes were implemented, as applicable: • The post-authorization exposure to ocrelizumab was updated in Part II: Module SV, in line with the most recent PBRER (1113817) with the DLP of 27 March 2022. • The characterization of the important potential risk of “PML” was updated in Part II: Module SVII.3.1, in line with the current knowledge. • Information on the missing information “Safety in pediatric population” was updated in Part II: Module SVII.3.2 and Part III. • Information on the missing information “Safety in pregnancy and lactation” and “Long-term safety of ocrelizumab treatment” were updated in Part II: Module SVII.3.2. • Annex 3 was updated with latest protocols version for BA39732 study (version 3.0), WA40404 study (version 4.0) and BN29739 study (version 8.0).

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		• Annex 4 was updated with latest version of post marketing infant guided questionnaires 'Infant's first year of life' and of clinical infant guided questionnaire ' Pregnancy Outcome and Infant Health Information on First Year of Life'. • MedDRA table and DSR for serious infections with decrease in Ig were removed from annex 7.
8.1	Evaluated Approved by CHMP on 16 March 2023	• Part II: Module SI: Diroximel fumarate was included in the overview of treatment options for multiple sclerosis. • In addition, since the MAH has recently received the Commission Decision for Ocrevus EU Renewal (issued on 21 September 2022) confirming that Ocrevus is no longer under additional monitoring in the EU, this was reflected in Part I: PRODUCT(S) OVERVIEW. • Minor editorial and formatting updates were made throughout, as needed, in line with PRAC rapporteur's comment in the Assessment Report.
9.0	Evaluated	The ocrelizumab EU RMP version 9.0 has been prepared to support an application for the extension of the marketing authorization for Ocrevus. The application relates to the registration of the subcutaneous (SC) formulation for all the currently approved indications for Ocrevus intravenous (IV), and it includes data from the pivotal clinical study CN42097 (OCARINA II) and from the supportive study CN41144 (OCARINA I). **Summary of significant changes in this RMP** Part II: Safety specifications • Module SI: Ublituximab was included in the overview of treatment options for multiple sclerosis (MS). • Module SII: A summary of the local tolerance studies conducted in rats and minipigs was added.

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		• Module SIII: The clinical trial exposure data was updated to reflect the newly proposed SC formulation. • Module SIV: Information related to pregnancy was updated to reflect the most updated post-marketing surveillance and registry data available. • Module SV: The post-marketing data on patient exposure was updated in line with the most recent PBRER with the data lock point 27 March 2023. The cumulative patient exposure per region has been moved to Annex 7. • Module SVII: The characterization of the safety concerns was updated with the available safety data from studies CN42097 and CN41144. Moreover, the important identified risk of infusion related reactions (IRRs) was updated to accommodate the different route of administration namely: injection reactions (IRs) with local or systemic symptoms. Local symptoms are the ones occurring at the SC injection site, and systemic symptoms can be similar to the IRR symptoms with IV infusions. Hence, the name of this important identified risk was updated to: infusion-related reactions (observed with the IV formulation) and injection reactions (observed with the SC formulation. Part V: Risk Minimization Measures • Part V.1 Routine Risk Minimization Measures and Part V.3 Summary of Risk Minimization Measures were updated to include the routine risk minimization measures associated with IRs. Part VI Summary of the Risk Management Plan • This part was updated to reflect the changes made in Parts I-V of the RMP. Annexes • Annex 3 was updated with the most recent PASS protocol versions; BA39732 version 4 and WA40404 version 5.

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		• Annex 7 was updated to include the most recent data on pregnancy and lactation in line with the most recent PBRER with the data lock point 27 March 2023. • Minor editorial and formatting updates were made throughout, as needed.
9.1 [b]	Parallel submission (under Evaluation)	Part II: Safety specifications • Module SI: Editorial changes were made to better describe the treatment regimen of cladribine in Table 2. • Module SII: Editorial changes were made to improve the clarity of the sentence regarding breast cancer and altered immune surveillance. • Module SIII: Editorial changes were made in the titles of the tables presenting the clinical trial exposure data for ocrelizumab IV to improve clarity and help distinguish them more easily from the tables presenting the clinical trial exposure data for ocrelizumab SC. • Module SVII: Changes were made to improve clarity, correct typographical errors, remove redundant information, and to indicate that data from the ocrelizumab SC development program is presented in an untabulated manner, while the tables present data from studies with ocrelizumab IV. Annexes • Annex 3 was updated to remove study BN29739 (VELOCE, listed as a category 3 study) which was completed with the final clinical study report dated 21 April 2022 and assessed within procedure EMEA/H/C/004043/II/0034/G. The protocol for study BN29739 was also removed from Annex 3. • Annex 4 was updated to include the route of administration in the Infant's First Year of Life follow-up questionnaire (Roche and Genentech versions).

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		• Annex 7 was updated to improve the document structure (numbering of appendices), so that it is clearer and more comprehensible. Minor editorial and formatting updates were made throughout, as needed.
Version 10.0	Current Submission	• Part II, SIV.3: Inclusion of the current data on Ocrevus use in lactating women. • The milestones for the submission date for the final clinical study report of Study WA40404 (O'HAND) has been updated to "June 2028" from "June 2024" and of Study BA39732 (MELODIC) has been updated to "June 2030" from "March 2030" in the following sections/Annex: – Part III.2 Additional Pharmacovigilance Activities. – Part III.3 Summary Table of additional pharmacovigilance activities. – Annex 2 "Tabulated Summary of Planned, Ongoing and Completed Pharmacovigilance Studies". • Part V.1 and Part V.3: the routine risk minimization activities to address the risk of safety in pregnancy and lactation, are updated to reflect the change to the breast-feeding recommendation proposed in the SmPC Section 4.6 Fertility, pregnancy and lactation. • Annex 7 was updated to remove the list of referenced material. In addition, this RMP reflects the updates proposed via the EU RMP 9.1 in the parallel ongoing procedure EMEA/H/C/004043/0039. Minor editorial and formatting updates were made throughout, as needed.

CHMP=Committee for Medicinal Products for Human Use; CSR = clinical study report; DLP=Data lock point; DMTs=disease-modifying therapies; DSR=Drug Safety Report; EPAR=European public assessment report; EU=European Union; FDA=Food and Drug Administration; GVP=good pharmacovigilance practices; IR = injection reactions; IRR = infusion related reactions; IV = intravenous; JAR=Joint Assessment Report; MAH=marketing authorization holder; MedDRA=Medical Dictionary for Regulatory Activities; MS = multiple sclerosis; PASS = post-authorization safety study; PMR= physical medicine and rehabilitation; PPMS=Primary-progressive multiple sclerosis; PRAC = Pharmacovigilance Risk Assessment Committee; PBRER=Periodic Benefit Risk Evaluation Report; PML=progressive multifocal leukoencephalopathy; RMP = risk management plan; SC = subcutaneous; SmPC=summary of product characteristics.

[a] Refers to the date of CHMP positive opinion. Note, not all versions of the EU RMP are approved by the CHMP.

[b] The CHMP Opinion for the EU RMP version 9.1 (procedure EMEA/H/C/004043/X/0039) is expected prior to the CHMP Opinion for the current procedure for version 10.0.