THE EU RISK MANAGEMENT PLAN FOR OCREVUS®/ OCRELIZUMAB

RMP version to be assessed as part of this application:

RMP Version number: 14.0

Data lock point for this RMP: 26 August 2025

Date of final sign off: See latest date in date stamps below

Date and Time (UTC)	Reason for Signing	Name
09-Sep-2025 08:03:51	Company Signatory (PV)	[redacted]
09-Sep-2025 08:19:18	Deputy QPPV	

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Rationale for submitting an updated EU RMP

The ocrelizumab EU Risk Management Plan (RMP) version 14.0 has been prepared to align the primary and secondary endpoints for Study WA40404 (O'HAND) with the current protocol and to update the milestone submission date for the final Clinical Study Report (CSR).

Furthermore, post-authorization exposure was updated to align with the latest Periodic Benefit Risk Evaluation Report (PBRER) with the data lock point (DLP) of 27 March 2025.

Summary of significant changes in this RMP:

- Part II, SIV.3: A correction was implemented regarding the unit of time for which 29 lactating women received ocrelizumab (corrected to months instead of weeks).
- Part II, SV.1: Post-authorization exposure was updated to align with the ocrelizumab PBRER 1137774 with a DLP of 27 March 2025.
- Part II, SVII.3.1.2.2: Information from post-authorization data on the important potential risk of progressive multifocal leukoencephalopathy (PML) has been updated to align with the ocrelizumab PBRER 1137774 with a DLP of 27 March 2025.
- Part II, SVII.3.1.3.3: The reference to the PBRER in the description of safety information in pediatric patients was updated to refer to the ocrelizumab PBRER 1137774 with a DLP of 27 March 2025.
- Part III, III.1: Based on feedback received from the European Medicines Agency (EMA), the text on the Roche standard pregnancy follow-up process included under Routine Pharmacovigilance Activities has been removed.
- Part III, III.2 (Table 57), III.3 (Table 59), and Annex 2: The primary and secondary endpoints, and the milestone submission date for the final CSR of Study WA40404 (O'HAND) have been updated.
- Part VI, II.C.2: The primary and secondary endpoints for Study WA40404 (O'HAND) have been updated.
- Annex 3: The latest protocol versions, Version 6.0 for Study WA40404 (O'HAND) and Version 6.0 for Study BA39732 (MELODIC), have been appended.
- Annex 4: The specific adverse drug reaction follow-up forms have been updated.
- Annex 7: The methodology used as well as the Summary Tabulations of Prospective and Retrospective Individual Case Safety Reports on Pregnancy, and the Table for Cumulative Exposure from Marketing Experience have been updated in line with the most recent PBRER (1137774) with a DLP of 27 March 2025.
- Annex 8: This has been updated to summarize the changes made to the RMP.

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

Other RMP Versions Under Evaluation

RMP Version Number: 13.0

Submitted: 8 August 2025

Procedure Number: EMA/VR/0000291534

Details of Currently Approved RMP

RMP Version Number: 12.1

Procedure Number: EMA/VR/0000286415

Date of approval (opinion date): 26 August 2025

See page 1 for signature and date

Dr. [redacted] (Deputy QPPV) Date

See page 1 for signature and date

Dr. [redacted] Date

PART I: PRODUCT(S) OVERVIEW

Table 1 Product(s) Overview

Active Substance(s) (INN or common name)	Ocrelizumab
Pharmacotherapeutic group(s) (ATC Code)	L04AG08
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.

Table 1 Product(s) Overview (Cont.)

	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.

Table 1 Product(s) Overview (Cont.)

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
JCV	JC virus
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

Abbreviation	Definition
PY	Patient Years
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

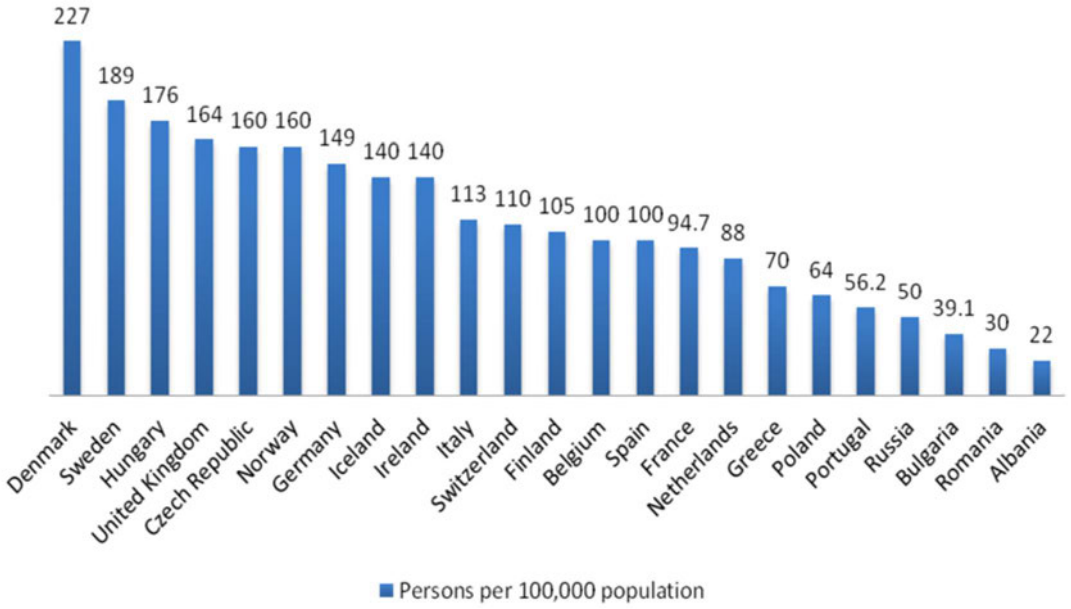
- Incidence and Prevalence

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[1]) 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).

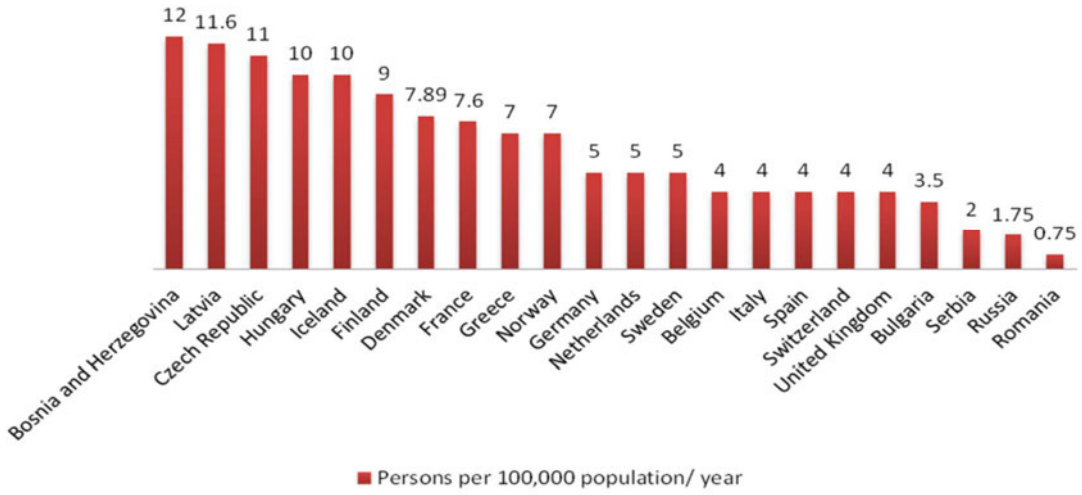
[1] Data specific to relapsing multiple sclerosis and primary progressive multiple sclerosis are not available. However, since approximately 85% of MS patients have relapsing multiple sclerosis, the prevalence of relapsing multiple sclerosis in North America and Europe can be estimated at 119 and 92 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

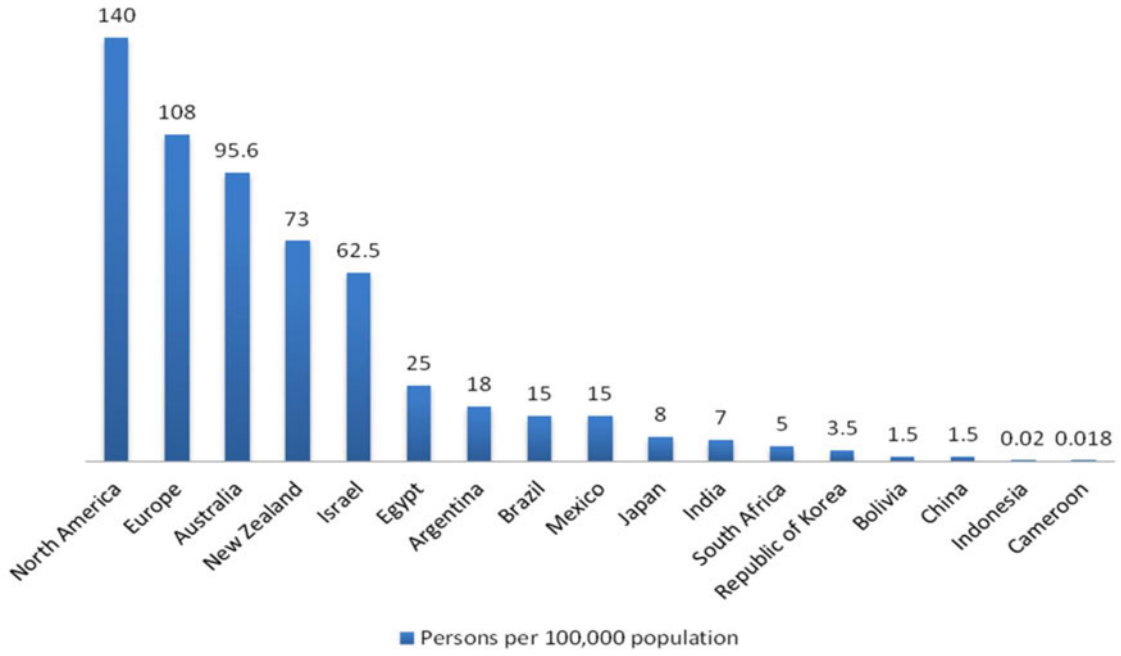


Note: Data may sometimes be based on unpublished studies or studies completed between 2008 and 2013. Source: MSIF 2013a.

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 2016a). 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 2016b; 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. 2015).

- 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.

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.

Program: root/clinical_studies/RO4964913/CDT30233/CN41144/data_analysis/CSR/prod/program/t_exp_cdose_py.sas
Output: root/clinical_studies/RO4964913/CDT30233/CN41144/data_analysis/CSR/prod/output/t_exp_cdose_py_SE_SC.out
21AUG2023 14:57 Page 1 of 1

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[2]

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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[2] 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[3]), 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[3]), 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[3]). 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.

[3] 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	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. 2020). 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 months 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 et al. 2023). Follow-up of 21 infants breastfed for at least 2 weeks showed 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. Relevant label changes were performed via Periodic Benefit Risk Evaluation Report (PBRER) procedure PSUSA/00010662/202403 and are reflected in Table 60 and Table 61.

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

The cumulative post-authorization exposure provided below is based on the data presented in the latest PBRER (DLP 27 March 2025).

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 point of DLP, i.e. 31 March 2025.

Dosing Assumptions

- **Intravenous (IV):** Each dose consists of two vials of 300 mg each, totaling 600 mg.
- **Subcutaneous (SC):** Each dose consists of a single 920 mg injection.

Persistence Assumption

In our current methodology, persistence rates reflect the proportion of patients remaining on therapy after each dose. Persistence rates have been updated, with changes taking effect after March 2023. These updates were based on extrapolated data from Germany, Canada, Italy, and Spain. While these adjustments do not alter past submissions, they are aimed at improving the precision of our present and future evaluations based on our latest understanding of ex-US persistence.

Since persistence rates are derived from consolidating and extrapolating available country data, this data may evolve over time, resulting in further updates.

Demographic breakdown

The demographic breakdown and the IV/SC split are based on IPSOS MS data for EU countries. In the demographic data, the breakdown by MS type simply reflects PPMS (Primary Progressive Multiple Sclerosis) and RMS (Relapsing forms of Multiple Sclerosis).

Patient-years methodology

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 the date of actual exposure within the month is not accurately available (month average estimate) until end of the period (March 2025), up to a maximum of 12 months. For each continuing patient, the exposure is estimated starting in the middle of the first month since the date of actual exposure within the month is not accurately available (month average estimate) until the end of the period (March 2025). This methodology is aligned with Global Safety and Reporting Team recommendations.

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, a constant steady state of 5% stocks was assumed. For EEA ex-EU5 countries (i.e., EEA countries except Germany, France, Italy, Spain, and United Kingdom), a constant steady state of 5% was also assumed. For the EU5 countries (Germany, France, Italy, Spain, and United Kingdom), country specific stock assumptions were made, 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.

For demographic breakdowns, U.S.-based assumptions were applied to ex-U.S. exposures up to the previous PBRER due to limited reliable data. For the current reporting interval, IPSOS data has been used to inform the demographic splits.

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 2025.

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.

Also, in the U.S., the subcutaneous formulation of ocrelizumab is marketed under the brand name OCREVUS ZUNOVO®.

Demographic breakdown

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.

Patient-years methodology

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 the date of actual exposure within the month is not accurately available (month average estimate) until end of the period (March 2025), up to a maximum of 12 months. For each continuing patient, the exposure is estimated starting in the middle of the first month since the date of actual exposure within the month is not accurately available (month average estimate) until the end of the period (March 2025). This methodology is aligned with Global Safety and Reporting Team recommendations.

Limitations to the U.S. Methodology

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

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

SV.1.2 Exposure

Since the IBD (28 March 2017) until 31 March 2025, an estimated cumulative total of 408,744 patients have received ocrelizumab (IV or SC) from marketing experience. This corresponds to an estimated 1,274,195 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	-	-	-	0	0
	Not recovered/Not resolved				0	0
	Recovered/Resolved				1/8 (12.5%)	13/13 (100.0%)
	Recovered/Resolved with sequelae				7/8 (87.5%)	0
	Recovering/Resolving				0	0
	Unknown				0	0
Dose 5 Infusion 1	Fatal	-	-	0	0	0
	Not recovered/Not resolved			0	0	0
	Recovered/Resolved			64/64 (100.0%)	9/9 (100.0%)	30/30 (100.0%)
	Recovered/Resolved with sequelae			0	0	0
	Recovering/Resolving			0	0	0
	Unknown			0	0	0
Dose 5 Infusion 2	Fatal	-	-	0	0	0
	Not recovered/Not resolved			0	0	0
	Recovered/Resolved			16/16 (100.0%)	3/3 (100.0%)	19/19 (100.0%)
	Recovered/Resolved with sequelae			0	0	0
	Recovering/Resolving			0	0	0
	Unknown			0	0	0
Dose 6 Infusion 1	Fatal	-	-	0	0	0
	Not recovered/Not resolved			1/26 (3.8%)	0	0
	Recovered/Resolved			25/26 (96.2%)	5/5 (100.0%)	28/28 (100.0%)
	Recovered/Resolved with sequelae			0	0	0
	Recovering/Resolving			0	0	0
	Unknown			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[4], 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%

[4] 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[5] 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[6] 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:

[5] Assumes 9% lower malignancy risk in MS vs. the general population (Catalá-López et al. 2014).
[6] 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:

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 March 2025, there have been 17 confirmed cases of PML in approximately 408,744 patients with MS treated with ocrelizumab reported from post-marketing sources. Of these 17 confirmed PML cases, 12 cases are carry-over cases of PML attributed to prior DMT exposure. In the remaining five cases, the patients had not had prior exposure to DMTs known to be causally associated with PML. One case was confounded by advanced age and the presence of pre-existing lymphopenia. In the second 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). In the third case, there was limited information regarding the patient's medical history, past drugs, concurrent conditions, concomitant medications and baseline levels of the JC virus (JCV) of the patient which precludes adequate medical assessment. The fourth case concerned a patient who was initially diagnosed with haemophilus encephalitis but as the situation deteriorated, he tested positive for JCV DNA and was diagnosed with PML. In the fifth case, a female was diagnosed with PML. Although, a potential causal association with ocrelizumab cannot be excluded in this case, concomitant immunosuppressive condition (renal cell carcinoma) was a possible risk factor.

Based on the amount of the post-marketing exposure and the cumulative number of PML cases, PML remains a very rare adverse event in patients treated with ocrelizumab.

Seriousness/Outcomes:

All 17 confirmed cases (as of 27 March 2025) were reported as serious. Of the 12 confirmed carry-over cases, 2 patients died, in the remaining 10 cases, event outcome was reported as not recovered/not resolved in 4, recovered/resolved in 3, recovering/resolving in 1, and was not reported in 2 cases. In the 5 confirmed non-carry-over cases, 4 patients died and one patient resolving.

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 2016). 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 neonates and infants exposed to ocrelizumab and the potential duration of B-cell depletion in neonates and infants is unknown (see Section 4.6 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 2025) of the most recent PBRER RDR 1137774 (reporting interval 28 March 2024 to 27 March 2025) 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 PBRER RDR 1122140 (reporting interval 28 March 2022 to 27 March 2023), 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).

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 with PPMS, on the basis of the composite 12-week CDP either in 9-HPT or EDSS score, whichever occurs earlier, as the primary efficacy outcome and the key secondary efficacy endpoints as below, in hierarchical order: • Time to 12-week CDP in 9-HPT • Time to 12-week CDP in EDSS • Time to 24-week CDP in 9-HPT • Time to 24-week CDP in EDSS • Annual rate of percent change from baseline in total volume of T2 lesions • Annual rate of percent change from Week 24 in total brain volume 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: January 2029

9-HPT = 9-Hole Peg Test; CDP = confirmed disability progression; 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 with PPMS exposed to ocrelizumab to	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 until September 2025 and annual safety reports from March 2026 onwards Interim report 1 Interim report 2 Interim report 3	2019 2028 Cumulative reports submitted with PBRER 2022 2024 2026

Study/ Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
	the safety profile of patients with PPMS not exposed to any DMTs.		Final report of study results	2029
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	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
	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 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 with PPMS, on the basis of the composite 12-week confirmed disability progression either in the 9-HPT or EDSS score, whichever occurs earlier, as the primary efficacy outcome and the key secondary endpoints as below in hierarchical order: • Time to 12-week CDP in 9-HPT • Time to 12-week CDP in EDSS • Time to 24-week CDP in 9-HPT • Time to 24-week CDP in EDSS • Annual rate of percent change from baseline in total volume of T2 lesions • Annual rate of percent change from Week 24 in total brain volume	Infection Malignancies including breast cancer Long-term safety of ocrelizumab treatment	Final report	January 2029

Study/ Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
	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			

9HPT = 9-Hole Peg Test; CDP = confirmed disability progression; 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 event.

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 4 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
	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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	(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-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	

Safety concern	Risk minimization measures	Pharmacovigilance activities
	reactions such as serious infusion related reactions (IRRs). **Additional risk minimization measures:** None	
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.	**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
	• 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. **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.	**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
	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. **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.	**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
	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. **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 4 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. Ocrelizumab	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire **Additional pharmacovigilance activities:** Study BA39732

Safety concern	Risk minimization measures	Pharmacovigilance activities
	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. **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 concern	Risk minimization measures	Pharmacovigilance activities
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 4 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	
	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 PPMS, on the basis of the composite 12-week CDP either in the 9-HPT or EDSS score, whichever occurs earlier, as the primary efficacy outcome and the key secondary endpoints as below in hierarchical order:

- Time to 12-week CDP in 9-HPT
- Time to 12-week CDP in EDSS
- Time to 24-week CDP in 9-HPT
- Time to 24-week CDP in EDSS
- Annual rate of percent change from baseline in total volume of T2 lesions
- Annual rate of percent change from Week 24 in total brain volume.

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 4:

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Questionnaire
Infant's first year of life follow-up

AER:		Type of ocrelizumab exposure:	☐ In utero exposure ☐ Exposure via breastfeeding
Site No:		Patient* ID/Initials:	
Local Case ID:		Patient* Date of Birth (DD-MMM-YYYY) / Age:	
Pregnancy Reporting Form:	☐ Form sent out, ☐ Form returned		

* 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 the last menstrual period or during pregnancy, we would like to ask you to complete this questionnaire (in addition to the company's global pregnancy reporting form). While available data on cumulative pregnancy outcomes in women with MS receiving OCREVUS have shown no increased risk of adverse outcomes, data on infant follow-up during the first year of life remains limited.. Similarly, data from two prospective trials, MINORE (MN42988) and SOPRANINO (MN42989) have shown minimal placental and breastmilk transfer of OCREVUS in pregnant and lactating women with MS as well as no B cell depletion in infants. However, data on B cell levels from infants whose mothers were given OCREVUS during pregnancy or mothers who received OCREVUS at higher doses are limited or completely missing. . In this questionnaire, we are seeking information on the health of the infant during his/her first year of life, focusing on B cell levels, 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**
Overall status of neonate / infant	☐ Normal ☐ Abnormal; specify abnormality: _____ ☐ Neonatal/infant death; specify cause and date of death:	

1

2. Status of neonate/infant during his/her first year of life *(table 2 to be filled out at each assessment)*		
	_____	
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 ***Please specify test result(s) (including units), normal range, test date (DD-MM-YYYY) and infant age (weeks):*** Test result (units): _____ Normal range: _____ Test date: _____ Infant age (weeks): _____	
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 at birth *(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: _____
Neutrophil 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)*			
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	□ 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.)**
			□ Booster		
□ Pneumococcal			□ Initial □ Booster	□ Yes, □ No	
□ 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	
□ Measles, Mumps and Rubella			□ Initial □ Booster	□ Yes, □ No	
□ Varicella			□ 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:

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Genentech
A Member of the Roche Group

Questionnaire
Infant's first year of life follow-up

AER:		Type of ocrelizumab exposure:	☐ In utero exposure ☐ Exposure via breastfeeding
Site No:		Patient* ID/Initials:	
Local Case ID:		Patient* Date of Birth (DD-MMM-YYYY) / Age:	
Pregnancy Reporting Form:	☐ Form sent out, ☐ Form returned		

* 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 the last menstrual period or during pregnancy, we would like to ask you to complete this questionnaire (in addition to the company's global pregnancy reporting form). While available data on cumulative pregnancy outcomes in women with MS receiving OCREVUS have shown no increased risk of adverse outcomes, data on infant follow-up during the first year of life remains limited.. Similarly, data from two prospective trials, MINORE (MN42988) and SOPRANINO (MN42989) have shown minimal placental and breastmilk transfer of OCREVUS in pregnant and lactating women with MS as well as no B cell depletion in infants. However, data on B cell levels from infants whose mothers were given OCREVUS during pregnancy or mothers who received OCREVUS at higher doses are limited or completely missing. . In this questionnaire, we are seeking information on the health of the infant during his/her first year of life, focusing on B cell levels, 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**
Overall status of neonate / infant	☐ Normal ☐ Abnormal; specify abnormality: _____ ☐ Neonatal/infant death; specify cause and date of death:	

1

2. Status of neonate/infant during his/her first year of life *(table 2 to be filled out at each assessment)*		
	_____	
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 ***Please specify test result(s) (including units), normal range, test date (DD-MM-YYYY) and infant age (weeks):*** Test result (units): _____ Normal range: _____ Test date: _____ Infant age (weeks): _____	
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 at birth *(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: _____
Neutrophil 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)*			
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	□ 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.)**
			□ Booster		
□ Pneumococcal			□ Initial □ Booster	□ Yes, □ No	
□ 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	
□ Measles, Mumps and Rubella			□ Initial □ Booster	□ Yes, □ No	
□ Varicella			□ 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:

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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: .....

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 in serum/plasma

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: .....

6

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 <u>in cerebrospinal fluid (CSF)</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 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 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

(NOT APPLICABLE)