THE EU RISK MANAGEMENT PLAN FOR OCREVUS®/ OCRELIZUMAB

RMP version to be assessed as part of this application:

RMP Version number: 8.1

Data lock point for this RMP: 21 April 2022

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

Date and Time (UTC)	Reason for Signing	Name
[redacted]		

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Rationale for submitting an updated EU RMP

The ocrelizumab EU risk management plan (RMP) version 8.1 has been prepared in response to the Committee for Medicinal Products for Human Use/Pharmacovigilance Risk Assessment Committee (CHMP/ PRAC) joint assessment report for the Ocrevus Grouped Type II Variation (C.I.13), procedure number EMEA/H/C/004043/II/0034/G, to address concern #5 of the Request for supplementary information (RSI): "The MAH is kindly asked to include diroximel fumarate in the overview of treatment options for MS (RMP Table 2, p. 22)".

Summary of significant changes in this RMP

- Part II: Module SI: Diroximel fumarate was included in the overview of treatment options for multiple sclerosis (MS).
- In addition, since the Marketing Authorisation Holder (MAH) has recently received the Commission Decision for Ocrevus EU renewal (issued on 21 September 2022) confirming that Ocrevus is no longer under additional monitoring in the EU, this was reflected in Part I: PRODUCT(S) OVERVIEW.
- Minor editorial and formatting updates were made throughout, as needed, in line with the PRAC Rapporteur's comment in the Assessment Report.

Other RMP versions under evaluation
Not applicable

Details of Currently Approved RMP versions:

RMP Version Number: 7.0

Procedure Number: EMEA/H/C/4043/II/21

Date of approval (opinion date): 21 February 2021

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PART I: PRODUCT(S) OVERVIEW

Table 1 Product(s) Overview

Active Substance(s) (INN or common name)	Ocrelizumab
Pharmacotherapeutic group(s) (ATC Code)	L04AA36
Marketing Authorization Holder (or Applicant)	Roche Registration GmbH.
Medicinal products to which this RMP refers	One
Invented name(s) in the European Economic Area (EEA)	Ocrevus®
Marketing authorization procedure	Centrally Authorized Product
Brief description of the product including:	Chemical Class: Recombinant humanized monoclonal antibody
	Summary of mode of action: Ocrelizumab selectively targets cluster of differentiation antigen 20 (CD20)-expressing B cells. CD20 is a cell surface antigen found on pre-B cells, mature and memory B cells but not expressed on lymphoid stem cells and plasma cells. The precise mechanisms through which ocrelizumab exerts its therapeutic clinical effects in multiple sclerosis (MS) are not fully elucidated but is presumed to involve immunomodulation through the reduction in the number and function of CD20-expressing B cells. Following cell surface binding, ocrelizumab selectively depletes CD20-expressing B cells through antibody-dependent cellular phagocytosis, antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and apoptosis. The capacity of B-cell reconstitution and preexisting humoral immunity are preserved. In addition, innate immunity and total T-cell numbers are not affected.
	Important information about its composition: Ocrelizumab is a humanised monoclonal antibody produced in Chinese Hamster Ovary cells by recombinant DNA technology. Each vial contains 300 mg of ocrelizumab in 10 mL at a concentration of 30 mg/mL. The final drug concentration after dilution is approximately 1.2 mg/mL. *Excipients:* Sodium Acetate Trihydrate, Glacial Acetic Acid, Trehalose Dihydrate, Polysorbate 20 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: Not applicable
Dosage in the EEA	Current: Ocrelizumab is administered by intravenous (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. Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Concentrate for solution for 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. 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.

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
AST	aspartate transaminase
BSRBR	British Society of Rheumatology Biologics Registers
CCOD	clinical cut-off date
CD	cluster of differentiation antigen
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CNS	central nervous system
COVID-19	coronavirus disease 2019
CRCL	creatinine clearance
CSF	cerebrospinal fluid
CSR	Clinical Study Report
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
ER+	estrogen receptor positive
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

Abbreviation	Definition
HB	hepatitis B
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HER2+	human epidermal growth factor 2
HIV	human immunodeficiency virus
IBD	international birth date
IFN	interferon
Ig	immunoglobulin
IR	incidence rates
IRR	infusion-related reaction
IV	Intravenous
JC	John Cunningham (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
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

Abbreviation	Definition
PSUR	Periodic Safety Update Reports
PV	Pharmacovigilance
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
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

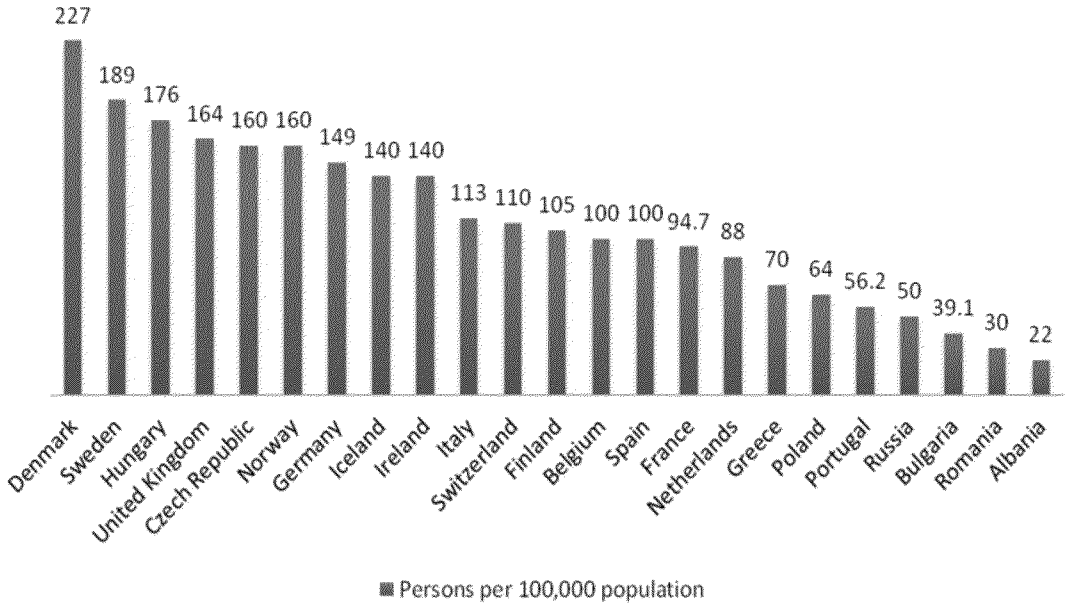
- Incidence and Prevalence

While 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).

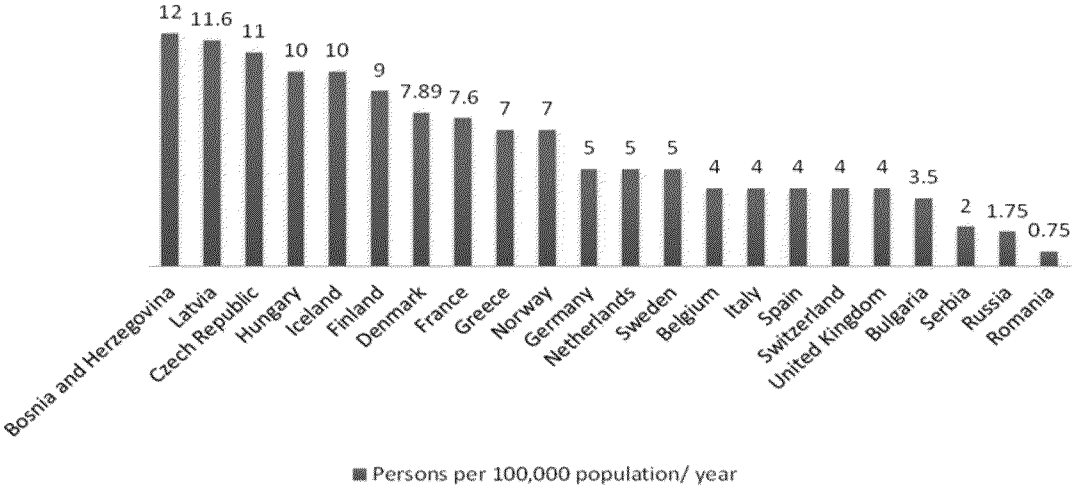
[1] Data specific to relapsing multiple sclerosis and primary progressive multiple sclerosis are not available. However, since approximately 85% of MS patients have relapsing multiple sclerosis, the prevalence of relapsing multiple sclerosis in North America and Europe can be estimated at 119 and 92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

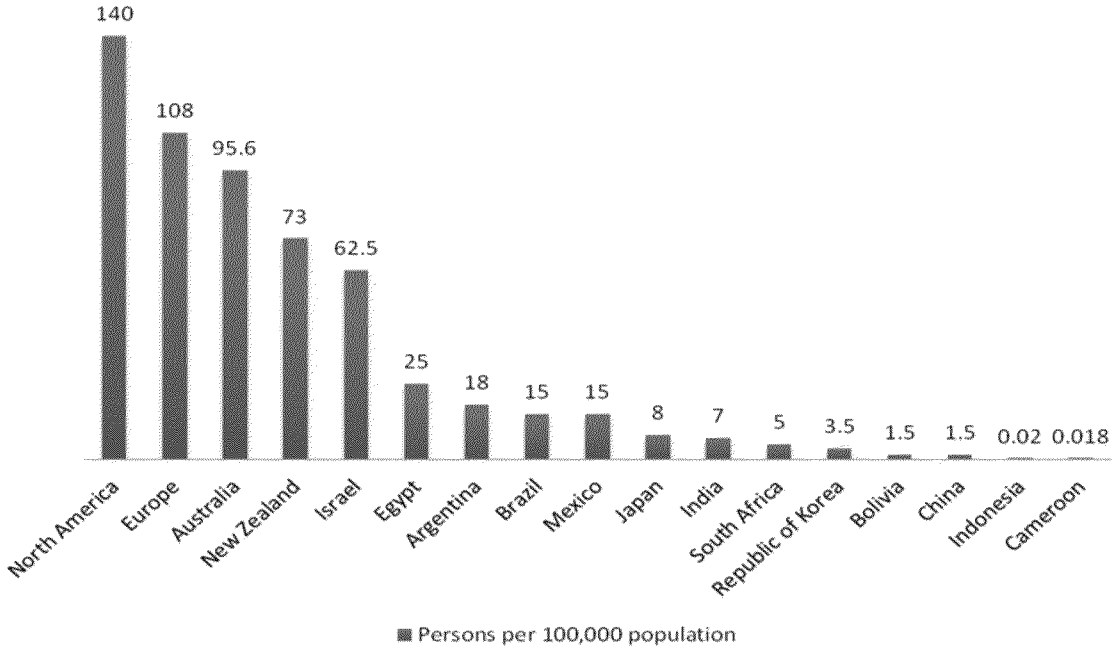


Note: Data may sometimes be based on unpublished studies or studies completed between 2008 and 2013. Source: MSIF 2013a.

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, women are affected by MS approximately twice to thrice as often as men (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 gender prevalence difference (Cottrell et al. 1999; Tremlett et al. 2005; Tullman et al. 2013; MSIF 2013a).

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

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

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

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

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

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

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

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

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

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

- The main existing treatment options:

In addition to treatments for the symptoms of MS and treatment of relapses (such as corticosteroids), there are currently more than a dozen (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
Mavenclad®	Cladribine	Oral	10 mg or 20 mg as a single daily dose for 4 or 5 days	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

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]
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
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.	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]
			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.		

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)

Symptom of Multiple Sclerosis	Medications used to treat the symptom
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
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

Symptom of Multiple Sclerosis	Medications used to treat the symptom
Oculomotor disorders	Memantine, gabapentin (also in combination; in pendular nystagmus), baclofen, amifampridine (in upbeat/downbeat nystagmus), high dose corticosteroids (only in initial treatment)

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

- Risk factors for the disease:

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

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

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

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

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

Patients with some autoimmune disorders (e.g., type 1 diabetes mellitus [Nielsen et al. 2006] or inflammatory bowel disease [Gupta et al. 2005]) have an increased risk of developing MS. (Nielsen et al. (2006) found the risk in patients with type 1 diabetes mellitus to be 3-fold higher (Nielsen et al. 2006). The shared risk for these diseases may be due to shared genetic susceptibility and/or environmental exposures such as smoking (Marrie et al. 2011; Marrie et al. 2015d).

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

Mortality and morbidity:

- Multiple sclerosis is a serious, disabling disease and the leading cause of non-traumatic 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 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. World Health Organization 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	N of pregnancies in PreMS (n=223)	N 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

The cynomolgus monkey was considered the most appropriate model for nonclinical safety studies as ocrelizumab is only known to bind to human and non-human primate cluster of differentiate 20 (CD20). For this reason, all nonclinical safety studies were conducted in cynomolgus monkeys.

SII.1 TOXICITY:

SII.1.1 General toxicity

SII.1.1.1 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.1.2 Reproductive and developmental toxicity studies (neonates)

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

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

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

Relevance to human usage: No

Discussion:

Exposure in utero to ocrelizumab and vaccination of neonates and infants with live or live-attenuated vaccines. Due to the potential depletion of B-cells in neonates and infants of mothers who have been exposed to ocrelizumab during pregnancy, it is recommended that vaccination with live or live-attenuated vaccines should be delayed until B-cell levels have recovered; therefore, measuring CD19-positive B-cell level, in neonates and infants, prior to vaccination is recommended.

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

SII.1.2.1 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 *Acinetobacter* 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.1.2.2 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 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 the 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.1.3 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.1.4 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. A variety of subtypes (e.g., estrogen receptor [ER] and/or progesterone receptor positive [PR+]; human epidermal growth factor 2 positive [HER2+]) was reported without a consistent pattern of biologic subtype, which is inconsistent with a hypothesis of causation due to altered immune surveillance. Moreover, there is not a clear biological rationale why an increased risk of breast cancer would occur over that of multiple solid tumors.

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. The additional experience available from the studies in non-MS indications (such as RA) is presented where it is considered relevant.

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 10. 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 10 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 10 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; 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.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.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 11, by cumulative doses in Table 12, and by treatment duration in Table 13. 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 11 Exposure to Ocrelizumab 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 11 Exposure to Ocrelizumab 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 12 Exposure to Ocrelizumab 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 13 Exposure to Ocrelizumab 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

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
> 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.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.1.2.1 Rheumatoid Arthritis

Exposure to ocrelizumab in clinical studies in RA by number of doses is presented in Table 14, by cumulative doses in Table 15, and by treatment duration in Table 16.

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 of RA patients in the 400 mg group and 947 of 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.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 14 Exposure to Ocrelizumab 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 15 Exposure to Ocrelizumab 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 16 Exposure to Ocrelizumab 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

Treatment Duration (Months)	Pool E (RA All Exposure) OCR (N=2926)	
	n (%)	PY
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 17 and by race in Table 18. 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 17 Exposure to Ocrelizumab 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 18 Exposure to Ocrelizumab 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. Patient Demography in Non-Multiple Sclerosis Indications

SIII.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 19 and by race in Table 20.

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 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 19 Exposure to Ocrelizumab 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; 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 20 Exposure to Ocrelizumab 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.3 Exposure in Special Patient Populations

SIII.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.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 pharmacokinetic (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.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[2]), 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[2]), 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[2]). 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.

[2] Normal ranges as per Merck Manual.

SIII.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 21 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 ($<300/\mu L$, and $<1.5\times10^3/\mu L$, 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.
CHFNYHA 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

Use in Pregnancy and Lactation

MS is a chronic, inflammatory, demyelinating, neurodegenerative disease of the CNS that primarily affects women of childbearing potential, with onset typically between 20 and 40 years of age (Walton et al. 2021). As pregnant and lactating women have been historically excluded from pre-authorisation 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 recently initiated 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 R. 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 31 March 2021, 1,223 MS pregnancies were reported in women treated with ocrelizumab (Dobson et al. 2021), a growth of approximately 100% over the previous year (n=608; Bove et al. 2020). Characterising 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 on use during breastfeeding are more limited; however, no serious infant adverse outcomes have been reported (Dobson et al. 2021; Ciplea et al. 2020).

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 1578 pregnancy cases with no safety concern identified for any risk of ocrelizumab associated with spontaneous/missed abortion, fetal death, stillbirth, induced abortion, premature birth, structural malformations, functional deficits, or growth abnormalities. The review of the cases did not reveal any safety signal or safety concern regarding ocrelizumab use in pregnancy and lactation that would warrant any changes to the label or the RMP.

While clinical outcomes reported for pregnancies are reassuring to date, there is a need for more granular information on biological effects that could influence rarer, or longer-term, risks (e.g., prolonged B cell depletion/repletion, susceptibility to certain type of infections, impaired immunization response). A little is known 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. Thirdly, 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, an 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).

Table 22 Exposure of Special Populations Included or not in Clinical Trial Development Program

Type of Special Population	Exposure
Pregnant women	46 patients[a]
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities	
Patients with moderate and severe hepatic impairment hepatic impairment	Not included in the clinical development program,
Patients with moderate and severe renal impairment	Not included in the clinical development program.
Patients with cardiovascular impairment	1 patient
Population with relevant different ethnic origin	Refer to Table 18 and Table 20 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 17 above

[a] Drug Safety Report 1067126.

PART II: MODULE SV— POST-AUTHORIZATION EXPERIENCE
SV.1 POST-AUTHORIZATION EXPOSURE
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 IQVIA and a combination of Symphony Health (SHA) claims data (Symphony Health Solutions/PRA Health Science) (for April 2017–March 2022) and shipment data from distributors.

Calculation of the estimated total patient exposure numbers and total patient-years 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 [COPA]). 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 data lock point (DLP) i.e. 31 March 2022.

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

Persistence rates indicate the proportion of patients remaining on therapy after each dose based on a proxy for ocrelizumab: real world data (RWD) for Gilenya (MSBase) compared to network meta-analysis of randomized controlled trial data for Gilenya suggests a 1.85 times higher discontinuation observed in the real world. Current assumption estimates 89% of patients remaining on therapy from first to second dose. Based on U.S. SHA Claims data the retreatment interval is assumed to be 28 weeks. In the United States, current assumption estimates 81% of patients remaining on therapy from first to second dose.

Overall exposure is calculated in PYs on ocrelizumab. Market exposure data provides estimates on new patients starting treatment each month in the period. For each new patient, the exposure is estimated starting in the middle of the first month since date of actual exposure within the month is not accurately available (month average estimate) until end of the period (March 2022), up to a maximum of 12 months. For each continuing patient, the exposure is estimated starting in the middle of the first month since date of actual exposure within the month is not accurately available (month average estimate) until end of the period (March 2022), up to a maximum of 12 months. This methodology is aligned with Global Safety and Reporting Team recommendation.

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

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

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

Limitations to the EU and RoW Methodology

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

The persistence rate at launch is based on MS analogues. There are currently no other approved products in MS with a dosing frequency every 6 months. Current assumptions may need to be revised once RWD are available to assess average number of doses per patient.

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

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

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

United States Methodology Assumptions:

In the United States, patient estimates are based on IQVIA and a combination of SHA claims data (for April 2017 – March 2022) and shipment data from distributors.

Consistent with the EEA and RoW data, the exposures reported represent data through 31 March 2022.

SHA claims for ocrelizumab are collected based on monthly adjudicated claims. This includes products distributed through specialty pharmacies and medical procedure data for IV products. Adjudicated claims take at least 6 weeks to be reported. Final claims data typically covers approximately 30% of the U.S. market. Final patient counts are projected up to the total market based on a syndicated data source (IMS National Sales Perspectives or NSP) to account for the incomplete claims capture.

An incremental 13% bulk-up is applied to account for non-commercial vials (Genentech Access to Care Foundation). This assumption is based on the volume of vials that are sent through the third party distributor responsible for free good distribution.

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

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

Overall exposure is calculated in PYs on ocrelizumab. Market exposure data provides estimates on new patients starting treatment each month in the period. For each new patient, the exposure is estimated starting in the middle of the first month since date of actual exposure within the month is not accurately available (month average estimate) until end of the period (March 2022), up to a maximum of 12 months. For each continuing patient, the exposure is estimated starting in the middle of the first month since date of actual exposure within the month is not accurately available (month average estimate) until end of the period (March 2022), up to a maximum of 12 months. This methodology is aligned with Global Safety and Reporting Team recommendation.

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

Limitations to the U.S. Methodology

As noted previously, claims data does not represent 100% capture rate of treated patients, and final patients are adjusted to account for this capture rate. Additionally, the adjudication process typically takes 6 weeks after a claim is submitted, and as a result restatements do occur (typically for the prior month). On average the level of restatement is <10%, but has been as large as 17% within the MS market in the last 12 months. Therefore, current estimated exposures may need to be revised over time as additional claims data becomes available.

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

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

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

The pandemic situation and national authorities calling out lockdowns has affected the data in this report: as the impact of coronavirus disease 2019 (COVID-19) is yet to be estimated, and the lack of reliable data for ex-U.S. make it difficult to be assessed. However, in anticipation of the rapidly evolving situation with COVID-19, Roche has been working with partners to make necessary arrangements regarding staff, equipment and support structure to minimize impact on business and business continuity.

SV.1.2 Exposure

Since the IBD (28 March 2017) until 31 March 2022, an estimated cumulative total of 250,428 patients have received ocrelizumab from marketing experience. This is equivalent to an estimated 510,060 patient years of exposure since IBD). (see Table 23).

Table 23 Cumulative Exposure from Marketing Experience in European Economic Area, Rest of World, and United States

Region	Indication			Sex			Age (years)				Total	PY
	RMS	PPMS	Unk	M	F	Unk	<18	≥18-65	≥66	Unk		
EEA	45,223	22,274	0	23,624	43,873	0	675	47,922	18,899	0	67,496	**126,081**
RoW	36,603	18,028	0	19,121	35,510	0	546	38,788	15,297	0	54,631	**95,881**
U.S.	85,962	42,339	0	44,905	83,396	0	1,283	91,094	35,924	0	128,301	**288,098**
Total	**167,787**	**82,641**	**0**	**87,650**	**162,778**	**0**	**2,504**	**177,804**	**70,120**	**0**	**250,428**	**510,060**

EEA=European Economic Area; F=female; M=male; PPMS=primary progressive multiple sclerosis; PY=patient-years; RMS=relapsing forms of multiple sclerosis, RoW=rest of world; U.S.=United States, Unk=unknown.

Note: RMS refers to RRMS and all forms of SPMS.

Rounding errors may be introduced in the total figures.

Age split is not available for Serbia (ExBP-Hemopharm), and thus included under 'Unkown'.

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

Not applicable.

SVII.1.2Risks 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; however, the safety concerns "Impaired immunization response" and 'Safety of ocrelizumab following immunosuppressive/immunomodulating DMTs other than Avonex, Betaferon, Copaxone, or Rebif' have been removed from the list of safety concerns:

Removal of the risk of "Impaired immunization response"

The final clinical study report (CSR) for Study BN29739 is provided with this application, in accordance with the required PV activities previously listed in Part III, which included submission of the final CSR (by the end of Quarter 1 in 2023) as a planned PV milestone for this Category 3 study.

With the submission of this Final CSR, the MAH proposes to make the following changes to the RMP:

- Remove Study BN29739, since the study is complete and the PV milestone has been met.
- Remove the corresponding risk of impaired immunization response, because it is reclassified from 'important identified risk' to 'identified risk' and, as per the current Guideline on good pharmacovigilance practices (GVP) (EMA 2017), not important risks are not to be included in the RMP.

The risk of impaired immunization response is no longer classified as important for the following reasons:

Study BN29739, the single outstanding PASS investigating the risk of impaired immunization response, is now complete.

- The Final CSR does not further characterize the risk of impaired immunization response described in the Primary CSR. Therefore, no additional PV activities or additional risk minimization measures other than the routine measures currently implemented (in the form of vaccination recommendations included in Section 4.4 of the Summary of Product Characteristics [SmPC]) are deemed necessary.
- Impaired immunization response remains an identified risk. Its clinical impact on patients (the clinical outcome being occurrence and severity of preventable infections) and its importance for the overall benefit-risk profile of ocrelizumab will continue to be assessed through characterization of the important identified risk of infections.

Removal of the missing information 'Safety of ocrelizumab following immunosuppressive/immunomodulating DMTs other than Avonex, Betaferon, Copaxone, or Rebif"

Safety of ocrelizumab following immunosuppressive/immunomodulating DMTs other than Avonex, Betaferon, Copaxone, or Rebif, previously classified as missing information is removed from the list of safety concerns since accumulated data from studies MA30005 and MN30035 provides sufficient understanding of the safety of ocrelizumab in this patient population.

Administration of ocrelizumab following immunosuppressive/immunomodulatory DMTs (other than Avonex, Betaseron, Copaxone, or Rebif) was not permitted in the ocrelizumab pivotal clinical trials, therefore this was considered to be missing information. Because of the potential for overlapping pharmacodynamic (PD) effects of sequential use of these medications and ocrelizumab, which theoretically may, for example, lead to an increased risk of infections, the safety profile in such patients may differ from the safety profile observed in clinical trials. The MAH initiated two Phase IIIb studies (MA30005 [conducted in 15 countries across Europe and in Turkey] and

MN30035 [conducted in the United States and Canada]) to further characterize the ocrelizumab treatment effect in this population.

Study MA30005 enrolled 681 patients (1 patient did not receive treatment). The Primary CSR presents safety data at the time of the primary analysis (clinical cutoff date [CCOD] 25 October 2019). The median treatment duration was 98.0 weeks.

There were no new safety findings associated with ocrelizumab in this study. The majority of AEs were of Grade 1 or 2 intensity; AEs of Grade 3 intensity or higher were reported in 11.9% of patients. There was one death (completed suicide), which was deemed unrelated to ocrelizumab. Infusion-related reactions (IRRs) were the most frequently reported AEs (reported in 43.2% of patients), and none were higher than Grade 3. IRRs were most common after the first infusion (reported in 31.9% of patients after the first infusion), occurring at lower frequencies after subsequent infusions, which is consistent with the results from the pivotal trials WA21092 and WA21093. SAEs were reported in 7.2% of patients, and SIs were infrequent (1.6% of patients). AEs led to withdrawal of ocrelizumab in 1.0% of patients. The safety profile of ocrelizumab was therefore consistent with prior experience, and no new safety signals were identified.

Study MN30035 enrolled 608 patients and most patients (96.1%) were on treatment for at least 48 weeks. The study is complete, with results reported in the Final CSR (CCOD 3 May 2019). There were no new safety findings associated with ocrelizumab in this study. The majority of AEs were of Grade 1 or 2; Grade 3-4 AEs were reported in 12.7% of patients, and no Grade 5 AEs were reported. IRRs were the most frequently reported AEs for ocrelizumab (reported in 43.3% of patients), and the highest incidence of IRRs was associated with the first ocrelizumab infusion of Dose 1 (Dose 1, Day 1: 33.9% of patients) and decreased following the second ocrelizumab infusion dose. Most IRRs were Grade 1 or 2 in severity, and no Grade 4 or 5 IRRs were reported. These findings are consistent with data from the pivotal trials WA21092 and WA21093. Overall, no patients discontinued treatment due to IRRs. SAEs were reported in 7.7% of patients, and AEs led to withdrawal of ocrelizumab in 1.3% of patients. Overall, the safety profile of ocrelizumab was consistent with prior experience, and no new safety signals were identified.

On the basis of the final results of Studies MA30005 and MN30035, the safety profile of ocrelizumab in patients with RRMS who had a suboptimal response to an adequate course of DMTs was consistent with the known safety profile of ocrelizumab and no new safety signals were observed, despite the differences in the studied populations (e.g., prior immunosuppressive/immunomodulatory DMTs [other than Avonex, Betaseron, Copaxone, or Rebif] were not permitted in the ocrelizumab pivotal clinical trials). The MAH considers that the accumulated data from these studies provide sufficient information on the safety of ocrelizumab in patients with RRMS who had a suboptimal response to an adequate course of DMTs to support the removal of the missing information "Safety of ocrelizumab following immunosuppressive/immunomodulating

DMTs other than Avonex, Betaferon, Copaxone, or Rebif" as a safety concern in the RMP.

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

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

MedDRA SMQ: Standard AEGT-Infusion Related Reactions + Hypersensitivity

Potential mechanisms:

The most likely mechanism for an IRR 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 monoclonal antibodies (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. 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, although typically would not present during the first infusion.

The clinical symptoms are similar regardless of the mechanism.

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.

Characterization of the risk:

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

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:
The percentage of patients in clinical studies with ocrelizumab 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 24.

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

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 25).

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 a 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 x 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 24 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 24 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 25 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:
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 26. 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 26 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 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:
The intensity of IRRs in patients 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) is summarized in Table 27. 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 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 additional 49 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 27 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:
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:

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

In patients receiving ocrelizumab, 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 and its severity are not predictable. Although IRRs have been more frequently reported during the first infusion, an IRR may occur during any infusion, and patients who did not have an IRR during the first infusion can still have an IRR at later infusions. IRRs can occur within 24 hours of the infusion.

Patients 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 to further reduce the frequency and severity of IRRs. 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:

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.

It is written in the EU SmPC that ocrelizumab 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. In addition, ocrelizumab 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

MedDRA SMQ AEGT - Roche Standard AEGT-Infections and Infestations

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, and MA30143.

Characterization of the risk:

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 28 and Table 29, 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 28 and Table 29, 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:

The incidence of infections and SIs reported in clinical studies with ocrelizumab in MS (Pool A, Study WA25046, Pool B) overall and by dose is summarized in Table 28 and

Table 29, 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 30. 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 32).

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 29). 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, 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 30) 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 28 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	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)
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 29 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 30 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 31 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 32 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 33 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:

The outcomes of infections and SIs reported in clinical studies with ocrelizumab in MS (Pool A, Study WA25046, Pool B) are summarized in Table 34 and Table 35 respectively. The outcomes of SIs reported in clinical studies with ocrelizumab in RA (Pool D and Pool E) are summarized in Table 36

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 related to treatment by the investigators

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 34 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 35 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 36 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%)

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:

The intensity (grades) of infections and SIs reported in clinical studies with ocrelizumab in MS are summarized in Table 37 and Table 38, respectively. The intensity of SIs reported in clinical studies with ocrelizumab in RA (Pool D and Pool E) is summarized in Table 39.

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 (≥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 (≥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 37 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 38 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 39 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 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 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 (≥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 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

MedDRA SMQ: Malignancies including Breast Cancer, Malignant or unspecified tumours.

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 and ML29966.

Characterization of the risk:

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 40.

Table 40 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
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 was 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 course of 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 41.

Table 41 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

Incidence rate per 100PY	Cancer type	Population	Reference
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
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[3], 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 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

[3] 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).

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 PRAC in the context of a rituximab Periodic Benefit-Risk Evaluation Report (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:

The incidence rates (IRs) of malignancies reported in clinical studies in MS (MS All Exposure Population; Pool B) are summarized in Table 42 and RA (RA All Exposure Population; Pool E) in Table 43.

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 IR of first malignancy was reported in MS patients treated with ocrelizumab (Pool B) (0.43 [95% 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. A variety of subtypes (e.g., ER and/or PR+; HER2+) was reported without a consistent pattern of biologic subtype, which is inconsistent with a hypothesis of causation due to altered immune surveillance. Moreover, there is not a clear biologic rationale why an increased risk of breast cancer would occur over that of multiple solid tumors.

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

IRs 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 IRs 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 IR 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[4] 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[5] 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: 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).

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

Table 42 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 43 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:

The outcomes reported in clinical studies in MS (MS All Exposure Population; Pool B) are summarized in Table 44 and in RA (RA All Exposure Population; Pool E) in Table 45. 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 a 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 44 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 45 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:

The intensity grades reported in clinical studies in MS (MS All Exposure Population; Pool B) are summarized in Table 46 and in RA (RA All Exposure Population; Pool E) in Table 47.

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 46 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 47 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 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 IR 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 to 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

MedDRA SMQ: AEGT Ocrelizumab Auto-label List - Risk PML

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 defence, 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, and MA30143.

Characterization of the risk:

Background Incidence/Prevalence:

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

Frequency with 95% CI:

No cases of PML were observed in the clinical trials of ocrelizumab in patients with rheumatoid arthritis, SLE, LN or NHL (for exposure, see Part II, Module SIII.1). These clinical development programs have been discontinued.

No cases of PML were identified in the controlled treatment period of the ocrelizumab MS clinical trials (pivotal Phase III studies and the Phase II study; for exposure, see Part II, Module SIII.1). To date, no cases have been observed in the ongoing OLEs of these studies or in the other ongoing MS clinical trials.

As of the 27 March 2022, there have been 12 confirmed cases of PML in approximately 250,000 patients with MS treated with ocrelizumab reported from post-marketing sources. Of these 12 confirmed PML cases, 10 cases are carry-over cases of PML attributed to prior DMT exposure. In the remaining two cases, the patients had not had prior exposure to DMTs known to be causally associated with PML. One case was confounded by advanced age (78 years) and the presence of pre-existing lymphopenia. In the remaining case, the patient had not been exposed to a confounding immunosuppressant but did have a concomitant immunosuppressive condition of treatment emergent lymphopenia of unknown etiology (maximum severity: Grade 2).

Seriousness/Outcomes:

All 12 confirmed cases (as of 27 March 2022) were reported as serious. Of the 10 confirmed carry-over cases, 1 patient died, in the remaining 9 cases, event outcome was reported as not recovered/not resolved in 4, recovered/resolved in 2, recovering/resolving in 1 and was not reported in 2 cases. In the 2 confirmed non-carry-over cases, both patients died.

Severity and Nature of Risk:

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

Impact on quality of life:

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

Risk factors and risk groups:

Primary infection with or reactivation of the John Cunningham (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). The European Medicines Agency (EMA's) recommendations to minimise the risk of PML with natalizumab outline that in patients who have not been treated with immunosuppressants before starting natalizumab, the level of anti-JC virus antibodies relates to the level of risk for PML. Patients with a high Ab index who have not used immunosuppressants before natalizumab and have been treated with natalizumab for more than 2 years are considered at higher risk of PML (EMA 2016b). The mechanisms by which natalizumab increases the risk of PML are unknown, but may involve an altered trafficking of lymphoid cells harboring latent JC virus, decreased immune surveillance, or a combination of these processes (Rudick 2006). A PML risk has also been associated with other MS DMTs, including fingolimod and dimethyl fumarate (Berger 2017).

Preventability:

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

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

The prescriber must monitor patients for early signs and symptoms of PML, which can include any new onset, or worsening of neurological signs or symptoms as these can be similar to an MS relapse. If PML is suspected, the prescriber must withhold dosing with ocrelizumab and evaluate, including magnetic resonance imaging (MRI) scan preferably with contrast (compared with pre-treatment MRI), confirmatory CSF testing for JC Viral DNA and repeat neurological assessments, should be considered. If PML is confirmed, treatment must be discontinued permanently.

Impact on the benefit-risk balance of the product:

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

PML may have a fatal or disabling outcome. To date, the available evidence for a causal association between ocrelizumab and PML, according to the Segec methodology, is

assessed as weak and corresponds to a potential (not identified) risk. The reporting rate for PML in the post-marketing setting is very low. Therefore, the impact of PML on the benefit-risk balance of ocrelizumab is considered low.

Public health impact:

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

SVII.3.1.3 Presentation of the Missing Information

SVII.3.1.3.1 Safety in pregnancy and lactation

Evidence source:

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

Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. Due to the potential depletion of B-cells in neonates and infants of mothers who have been exposed to ocrelizumab during pregnancy, it is recommended that vaccination with live or live-attenuated vaccines should be delayed until B-cell levels have recovered; therefore, measuring CD19-positive B-cell level, in neonates and infants, prior to vaccination is recommended.

In an embryo-fetal development study in cynomolgus monkeys, there was no evidence of maternal toxicity, teratogenicity, or embryotoxicity following ocrelizumab treatment at 75/100 mg/kg (loading dose/study dose). Flow cytometric analyses demonstrated reductions in B cells (the anticipated pharmacological effect) in maternal and fetal peripheral blood (see Section SII.1.2).

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) plans to evaluate B cell levels in infants potentially exposed to ocrelizumab during pregnancy. The MAH recently-initiated Study MN42989, a 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.

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 11, 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 Later in their Disease Course" and Study MN39158 (LIBERTO): 'A single arm, open-label multicentre 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 first patient enrolled in May 2022. This study will evaluate safety and efficacy of ocrelizumab in comparison with fingolimod in children and adolescent with RRMS.

At the DLP (27 March 2022) of the recent PBRER RDR 1113817 (reporting interval 28 March 2021 to 27 March 2022) 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.

Cumulatively, there were 293 events reported in 135 pediatric patients (mostly from spontaneous sources or from non-interventional study/program (NIS/NIP).

Based on the cumulative and interval analyses of reported cases in the PBRER (RDR 1113817; 28 March 2021 to 27 March 2022), 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 concerns specific to the pediatric population have 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.1.2.1.

PART II: MODULE SVIII— SUMMARY OF THE SAFETY CONCERNS

Table 48 Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Infusion-related reactions • 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

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 of 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 in order to better assess and describe potential adverse infant outcomes (e.g., infections and impaired vaccination response) among women treated with ocrelizumab during pregnancy or within six months prior to conception or of breastfeeding women. This infant's first year of life follow-up questionnaire has been implemented for worldwide use for pregnancies where the pregnancy outcome was reported as live birth and the pregnant mother had been exposed to ocrelizumab during pregnancy and/or during the six months prior to conception, or where the infant was exposed to ocrelizumab via breastfeeding (which is defined as partial or complete breastfeeding of an infant whose mother received an ocrelizumab infusion during the past 6 months).

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

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

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

Refer to Annex 4 for questionnaires.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES
Safety concern: Infections
Table 49 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 monthsCumulative 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 and PPMS= primary progressive multiple sclerosis.

Table 50 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 Later in their Disease Course
Rationale and Study Objectives: To evaluate the safety and efficacy of ocrelizumab (Ocrevus®) compared with placebo in patients EDSS 3 to 8 using 9-Hole Peg Test as the primary efficacy outcome, and 12 week confirmed disability progression as a key secondary endpoint. Baseline assessment of features characteristic of imaging inflammatory activity (T1 Gd enhancing MRI lesions and/or new/enlarging T2 lesions and/or ≥9T2 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

EDSS = Expanded Disability Status Scale; MRI = Magnetic resonance imaging.

Milestones:

Final report June 2024

Safety concern: Malignancies including breast cancer

Study BA39730 is described in Table 49 above and study WA40404 are described in Table 50 (above).

Safety concern: Progressive multifocal leukoencephalopathy

Study BA39730 described in Table 49 above.

Safety concern: Safety in pregnancy and lactation

Table 51 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

DMT = disease-modifying therapies; MS = multiple sclerosis.

Milestones:

Protocol submission: November 2019

Start of study dataset creation: 2018

Study finish: March 2029

Final report: March 2030

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

Study BA39730 described in Table 49 above and study WA40404 are described in Table 50 (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 the 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 first patient enrolled in May 2022. This study will evaluate safety and efficacy of ocrelizumab in comparison with fingolimod in children and adolescent with RRMS.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 52 On-going and planned additional pharmacovigilance

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 Interim report 1 Interim report 2 Interim report 3 Final report of study results	2019 2028 Cumulative reports submitted with PBRER 2022 2024 2026 2029

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

Study/ Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
	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 Later in their Disease Course Ongoing	To evaluate the safety and efficacy of ocrelizumab (Ocrevus®) compared with placebo in patients EDSS 3 to 8 using 9HPT as the primary efficacy outcome, and 12 week confirmed disability progression as a key secondary endpoint. Baseline assessment of features characteristic of imaging inflammatory activity (T1 Gd enhancing MRI lesions and/or new/enlarging T2 lesions) will be undertaken to explore treatment effect in subgroups with different inflammatory profiles	Infection Malignancies including breast cancer Long-term safety of ocrelizumab treatment	Final report	June 2024

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

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 53 Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk minimization activities
Infusion-related reactions	**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:** • 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*:**

Safety concern	Routine risk minimization activities
	Ocrelizumab is a medicinal product subject to restricted medical prescription: Section 4.2 of the EU SmPC states: Ocrevus 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).
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 experts 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.

Safety concern	Routine risk minimization 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.
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

Safety concern	Routine risk minimization activities
	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 John Cunningham Viral Deoxyribonucleic acid and repeat neurological assessments, should be considered. If PML is confirmed treatment must be discontinued permanently. As for any other active infection, current PML is a contraindication for treatment with ocrelizumab. Refer to Section 4.3 of the EU SmPC- (Contraindications) and to Section 4.4 (Special warnings and precautions for use) for detailed information **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** Ocrelizumab is a medicinal product subject to restricted medical prescription.
Safety in pregnancy and lactation	**Routine risk communication:** Section 4.4 of the EU SmPC- Special warnings and precautions for use Section 4.6 of the EU SmPC- Section 4.6 Fertility, pregnancy and lactation Section 5.3 of the EU SmPC-Preclinical safety data Section 2 of the EU Package Leaflet. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Women of childbearing potential should be instructed that they should use contraception while receiving ocrelizumab and for 12 months after the last infusion of ocrelizumab.

Safety concern	Routine risk minimization activities
	• For activities required in case that an infant is exposed in utero to ocrelizumab, please refer to the risk of impaired immunisation response. • Women should be advised to discontinue breast-feeding during ocrelizumab therapy. 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*:**

Safety concern	Routine risk minimization activities
	Ocrelizumab is a medicinal product subject to restricted medical prescription.

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

V.2. ADDITIONAL RISK MINIMIZATION MEASURES

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

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 54 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Infusion-related reaction	**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:** • 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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	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: Ocrevus treatment should be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions and who have access to appropriate medical support to manage severe reactions such as serious infusion related reactions (IRRs). **Additional risk minimization measures:** None	
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.	**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
	• 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 experts 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. **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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	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. **Additional risk minimization measures:** None	**Additional pharmacovigilance activities:** Study BA39730 Study WA40404
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 pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Follow-up questionnaire

Safety concern	Risk minimization measures	Pharmacovigilance activities
	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 John Cunningham 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 contradication 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. **Additional risk minimization measures:** None	**Additional pharmacovigilance activities:** Study BA39730
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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Section 2 of the EU Package Leaflet. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Women of child bearing potential should be instructed that they should use contraception while receiving ocrelizumab and for 12 months after the last infusion of ocrelizumab. • For activities required in case that an infant is exposed in utero to ocrelizumab, please refer to the risk of impaired immunisation response. • Women should be advised to discontinue breast-feeding during ocrelizumab therapy. 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	**Additional pharmacovigilance activities:** Study BA39732
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*:**	**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
	Ocrelizumab is a medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None	
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, PML= Progressive multifocal leukoencephalopathy, MRI = Magnetic resonance imaging, 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 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 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 • 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

II.B Summary of Important Risks

Important identified risk: Infusion-related reactions	
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.

Important identified risk: Infusion-related reactions	
Risk factors and risk groups	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:** • 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 anti-histamine 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 reaction, 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.

Important identified risk: Infusion-related reactions	
	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. Treatment with ocrelizumab should be initiated and supervised by specialized 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. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None See section II. C of this summary for an overview of the post-authorization development plan.

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, and MA30143.
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 the 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

Important identified risk: Infections	
	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 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

Important identified risk: Infections	
	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 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 and ML29966
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,

Important potential risk: Malignancies including breast 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. 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, and MA30143.

Important potential risk: Progressive multifocal leukoencephalopathy	
Risk factors and risk groups	Primary infection with or reactivation of the John Cunningham (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 progressive multifocal leukoencephalopathy (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 progressive multifocal leukoencephalopathy is suspected, dosing with

Important potential risk: Progressive multifocal leukoencephalopathy	
	ocrelizumab must be withheld. Evaluation including magnetic resonance imaging (MRI) scan preferably with contrast (compared with pre-treatment MRI), confirmatory cerebrospinal fluid testing for John Cunningham Viral Deoxyribonucleic acid presence, and repeat neurological assessments, should be considered. If progressive multifocal leukoencephalopathy is confirmed, treatment must be discontinued permanently. As for any other active infection, current progressive multifocal leukoencephalopathy 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; JC = John Cunningham; MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy.

Missing information: Safety in pregnancy and lactation	
Risk minimization measures	**Routine risk communication:** Section 4.4 of the European Union Summary of Product Characteristics - Special warnings and precautions for use Section 4.6 of the European Union Summary of Product Characteristics - Section 4.6 Fertility, pregnancy and lactation Section 5.3 of the European Union Summary of Product Characteristics -Preclinical safety data Section 2 of the European Union Package Leaflet. **Routine risk minimization activities recommending specific clinical measures to address the risk**: • Women of childbearing potential should be instructed that they should use contraception while receiving ocrelizumab and for 12 months after the last infusion of ocrelizumab. • For activities required in case that an infant is exposed in utero to ocrelizumab, please refer to the risk of impaired immunization response. • Women should be advised to discontinue breast-feeding during

Missing information: Safety in pregnancy and lactation	
	ocrelizumab therapy. 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 **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 See section II.C of this summary for an overview of the post-authorization development plan.

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 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 later in their disease course.

Purpose of the study:

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

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

ANNEX 4:

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Questionnaire
Infant's first year of life follow-up

AER:	
Site No:	
Local Case ID:	
Pregnancy Reporting Form:	☐ Form sent out, ☐ Form returned

Type of ocrelizumab exposure:	☐ In utero exposure ☐ Exposure via breastfeeding
Patient* ID/Initials:	
Patient* Date of Birth (DD-MMM-YYYY) / Age:	

* Patient = pregnant mother (not her child)

Following the recent report to Roche regarding the birth of a baby to a woman with MS who had received OCREVUS in the 6 months prior to conception or during the pregnancy, we would like to ask you to complete this questionnaire (in addition to the company's global pregnancy reporting form). It is not known whether OCREVUS can impact pregnancy outcome or infant outcomes in humans. It is unknown whether OCREVUS is excreted in human breast milk or has any effect on the breastfed child and on milk production. OCREVUS is a recombinant humanized monoclonal antibody that selectively targets CD20-expressing B-lymphocytes. B-cell levels in human neonates following maternal exposure to OCREVUS have not been studied in clinical trials; however transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. In this questionnaire, we are seeking information on the health of the infant during his/her first year of life, focusing on B cells, infections and vaccination response because of the immunomodulatory effects of ocrelizumab. This will help us to have a better understanding of any potential adverse infant health complications that should be communicated to health authorities, healthcare professionals and patients.

If twin/multi-gestational pregnancy, this questionnaire must be filled out separately for each infant born in the multi-gestational pregnancy.

For each of the four predefined assessment time points of the infant's first year of life (at birth, at 3, 6, and 12 months of age), a separate form needs to be filled out.

Reporter information

1. Reporter information *(table 1 to be filled out at each assessment)*		
First name and surname of reporter completing this form (*if other than addressee, please provide contact information below*) _____		
Health care provider? ☐ Yes ☐ No – Please specify:		
Phone number:	Fax number:	Email address:
Address:		Country:

Status of neonate/infant during his/her first year of life, focus: infections

2. Status of neonate/infant during his/her first year of life *(table 2 to be filled out at each assessment)*		
Date of Assessment (DD-MMM-YYYY): _____ **At birth ☐, age 3 months ☐, age 6 months ☐, age 12 months ☐**		**Comments**
Overall status of neonate / infant	☐ Normal ☐ Abnormal; specify abnormality: _____ ☐ Neonatal/infant death; specify cause and date of death: _____	

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 ***If abnormal, specify test result, normal range and test date (DD-MM-YYYY):*** Test result: _____ Normal range: _____ Test date: _____	
Infection	Any infection detected? ☐ Yes, ☐ No, ☐ Unknown *- If infection detected at birth: please fill out Table 3,* *- If no infection detected at birth, however an infection developed later during the first year of life, please move directly to Table 4,* *- If no infection detected at birth, and if also no infection developed during the first 12 months then move directly to Table 5.*	

3. Information on infection in neonate 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: _____
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 at birth

3. Information on infection in neonate <u>at birth</u> *(table 3 only to be filled out if infection at birth present)*			
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***	***If abnormal, test***

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 ☐**			
		result and normal range	***date (DD-MMM-YYYY)***
CD19 count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:
IgG levels	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:
White blood cell count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:
Neutrophil count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:
Lymphocyte count	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:
Other, specify: _____	☐ Normal, ☐ abnormal, ☐ unknown	Test result: _____ Normal range: _____	Date:

5. Vaccinations administered to infant at birth and during first year of life (*table 5 to be filled out at each assessment)*					
Vaccinations administered at birth and during first year of life	**Date administered** (DD-MMM-YYYY):	**Infant's age on day of vaccination** (weeks)	**Initial vaccination or booster dose**	**Vaccination postponed to later date than scheduled**	**Comments (abnormal outcome, reason for postponing vaccination, etc.)**
☐ Hepatitis B			☐ Initial ☐ Booster	☐ Yes, ☐ No	
☐ Rotavirus			☐ Initial ☐ Booster	☐ Yes, ☐ No	
☐ Diphtheria, tetanus, and pertussis			☐ Initial ☐ Booster	☐ Yes, ☐ No	
☐ Haemophilus influenzae type b			☐ Initial ☐ Booster	☐ Yes, ☐ No	
☐ Pneumococcal			☐ Initial ☐ Booster	☐ Yes, ☐ No	
☐ Poliovirus ☐ Attenuated oral Polio vaccine ☐ Inactivated Polio vaccine			☐ Initial ☐ Booster	☐ Yes, ☐ No	
☐ Meningococcal group B bacteria			☐ Initial ☐ Booster	☐ Yes, ☐ No	
☐ Tuberculosis (Bacille Calmette Guérin, BCG) bacteria			☐ Initial ☐ Booster	☐ Yes, ☐ No	
☐ Other vaccination, specify: _____			☐ Initial ☐ Booster	☐ Yes, ☐ No	

Completed by:

Name: ..... Position: .....

Signature: ..... Date: .....

4

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:

5

Detailed information on abnormal health related findings in neonate/infant during first year of life

Please enter text in box below:

6

Protocol		CTRN/Site:		CRF / Subject:	

For Internal Use Only	AER/MCN:		Company Received Date DD/MMM/YYYY	

Pregnancy Outcome and Infant Health Information on First Year of Life

If twin or multi-gestational pregnancy, this questionnaire has to be filled out separately for each baby born in the multi-gestational pregnancy.

Please check all that apply and provide detailed information on complications in infant on last page.

Table 1: Parent's (or person with parental responsibility in law) consent to data collection

Has parent's (or person's with parental responsibility in law) data authorisation form been signed?	☐ Yes ☐ No	Date signed _____	Other – comment _____
	Date consent withdrawn: (if applicable)		

Table 2: Information on birth

Mode of birth	☐ Vaginal delivery Forceps / vacuum: - Yes ☐ - No ☐ ☐ Cesarean section (CS) - scheduled CS ☐ - emergency CS ☐	Reason for assisted delivery/Cesarean section_____
Gestational age at birth	----------weeks - since conception ☐ - since LMP ☐	Induced labour - Yes ☐ - No ☐

Table 3: Growth alteration, congenital anomalies and functional deficits

Date of Assessment			
Growth alteration - Yes ☐ - No ☐	☐ Small for gestational age (SGA) ☐ Low birth weight ☐ Short birth length	If Growth alteration present:: Specify weight:_____: Specify length:_____	Contributing factors:
Congenital anomalies - Yes ☐ - No ☐	☐ Major structural malformation A defect that has either cosmetic or functional significance to the child	Specify: _____ _____ _____	Contributing factors: _____ _____
	☐ Minor structural malformation A defect that occurs infrequently but has neither cosmetic nor functional significance to the child	Specify: _____ _____ _____	Contributing factors: _____ _____
	☐ Deformation A defect attributable to deformation of a structure, which had previously formed normally (usually due to mechanical force)	Specify: _____ _____ _____	Contributing factors: _____ _____
	☐ Disruption A defect due to destruction of a structure, which has previously formed normally (may be of vascular, infectious, or mechanical origin)	Specify: _____ _____ _____	Contributing factors: _____ _____
Functional deficit (except for infections, which	☐ Functional deficit	Specify: _____ _____ _____	Contributing factors: _____ _____

should be described in separate table below) - Yes ☐ - No ☐			

Infant status at the time of latest follow-up (at birth, 3 months, 6 months, 12 months)

Table 4: Status of infant

Date of Assessment		Contributing factors / Comments
Status of infant	☐ Normal ☐ Abnormal, specify abnormality: _____ ☐ Neonatal/infant death, specify cause and date of death: _____	_____ _____
Nursing status	☐ Exclusive breastfeeding ☐ Mixed feeding (partial breastfeeding along with infant formula and/or baby food), specify date since when: _____ ☐ Fully weaned, specify date since when: _____	_____ _____ _____

Infections in neonate and infant during first year of life

Any infection detected at birth?

☐ Yes
☐ No
☐ Unknown

If available, please provide CD19 count (B cell values) at birth (regardless of infection)?

☐ **normal**
☐ **abnormal**
☐ **unknown**

If abnormal, specify test result: _____
If abnormal, date of test: _____

If infection detected at birth then Tables 5 and 6 should to be filled out and additional detailed information may be provided on last page.
If no infection detected at birth, however an infection developed later during the first year of live, please move directly to Table 7.
If no infection detected at birth, and if also no infection developed during the first 12 months then move directly to Table 8.

Table 5: Information on infection in neonate at birth

Specify the event term:	**Event number**		
Location of infection present in neonate at birth? Site of infection (specify): _____		**Outcome of infection?**	**Duration of infection?**
		☐ Resolved ☐ Improving	**Duration:**_____

Protocol		CTRN/Site:		CRF / Subject:	

		□ Fatal □ Persisting □ Unknown	
Intensity of infection (Grade 1-5 NCI CTCAE)?	**Seriousness of infection?**	**Treatment with anti-infective?**	**Pathogen causing infection known?**
Severity: □ Mild (Grade 1) □ Moderate (Grade 2) □ Severe (Grade 3) □ Life-threatening (Grade 4) □ Death (Grade 5)	Serious: □ Yes □ No	□ Yes, specify: _____ □ No □ Unknown	□ Yes (specify): _____ □ No □ Unknown
Relevant laboratory test results (in newborn infant):			
CD19 count	□ normal □ abnormal □ unknown	If abnormal, specify test result: _____	If abnormal, date of test: _____
IgG levels	□ normal □ abnormal □ unknown	If abnormal, specify test result: _____	If abnormal, date of test: _____
White blood cell count	□ normal □ abnormal □ unknown	If abnormal, specify test result: _____	If abnormal, date of test: _____
Neutrophil count	□ normal □ abnormal □ unknown	If abnormal, specify test result: _____	If abnormal, date of test: _____
Lymphocyte count	□ normal □ abnormal □ unknown	If abnormal, specify test result: _____	If abnormal, date of test: _____
Other, specify:	□ normal □ abnormal □ unknown	If abnormal, specify test result: _____	If abnormal, date of test: _____

Table 6: Maternal risk factors for neonatal infection (during most recent pregnancy, if infant developed neonatal infection at birth)

Maternal risk factors for neonatal infection	**Date of diagnosis**	**If diagnosed, was pregnant mother treated with anti-infective prior to delivery?**
□ Maternal intrapartum colonisation or infection with group B streptococcus (GBS) □ Maternal listeriosis □ Premature rupture of membranes (PROM) □ Meconium in amniotic fluid (meconium-stained liquid) □ Active genital herpes infection □ CMV □ HPV (papilloma virus) □ Other, specify	_____ _____ _____ _____ _____	_____ _____ _____ _____ _____

Relevant laboratory test results in pregnant mother:			
CD19 count	□ normal □ abnormal □ unknown	If abnormal, specify test result: _____	If abnormal, date of test: _____
IgG levels	□ normal □ abnormal □ unknown	If abnormal, specify test result: _____	If abnormal, date of test: _____

Protocol		CTRN/Site:		CRF / Subject:	

White blood cell count	□ normal □ abnormal □ unknown	If abnormal, specify test result: _____	If abnormal, date of test: _____
Neutrophil count	□ normal □ abnormal □ unknown	If abnormal, specify test result: _____	If abnormal, date of test: _____
Lymphocyte count	□ normal □ abnormal □ unknown	If abnormal, specify test result: _____	If abnormal, date of test: _____
Other, specify: (e.g. any specific antibodies and their titers)	□ normal □ abnormal □ unknown	If abnormal, specify test result: _____	If abnormal, date of test: _____

Any infection detected during first year of infant's life?

□ Yes

□ No

□ Unknown

If infection detected during first year of infant's life, then Table 7 should to be filled out and additional detailed information may be provided on last page. If no infection developed during first 12 months of life, then please move directly to Table 8.

Table 7: Information on infection detected during first year of infant's life

Specify the event term:	**Event number (automatically populated by the system?)**		
Location of infection?	**Infant's age on day of onset of infection?**	**Outcome of infection?**	**Duration of infection?**
Site of infection (specify): _____	**Age:**_____	□ Resolved □ Improving □ Fatal □ Persisting □ Unknown	**Duration:**_____
Intensity of infection (Grade 1-5 NCI CTCAE)?	**Seriousness of infection?**	**Treatment with anti-infective?**	**Pathogen causing infection known?**
Severity: □ Mild (Grade 1) □ Moderate (Grade 2) □ Severe (Grade 3) □ Life-threatening (Grade 4) □ Death (Grade 5)	Serious: □ Yes □ No	□ Yes, specify: _____ □ No □ Unknown	□ Yes (specify): _____ □ No □ Unknown
Relevant laboratory test results (in infant):			
CD19 count	□ normal □ abnormal □ unknown	If abnormal, specify test result: _____	If abnormal, date of test: _____
IgG levels	□ normal □ abnormal □ unknown	If abnormal, specify test result: _____	If abnormal, date of test: _____

Protocol		CTRN/Site:		CRF / Subject:	

White blood cell count	□ normal □ abnormal □ unknown	If abnormal, specify test result: _____	If abnormal, date of test: _____
Neutrophil count	□ normal □ abnormal □ unknown	If abnormal, specify test result: _____	If abnormal, date of test: _____
Lymphocyte count	□ normal □ abnormal □ unknown	If abnormal, specify test result: _____	If abnormal, date of test: _____
Other, specify:	□ normal □ abnormal □ unknown	If abnormal, specify test result: _____	If abnormal, date of test: _____

Table 8: Vaccinations administered to infant at birth and during first year of age

Vaccinations administered at birth and during first year of age	Date administered	Infant's age on day of vaccination	Comments (abnormal outcome, reason for postponing vaccination, etc)
□ Hepatitis B			
□ Rotavirus			
□ Diphtheria, tetanus, and pertussis			
□ Haemophilus influenzae type b			
□ Pneumococcal			
□ Poliovirus □ Attenuated oral Polio vaccine □ Inactivated Polio vaccine			
□ Meningococcal group B bacteria			
□ Tuberculosis (Bacille Calmette Guérin, BCG) bacteria			
□ Other vaccination, specify: _____			

Table 9: Fetal/neonatal abnormalities in previous pregnancies

Fetal/neonatal abnormalities (in previous pregnancies)			Please, provide specifics including contributing factors
None □	Yes □	Unknown □	
Infection; if yes, specify			
Death in utero; if yes, specify reason			
Birth defects; if yes, specify			
Family history of birth defects; if yes, specify			
Small for gestational age at birth (or Intrauterine growth retardation)			
Premature delivery (before 37 weeks)			
Other; specify			

Detailed information on health-related findings in infant during first year of

Protocol		CTRN/Site:		CRF / Subject:	

life

Please enter text in the free text box below:

Guided Questionnaire: PML

This request for follow up information is being sent to obtain additional details about this adverse event. By filling in this questionnaire, you will help us to understand more fully the risk factors for this condition.

Patient Information

AER:		Gender	
Patient ID/Initials		Country	
Birthday:		Local Case ID:	

Reporter Information

Name of reporter completing this form **(if other than addressee, provide contact information below)**:
Health Care Provider? ☐ Yes ☐ No - Please specify:
Phone Number: Fax Number: Email Address:

Roche Drug Therapy Details

Roche Drug Therapy Details	
Roche product used by the patient	
Indication for Roche Product and date of diagnosis	
Start Date/Stop Date of Roche product (MM/DD/YYYY)	Date of Start:_____ Date of Stop:_____
Frequency that the Roche product was taken	☐ Daily, if yes, how many times per day: _____ ☐ Weekly ☐ Monthly ☐Other, please specify:_____ ☐ Cycles (please specify):_____
Starting Dose	a Flat dose: _____mg b. _____mg/kg c. _____mg/m^2
Dose used prior to event	Date of last dose:_____ a. Flat dose: _____mg b. _____mg/kg c. _____mg/m^2
Route	☐ Oral ☐ IV Infusion ☐ Injection SC ☐ Injection IM ☐ Other, please specify:_____ ☐ Indicate if route of administration changed during therapy:_____
If route of administration changed during therapy, please specify	Date of change:_____ Type of change:_____ Other information or comments: _____
Additional treatment details	

Adverse Event:

List the signs and symptoms and their dates of occurrence: Please provide final diagnosis:

Relevant Diagnostic Data

Diagnostic	Baseline (pre-event onset) Status / Date / Results	At/After Event Onset 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 <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)