WHO 24th Expert Committee on the Selection and Use of Essential Medicines – 2023

Application for the addition of ocrelizumab on the WHO Model List of Essential Medicines

Submitted by
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Acronyms and abbreviations

23-PPV	23-valent pneumococcal polysaccharide vaccine, 23-PPV
9HPT	Nine-Hole Peg Test
AAN	American Academy of Neurology
ABN	Association of British Neurologists
ACTRIMS	American Committee for Treatment and Research in Multiple Sclerosis
ADA	antidrug antibody
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
ADR	adverse drug reaction
AE	adverse event
ATC	anatomical therapeutic chemical
ARR	annualized relapse rate
BVMT-R	Brief Visuospatial Memory Test - Revised
CCOD	clinical cutoff date
CDC	complement-dependent cytotoxicity
CDP	confirmed disability progression
CHMP	Committee for Medicinal Products for Human Use
CIS	clinically isolated syndrome
CNS	central nervous system
CSF	cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
CVLT-II	California Verbal Learning Test - Second Edition
DBP	double-blind period
DMT	disease-modifying therapy
EAN	European Academy of Neurology
ECTRIMS	European Committee for Treatment and Research in Multiple Sclerosis
EDSS	Expanded Disability Status Scale
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	U.S. Food and Drug Administration
GBM	glomerular basement membrane
GBS	Guillain-Barré syndrome
Gd+	gadolinium-enhancing
GDP	gross domestic product
HB	Hepatitis B
HBV	Hepatitis B virus
HDI	Human Development Index
HIO	Health Insurance Organization
HR	hazard ratio

HRQoL	health-related quality of life
HTA	health technology assessment
IBD	international birth date
ICH	International Council for Harmonisation
ICSR	Individual Case Safety Reports
IDP	International Differential Pricing
IFN	interferon
IFNβ1a	interferon beta-1a
INN	international non-proprietary name
IQR	interquartile range
IRRs	infusion-related reactions
ITT	intention-to-treat
IV	intravenous
LCVA	low contrast visual acuity
LLN	lower limit of normal
LMP	last menstrual period
mAb	monoclonal antibody
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MFIS	Modified Fatigue Impact Scale
mITT	modified ITT population
MRI	magnetic resonance imaging
MS	multiple sclerosis
MTX	methotrexate
NCDs	non-communicable diseases
NEDA	no evidence of disease activity
NEP	no evidence of progression
NEPAD	no evidence of progression or active disease
NfL	neurofilament light chain
NHL	non-Hodgkin's lymphoma
NMSC	nonmelanoma skin cancer
non-SELs	non-slowly expanding/evolving lesions
OCR	ocrelizumab
OCT	optical coherence tomography
OI	opportunistic infection
OLE	open-label extension
PASS	post-authorization safety studies
PBRERs	periodic benefit-risk evaluation reports
PD	pharmacodynamics
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PMR	post-marketing requirement
PMS	progressive multiple sclerosis

PMST	prior MS specific therapies
PPMS	primary progressive multiple sclerosis
PRAC	Pharmacovigilance Risk Assessment Committee
PROs	patient-reported outcomes
PYs	patient years
QoL	quality of life
RCTs	randomized controlled trials
RMP	risk management plan
RMS	relapsing forms of multiple sclerosis
Roche	F. Hoffmann-La Roche Ltd
RoW	rest of the world
RR	risk reduction
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SC	subcutaneous
SDMT	Symbol Digit Modalities Test
SELs	slowly expanding/evolving lesions
SF-36 MCS	Short Form 36 Mental Component Summary
SF-36 PCS	Short Form 36 Physical Component Summary
SFSEP	French Multiple Sclerosis Society
SLE	systemic lupus erythematosus
SOC	system organ class
SPMS	secondary progressive multiple sclerosis
SUCRA	surface under the cumulative ranking curve
T1DM	type 1 diabetes mellitus
T25FW	Timed 25-Foot Walk
TN	treatment naïve
TNF	tumor necrosis factor
TRIBUNE	Treatment Experience, Burden and Unmet Needs
TT	Tetanus Toxoid
TV	thalamic volume
USA	United States of America
URTI	upper respiratory tract infection
UTI	urinary tract infection
VAS	visual analogue scale
VZV	Varicella Zoster Virus
WHO	World Health Organization
WMV	white matter volume
WPAI	work productivity and activity impairment

1. Title page

This submission proposes the inclusion of ocrelizumab on the complementary list of the WHO Model List of Essential Medicines for the treatment of adult patients with relapsing and primary progressive forms of multiple sclerosis (RMS and PPMS).

The contact details of the applicant are as follows:

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2. Summary statement of the proposal for **inclusion**

F. Hoffmann-La Roche Ltd (hereafter referred to as Roche) proposes the inclusion of ocrelizumab, as an individual medicine, on the complementary list of the WHO Model List of Essential Medicines for the treatment of adult patients with relapsing and primary progressive forms of multiple sclerosis (RMS and PPMS).

The principal reasons for requesting this inclusion are as follows:

- There is a significant global disease burden of multiple sclerosis (MS), which affects approximately 2.8 million people worldwide (1). MS primarily affects young adults, with patients usually being diagnosed between the ages of 20 and 40 (2), and a mean age of diagnosis of approximately 30 years (3). MS is at least two to three times more frequent in women than in men, except in PPMS, where men and women are equally affected (1,4).
- In all forms of MS, there is a clear unmet need for a disease-modifying therapy (DMT) that has a benefit–risk profile which supports initiation at any time during the disease course and preserves neurological function, inhibits the accumulation of irreversible disability and improves health-related quality of life (HRQoL).
- Other than ocrelizumab, there are no approved therapies for PPMS.
- Ocrelizumab was shown to be safe and effective in two pivotal phase 3 studies on RMS, OPERA I (WA21092) and OPERA II (WA21093) (5), and in one phase 3 study on PPMS, ORATORIO (WA25046) (6).
- Updated analyses of efficacy and safety for patients who have continued in the open-label extension (OLE) phase of the three pivotal studies for up to nine years have confirmed continued benefit after the controlled treatment phase. No new safety signals have been identified (7–14).
- Benefit has been further confirmed in real-world observational studies on both RMS and PPMS (15,11,16–22).
- Due to the requirement for specialized tests such as magnetic resonance imaging (MRI) for diagnosis and follow-up of MS, as well as specialized care for management of adverse events such as infusion-related reactions (IRRs), inclusion in the complementary list is proposed.

Ocrelizumab is a recombinant humanized monoclonal antibody (mAb) to CD20, a cell surface antigen found on pre-B cells, mature B cells, and memory B cells but not on lymphoid stem cells and plasma cells. The precise mechanisms through which ocrelizumab exerts its therapeutic clinical effects in MS are not fully elucidated but is presumed to involve immunomodulation by way of the selective depletion of CD20-expressing B cells through antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and apoptosis (23).

The capacity of B-cell reconstitution and preexisting humoral immunity are preserved. In addition, innate immunity and total T-cell numbers are not affected (23).

Treatment with ocrelizumab leads to rapid depletion of CD19+ B cells in blood by 14 days post-treatment (first time point of assessment) as an expected pharmacologic effect. This is sustained throughout the treatment period (23).

The therapeutic indications of ocrelizumab are (23):

- For the treatment of patients with relapsing forms of multiple sclerosis (RMS) to suppress relapses and disease progression (clinical and subclinical disease activity)
- For the treatment of patients with primary progressive multiple sclerosis (PPMS) to delay disease progression and reduce deterioration in walking speed.

3. Consultation with WHO technical department

Not applicable.

4. Other organisation(s) consulted and/or supporting the submission

Not applicable.

5. Key information for the proposed medicine

5.1 International non-proprietary name (INN) of the proposed medicine

Ocrelizumab.

5.2 Anatomical therapeutic chemical (ATC) code of the proposed medicine

Therapeutic/pharmacologic class of drug: Recombinant humanized anti-CD20 monoclonal antibody (mAb)
ATC code: L04AA36

5.3 Dosage form(s) and strength(s) of the proposed medicine

Ocrelizumab is a clear or slightly opalescent, and colorless to pale brown solution supplied as a single-use formulation containing 30 mg/mL ocrelizumab in 20 mM sodium acetate, 106 mM trehalose dihydrate and 0.02% (w/v) polysorbate 20 at pH 5.3. The drug product is supplied at a volume of 10.0 mL in a 15 mL glass vial, and water for injection (23).

5.4 Indication(s)

The therapeutic indications of ocrelizumab are (23):

- For the treatment of patients with relapsing forms of multiple sclerosis (RMS) to suppress relapses and disease progression (clinical and subclinical disease activity)
- For the treatment of patients with primary progressive multiple sclerosis (PPMS) to delay disease progression and reduce deterioration in walking speed.

The International Classification of Diseases, 11th Revision (ICD-11), classifies ocrelizumab among the "Selective immunosuppressants" with the specific code XM2B74.

6. Proposal for an individual medicine

Individual medicine.

7. Information supporting the public health relevance

7.1 Epidemiological information on multiple sclerosis

7.1.1 Background

Multiple sclerosis (MS) is a chronic autoimmune disease characterized by inflammation of the central nervous system (CNS) that leads to demyelination, axonal loss, and progressive neuronal degeneration, resulting in irreversible disability and cognitive impairment (24,25).

Commonly, MS is divided into relapsing forms of MS (RMS) and progressive forms of MS (PMS), more accurately classified in three different clinical phenotypic patterns based on the presence of transient attacks of neurological symptoms and/or a progressive worsening of the neurological function. These clinical phenotypes are (26):

- relapsing–remitting MS (RRMS)
- secondary progressive MS (SPMS)
- primary progressive MS (PPMS)

RRMS is characterized by clearly defined relapses, i.e., clearly defined attacks of new or increasing neurological symptoms, which are followed by recovery periods (remissions), during which symptoms improve (27). Remissions can be full, with all symptoms disappearing, or partial, with some symptoms persisting and becoming permanent. There is no apparent progression of the disease during the periods of remission; however, patients with RRMS may accumulate disability as a result of incomplete recovery from relapses (26).

SPMS is characterized by a progressive worsening of neurological function, typically without relapses (28). However, in some patients, progression of disability may be accompanied by occasional superimposed relapses. Relapses in SPMS typically decrease in frequency over time, and the occurrence of relapses does not appear to predict long-term accumulation of disability (29).

PPMS is characterized by a progressive worsening of neurological function from the outset (30,31). Some patients with PPMS experience relapses and periods of remission (this form of disease used to be classified as progressive relapsing MS), but they have similar long-term rates of disability accumulation, compared with other patients with PPMS (32). Most studies suggest that PPMS is part of the spectrum of MS phenotypes and that differences are relative rather than absolute (26,33,34).

RMS includes both RRMS and SPMS[1] when the disease course is characterized by the presence of relapses. PMS includes those forms of MS that are not characterized by the presence of relapses but rather show a progressive worsening of neurological function. This includes the later stages of SPMS, which usually evolves into a purely progressive course, and PPMS, which is typified by progressive worsening of symptoms leading to a temporarily accelerated disease course. The typical disease courses associated with different forms of MS are shown in Figure 1.

[1] R(R)MS is used throughout this document when discussing RMS and RRMS together (i.e. RMS and/or, more narrowly, RRMS).

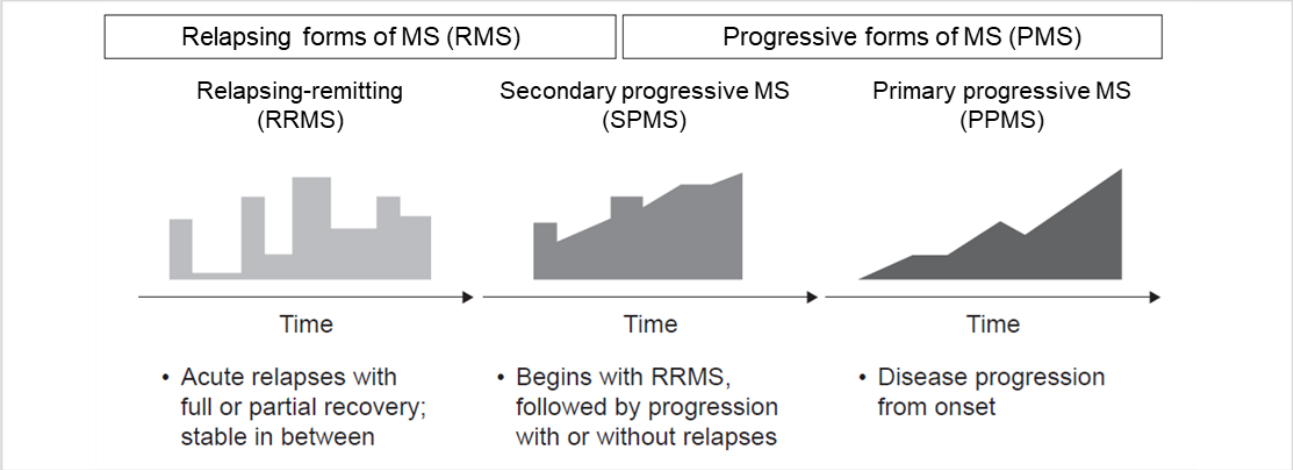

Figure 1: Typical Disease Course for Relapsing and Progressive Forms of MS [Adapted from Klineova and Lublin (35)]

Clinically isolated syndrome (CIS) is an initial episode, lasting at least 24 hours (36), of neurological symptoms consistent with inflammatory demyelination in one or more sites in the CNS (26,37). CIS is considered to be an early part of the spectrum of MS phenotypes and should be followed to determine subsequent disease course (31).

7.1.2 Epidemiology of multiple sclerosis

In 2020, it was estimated that 2.8 million patients had MS worldwide, corresponding to a prevalence of 1 case in 3000 people. While MS is present in all regions of the world, its prevalence varies greatly. MS is most prevalent in USA and Europe (288 and 133 per 100 000, respectively) and least prevalent in Sub-Saharan Africa and South-East Asia (5 and 9 per 100 000, respectively) (1).

RRMS is the most common MS disease course: approximately 85% of patients with MS are initially diagnosed with RRMS (1), typically between the age of 20 to 45 years old (mean 30 years (24,1,38). PPMS is the initial diagnosis in approximately 12% of patients with MS (1), typically at about 40 years of age (24).
There are at least twice as many females (69%) with MS as there are males (31%).

7.1.3 Burden of the disease

The course of MS is highly variable and unpredictable; patients with MS may have a broad range of neurological symptoms or signs, depending on the location and degree of inflammation in the CNS. Life expectancy for patients with MS is five to ten years shorter than for the general population (24,39,40).

Disease progression is linked to the accumulation of disability and overall, disability accumulation is more rapid for patients with PPMS than in those with RRMS. If left untreated, RRMS will eventually transition to SPMS in most patients (24). Approximately half of patients develop SPMS within approximately 20 years of the onset of RRMS (24,41,42). In a long-term cohort study in Sweden, RRMS transitioned to SPMS within 40 years in 78% of patients (43). A higher number of relapses in the first two years after disease onset is significantly associated with worse outcomes (29). After patients with RRMS progress to SPMS, the rate of disability progression is similar to the rate of progression in patients with PPMS (44,32).

MS has a substantial negative impact on health-related quality of life (HRQoL) (45–47). Typical symptoms of progressive disease include increasing difficulty with walking, fatigue, and cognitive impairment, with variable symptoms in other systems (30,48). Patients with MS have significantly lower HRQoL scores than patients who have other chronic diseases, such as chronic ischemic heart disease, gastro-esophageal reflux disease, Crohn's disease, non-insulin-dependent diabetes mellitus, or ulcerative colitis (49). Relapses, higher levels of disability, and progressive disease have all been shown to be associated with significant reductions in HRQoL (50).

As a result of the impact of disease on HRQoL, compared with the general population, patients with MS are less likely to be employed, more likely to take time off work when they are employed, and more likely to retire early (51–53). Workforce participation decreases rapidly with advancing stages of MS characterized by the Expanded Disability Status Scale (EDSS), from normal population levels at EDSS 0 to only a few patients being able to work at EDSS 9 (Figure 2) (54).

PPMS and SPMS have greater effects than R(R)MS on employment (55), and caregivers' employment may also be affected (56). Caregivers of patients with MS also experience high levels of distress and reduced quality of life (56,57).

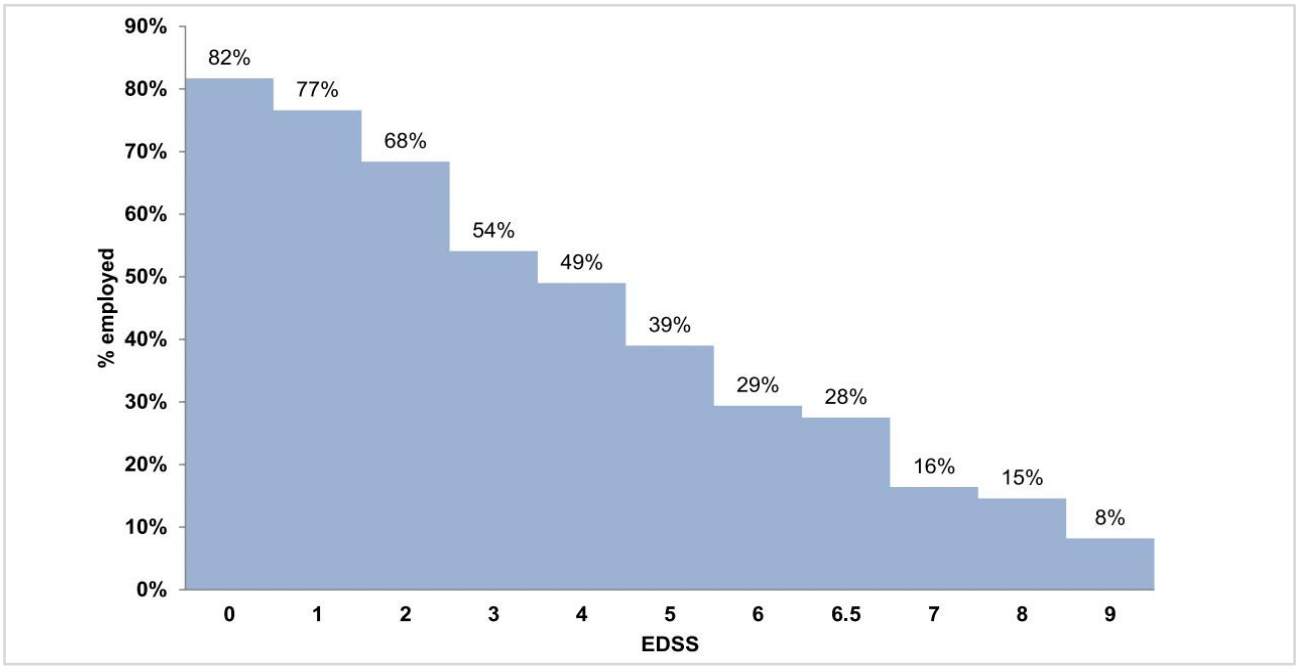

Figure 2: Workforce Participation: Proportion of Patients below Retirement Age (N = 13,391) Employed or Self-Employed (N = 6769) (54)

MS is associated with a substantial economic burden (58). The total yearly cost of MS in Europe was calculated to be €14.6 billion in 2010 (59). MS accounts for 1.8% of the total yearly cost of brain disorders, which was estimated at €798 billion per year. Those should be regarded as conservative estimates because many disorders or cost items could not be included due to lack of data (46).

A cross-sectional study conducted by Kobelt et al. (54), in collaboration with national MS societies and local clinical and economic experts, aimed to characterize the cost of MS from 16,808 patients with MS in 16 European countries. The countries included were Austria, Belgium, the Czechia, Denmark, France, Germany,

Hungary, Italy, the Netherlands, Poland, Portugal, Russia, Spain, Sweden, Switzerland and the United Kingdom. Patients reported on their disease, HRQoL, and resource consumption. Descriptive analyses were performed by disease severity (mild, moderate, and severe). All costs were reported from a societal perspective. Costs and utility were highly correlated with disease severity, but resource consumption was heavily influenced by healthcare system and availability of services. There was a wide variation among countries, leading to very different mean annual costs per patient across countries (Figure 3). Costs were related to disease severity (EDSS score) in all countries and were dominated by production losses and non-healthcare costs.

Although direct healthcare costs alone are substantial (59,60), several European studies have reported that indirect costs – arising mostly from productivity losses – account for more than half of the total economic burden of MS (61–63).

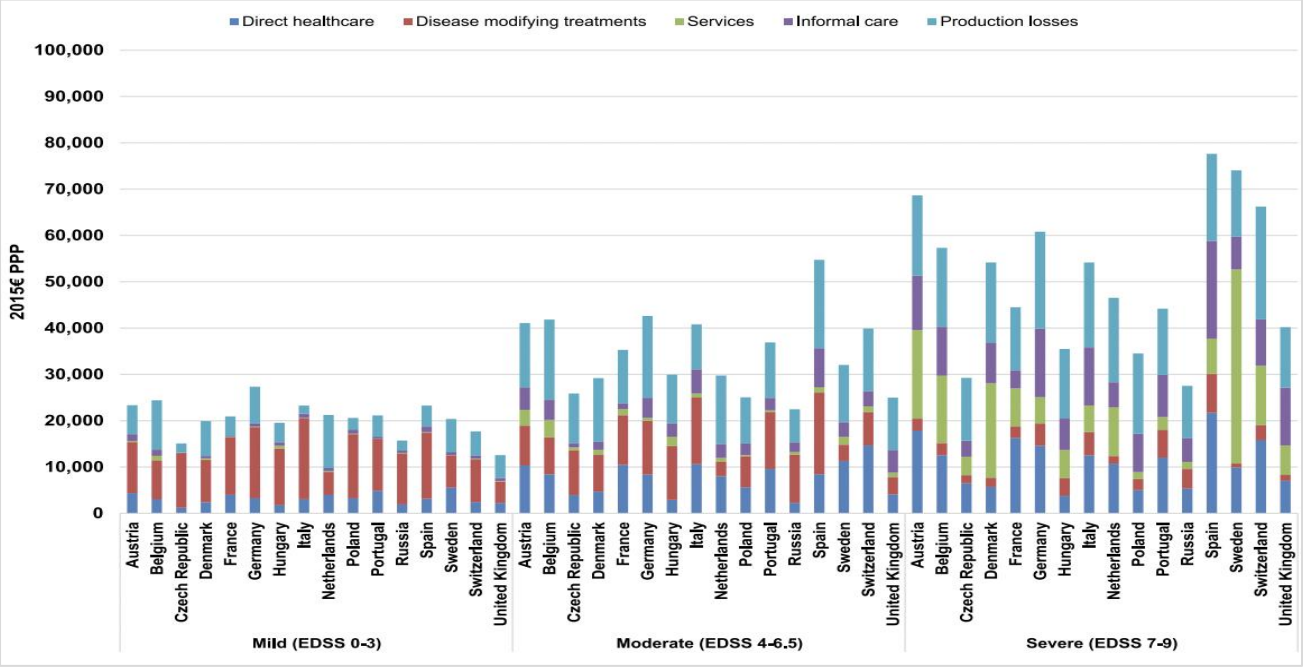

Figure 3: Mean Total Annual Cost per Patient by Disease Severity and Resource Type across 16 European Countries, 2015€ PPP (N = 16,808) (54)

The cost of MS increases as patients reach higher levels of disability (64,65). In the Treatment Experience, Burden and Unmet Needs in MS study (TRIBUNE), costs across five European countries were €13,534–22,461 for patients with no/mild disability (EDSS scores ≤ 3), €28,524–43,948 for patients with moderate disability (EDSS scores of 4.0–6.5), and €39,592–65,395 for those with severe disability (EDSS scores ≥ 7.0) (65). In the Kobelt et al. study (54), mean costs were €22,800 PPP in mild, €37,100 PPP in moderate and €57,500 PPP in severe disease. A recent systematic literature review conducted by Paz-Zulueta et al. (66) found similar results, supporting the fact that whilst total cost per patient and year varies among studies and countries, the higher the severity of MS, the higher the associated cost. In this review, total costs for the selected European studies stand at €40,303 per patient per year (ranging from €23,707 for mild MS to €59,611 for severe MS) (66).

Although the economic burden of MS in high-income countries has been extensively studied, information on the costs of MS in low- and middle-income countries remains scarce. A recent systematic literature review

conducted by Dahham et al. identified a total of 14 studies, all of which were conducted in upper-middle-income economies (67). The total annual cost per patient ranged between $US463 and 58,616. Costs varied across studies and countries, mainly because of differences regarding the inclusion of costs of DMTs, the range of cost items included, the methodological choices such as approaches used to estimate healthcare resource consumption, and the inclusion of informal care and productivity losses. As with other studies, the total costs increased with greater disease severity. MS drug costs were the main cost driver for less severe MS, whereas the proportion of direct non-medical costs and indirect costs increased with greater disease severity. These results suggest that MS imposes a significant economic burden in low- and middle-income countries.

7.2 Medical need

There is no cure for MS. The current therapeutic approach involves symptomatic treatment, treatment of acute relapses, and treatment with DMTs. The aim of treatment with DMTs is to slow the progression of disability, and to reduce the number and severity of relapses.

Symptomatic treatment refers to all therapies applied to improve symptoms and complications caused by the disease.

More specific treatments are designed to interfere with the pathophysiology of MS, e.g., facilitate remyelination or axonal conductivity. The standard of care for acute relapses is intravenous (IV) methylprednisolone, which shortens the duration of a relapse but has no influence on its sequelae.

DMTs aim to modify the course of the disease, mainly by suppressing or modulating immune responses involved in MS pathogenesis. Biologicals (monoclonal antibodies and other therapeutic proteins) and small molecules have been approved for use in this therapeutic context. These therapies aim to prevent relapses and ultimately intend to decrease the rate of accumulation of disability. Due to the risks (identified or potential) of opportunistic infections, malignancies, and other systemic adverse drug reactions, several of these treatment options are considered as second-line options based on label restrictions, and treatment is restricted to patients with rapidly evolving MS or those who had a suboptimal response to prior therapies.

It is often recommended that patients should be able to take a DMT as early as they are diagnosed. Two conceptually different treatment approaches have emerged:

- The “escalation approach” advocates the first-line use of moderately-effective DMTs (i.e., classical first-line therapies, e.g., interferons and glatiramer acetate) and a later escalation to high-efficacy therapies only if new disease activity breaks through, i.e., there are relapses or new lesions as shown by MRI.
- The “highly-effective treatment early approach” advocates initiation of high-efficacy therapies early on (as first-line therapy). Treatment-related risks are weighed against the expected occurrence of brain damage caused by the disease.

Several DMTs/DMT classes are currently available and approved for use in RMS, which vary in their mechanism of action, efficacy, safety, mode of administration, and ease of use, including (in alphabetical order): alemtuzumab, beta-interferons, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate, mitoxantrone, natalizumab, ocrelizumab, ofatumumab, ozanimod, siponimod, and teriflunomide.

Ocrelizumab, a humanized anti-CD20 monoclonal antibody (mAb), is a high-efficacy therapy with a well-documented safety profile. Ocrelizumab was the first mAb targeting B cells approved for the treatment of relapsing and primary progressive forms of MS (RMS and PPMS). Ocrelizumab is administered via the IV route every six months.

7.3 Potential global impact of ocrelizumab

Currently, there are no approved therapies for PPMS other than ocrelizumab. Ocrelizumab was shown to be safe and effective in two pivotal phase 3 studies in RMS, OPERA I (WA21092) and OPERA II (WA21093) (5), and in one phase 3 study in PPMS, ORATORIO (WA25046) (6). These studies have formed the basis of regulatory approvals for ocrelizumab from 2017 onwards (see Section 12 for more details). Updated analyses of efficacy and safety for patients who have continued in the open-label extension (OLE) phase of the three pivotal studies for up to nine years have confirmed continued benefit after the controlled treatment phase, and no new safety signals have been identified (7–14).

The benefit of ocrelizumab has been further confirmed in real-world observational studies in both RMS and PPMS. More than 250,000 people have been treated with ocrelizumab globally and data continues to show a consistent and favorable benefit-risk profile in clinical trial and real-world settings (15,11,16–22).

The benefit of ocrelizumab has also been confirmed in ongoing studies, e.g. in early-stage RRMS in the Phase 3b ENSEMBLE study (68) and in progressive MS (patients with either PPMS or SPMS) in the Phase 3b CONSONANCE study (69). Two phase 3b studies testing higher doses of ocrelizumab in patients with RMS (MUSETTE) and PPMS (GAVOTTE) have also been initiated.

The pivotal RMS and PPMS studies were conducted mainly in North America and Europe (5,6). However, ocrelizumab benefit has been demonstrated in a subgroup of patients of African descent in the OPERA I and II pivotal studies (70); more details in Section 9.3.1), as well as across racial/ethnic groups in a real-world analysis (71); more details in Section 9.3.3).

Patients are often diagnosed at an age when they may be planning to have a family (1). Women with MS who wish to become pregnant face a difficult choice, as most DMTs are contraindicated in pregnancy and recommended against during breastfeeding (72). To address this unmet need, two studies in pregnant and lactating women are currently under way: MINORE (NCT04998812), which will assess the impact of potential ocrelizumab exposure during pregnancy on infants born to women with MS/CIS, and SOPRANINO (NCT04998851), which will similarly assess the impact on infants potentially exposed to ocrelizumab through breastfeeding (73). In parallel with these studies, other efforts to understand the risks and benefits of ocrelizumab in pregnant and lactating women include a pregnancy registry (74), a post-marketing study (MELODIC; (75)), and periodic analyses of post-marketing surveillance data (76–78).

Currently, ocrelizumab is available for IV infusion given every six months and should be administered by trained staff under the supervision of a healthcare professional (79). Roche is currently investigating the use of an SC formulation of ocrelizumab in a phase 1b study (CN41144 [OCARINA 1]; more details in Appendix A). Finally, ocrelizumab is also being studied in pediatric RRMS patients in the phase 2 study WA39085 (OPERETTA 1) and the phase 3 study WN42086 (OPERETTA 2); more details on both studies are available in Appendix A.

7.4 Target populations

- Ocrelizumab is indicated for the treatment of patients with relapsing forms of multiple sclerosis (RMS) to suppress relapses and disease progression (clinical and subclinical disease activity).
- Ocrelizumab is indicated for the treatment of patients with primary progressive multiple sclerosis (PPMS) to delay disease progression and reduce deterioration in walking speed.

7.5 Alternative medicines currently included on the model lists for the proposed indication(s)

The WHO model lists do not currently include medicines for any form of MS.

8. Treatment details

8.1 Diagnosis of MS, RMS, and PPMS

Diagnosis of MS is based on the application of structured diagnostic criteria that rely on clinical observation, neurological examination, brain and spinal cord magnetic resonance imaging (MRI) scans, and at times, evoked potentials and cerebral spinal fluid (CSF) examination (80). Prognosis is highly variable and, if left untreated, half of patients with MS require assistance to walk within 15 years of disease onset (representing an Expanded Disability Status Scale [EDSS] of 6) (81).

In approximately 85% of patients, MS begins as a relapsing, episodic disorder with gradual complete or incomplete recovery (relapsing-remitting multiple sclerosis [RRMS]). If left untreated, the majority of these patients will transition to a progressive form characterized by worsening neurologic disability either with or without occasional superimposed relapses (relapsing or non-relapsing secondary progressive MS). The term "relapsing (forms of) MS (RMS)" is used to describe those patients with either RRMS or SPMS who continue to experience relapses. Patients accumulate disability as a result of incomplete recovery from acute relapses and/or gradual disease progression (81).

Advances in diagnostic criteria, greater awareness, and increased availability of MRI to detect subclinical disease pathology (such as T1 gadolinium [Gd]-enhancing and T2 hyperintense lesion burden) have made the early diagnosis of MS a reality. RMS diagnostic criteria rely upon the general concept of white matter demyelinating lesions, separated in space (i.e., in different anatomical locations in the CNS) and time (i.e., onset of sub-acute to acute bouts of neurologic dysfunction, separated by neurological stability or improvement). Pathologically, MS is characterized by focal infiltrates of inflammation (plaques) in the CNS which lead to demyelination, axonal interruption, and neuronal degeneration (81).

Clinically, MS attacks (or relapses) consist of transient episodes of neurological dysfunction occurring at different times and not explained by other etiologies, such as infections, vascular disorders, or other autoimmune disorders. Several clinical variants of MS have been defined on the basis of the presence and/or frequency of relapses and the pattern of progression in neurological disability. Of these, RMS has been the most intensively studied since this variant comprises the largest cohort of patients and is the population where treatments have demonstrated benefit, as well as being the stage of disease that might make the most meaningful impact on ultimate disease progression. Primary progressive MS (PPMS) is a less common form of MS, accounting for approximately 10% of all cases (approximately 40,000 individuals in the US). It is characterized by a progressive course from disease onset, with infrequent superimposed discrete clinical attacks or relapses (81).

The mean age of onset for PPMS is approximately 40 years, and men are affected nearly as often as women. In PPMS, diagnostic criteria requires that there is evidence of disease progression for at least one year from the first symptoms, plus a combination of lesions in brain or spinal cord and/or presence for oligoclonal bands or elevated immunoglobulin (Ig)G index in CSF. Natural history studies of PPMS patients demonstrate a steadily disabling course from symptom onset. In a well-characterized cohort of PPMS patients from Ontario, Canada, the median time to the use of aids for ambulation (representing a Disability Status Scale [DSS] landmark of 6) was eight years and the median time to wheelchair use (representing a DSS landmark of 7) was under 20 years, which is twice as fast as from onset of RRMS. This likely reflects the absence of a

relapsing phase of disease as the age at which higher levels of disability are achieved are comparable between subtypes, despite the later age of onset in PPMS. The actual rate of progression of disability seems not to differ between subtypes once steady progression of disability has commenced. A higher proportion of PPMS patients present initially with motor impairment, cerebellar ataxia, and brainstem symptoms than relapsing-onset patients, and spastic paraparesis is a common early clinical presentation. The diagnosis of PPMS utilizes specific criteria which include CSF abnormalities, CNS lesions separated in space, and continued disease progression – specifically, clinical evidence that the disease has progressed for at least one year from symptom onset (81).

8.2 Dosage regimen and duration of treatment

8.2.1 Posology

Initial Dose

Ocrelizumab is administered by intravenous infusion as a 600 mg dose every six months.

The initial 600 mg dose is administered as two separate intravenous infusions; first as a 300 mg infusion, followed two weeks later by a second 300 mg infusion (Table 1).

Subsequent Doses

Subsequent doses of ocrelizumab are administered as a single 600 mg intravenous infusion every six months (Table 1). If patients did not experience a serious infusion-related reaction (IRR) with any previous ocrelizumab infusion, a shorter (two-hour) infusion can be administered for subsequent doses (Table 1, Option 2).

A minimum interval of five months should be maintained between each dose of ocrelizumab.

Table 1: Dose and Schedule of Ocrelizumab

		Amount of ocrelizumab to be administered*	Infusion instructions
Initial Dose (600 mg) divided into 2 infusions	Infusion 1	300 mg in 250 mL	▪ Initiate the infusion at a rate of 30 mL/hour for 30 minutes ▪ Thereafter, the rate can be increased in 30 mL/hour increments every 30 minutes to a maximum of 180 mL/hour. ▪ Each infusion should be given over approximately 2.5 hours
	Infusion 2 (2 weeks later)	300 mg in 250 mL	
Subsequent Doses (600 mg)** single infusion once every 6 months	**OPTION 1**		
	Infusion of approximately 3.5 hours duration	600 mg in 500 mL	▪ Initiate the infusion at a rate of 40 mL/hour ▪ The rate can be increased in 40 mL/hour increments every 30 minutes to a maximum of 200 mL/hour ▪ Each infusion should be given over approximately 3.5 hours
	OR **OPTION 2*** **		
	Infusion of approximately 2 hours duration	600 mg in 500 mL	▪ Initiate the infusion at a rate of 100 mL/hour for the first 15 minutes ▪ Increase the infusion rate to 200 mL/hour for the next 15 minutes ▪ Increase the infusion rate to 250 mL/hour for the next 30 minutes ▪ Increase the infusion rate to 300 mL/hour for the remaining 60 minutes ▪ Each infusion should be given over approximately 2 hours

* Solutions of ocrelizumab for intravenous infusion are prepared by dilution of the drug product into an infusion bag containing 0.9% sodium chloride, to a final drug concentration of approximately 1.2 mg/mL.
** First single infusion should be administered six months after Infusion 1 of Initial Dose.
*** If patients did not experience a serious IRR with any previous ocrelizumab infusion, a shorter (two-hour) infusion can be administered for subsequent doses.

8.2.2 Premedication for infusion-related reactions

Premedicate with 100 mg IV methylprednisolone (or an equivalent) approximately 30 minutes prior to each ocrelizumab infusion (see Section 10.4.4.1, Infusion-Related Reactions) and with an antihistaminic drug (e.g., diphenhydramine) approximately 30-60 minutes before each infusion of ocrelizumab to reduce the frequency and severity of infusion-related reactions.

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

8.2.3 Infusion adjustments during treatment

No dose reductions of ocrelizumab are recommended. In case of IRRs during any infusion, see the following adjustments.

Life-threatening IRRs
Immediately stop ocrelizumab if there are signs of a life threatening or disabling IRR during an infusion, such as acute hypersensitivity or acute respiratory distress syndrome. The patient should receive appropriate supportive treatment. Permanently discontinue ocrelizumab in these patients.

Severe IRRs
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.

Mild to Moderate IRRs
If a patient experiences a mild to moderate IRR (e.g., headache), 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.

8.2.4 Delayed or missed doses
If an infusion of ocrelizumab is missed, it should be administered as soon as possible; do not wait until the next planned dose. The treatment interval for ocrelizumab should be maintained between doses (see Table 1).

8.2.5 Method of administration
Ocrelizumab is administered as an IV infusion through a dedicated line under the close supervision of an experienced healthcare professional with access to appropriate medical support to manage severe reactions such as serious IRRs. Ocrelizumab infusions should not be administered as an IV push or bolus. Use isotonic 0.9% sodium chloride solution as the infusion vehicle. In the event that an IV infusion cannot be completed the same day, the remaining liquid in the infusion bag must be discarded.

Observe the patient for at least one hour after the completion of the infusion (see Section 10.4.4.1, Infusion-Related Reactions).

8.2.6 Special populations
Geriatric use
The safety and efficacy of Ocrelizumab in patients ≥65 years of age has not been studied.

Renal impairment
The safety and efficacy of ocrelizumab in patients with renal impairment has not been formally studied. Patients with mild renal impairment were included in clinical trials. As a mAb, ocrelizumab is cleared via catabolism (rather than renal excretion), and a change in dose is not expected to be required for patients with renal impairment.

Hepatic impairment
The safety and efficacy of ocrelizumab in patients with hepatic impairment has not been formally studied. Patients with mild hepatic impairment were included in clinical trials. As a mAb, ocrelizumab is cleared via

catabolism (rather than hepatic metabolism), and a change in dose is not expected to be required for patients with hepatic impairment.

Pediatric use
The safety and efficacy of ocrelizumab in children and adolescents (<18 years of age) has not been studied.

Pregnancy
Ocrelizumab is a humanized monoclonal antibody of an immunoglobulin G1 subtype, and immunoglobulins are known to cross the placental barrier.

Ocrelizumab should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus. There is no adequate or well-controlled data from studies in pregnant women; however transient peripheral B cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy.

Postponing vaccination with live or live-attenuated vaccines should be considered for neonates and infants born to mothers who have been exposed to ocrelizumab in utero. B cell levels in neonates and infants following maternal exposure to ocrelizumab have not been studied in clinical trials, and the potential duration of B cell depletion in neonates and infants is unknown.

Labor and Delivery: The safe use of ocrelizumab during labor and delivery has not been established.

Lactation
It is unknown whether ocrelizumab is excreted in human breast milk or has any effect on the breastfed child and on milk production. Animal studies have shown excretion of ocrelizumab in breast milk. Because human immunoglobulin G (IgG) is excreted in human milk, and the potential for ocrelizumab absorption leading to B cell depletion is unknown, women should be advised to discontinue breastfeeding during ocrelizumab therapy.

Ongoing studies
Additional studies to investigate use of ocrelizumab in special populations, including pediatric patients and lactating women, are being conducted. For more information regarding these, refer to Section 10.3.1 and Appendix A.

8.2.7 Contraindications, special warnings and precautious for use

Physicians should refer to the local product label which is publicly available in most regions (e.g., on the EMA website for the European Union's (79) and on the FDA website (82) as well as on the Roche product website [https://www.gene.com/download/pdf/ocrevus_prescribing.pdf] for the US), for contraindications, and warnings and precautions regarding IRRs, hypersensitivity reactions, infection, progressive multifocal leukoencephalopathy (PML), hepatitis B reactivation, late neutropenia, malignancies, treatment of severely immunocompromised patients, vaccinations, use with other immunosuppressants, and use in pregnancy and lactation. More details are also provided in Section 10.4.4.

8.3 Requirements to ensure appropriate use of the medicine

No companion diagnostics, other *in vitro* diagnostic tests or special facilities are necessary for the use of ocrelizumab. However, the diagnosis of relapsing forms of MS (RMS) and primary progressive MS (PPMS) must be made by specialized physicians/neurologists experienced in the diagnosis and treatment of neurological conditions. Treating physicians must also have access to appropriate medical support to manage severe reactions such as serious IRRs and infections. Ocrelizumab administration should be delayed in patients with an active infection until the infection is resolved. Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with ocrelizumab, as per local guidelines.

Routine risk minimization measures (79) are sufficient to ensure appropriate use.

8.4 Recommendations in existing WHO guidelines

There are no applicable WHO guidelines for the treatment of MS.

8.5 Recommendations in other current clinical guidelines

The American Academy of Neurology (AAN) practice guideline for disease-modifying treatments (DMTs) in MS (83) recommends ocrelizumab as a first-line option for PPMS, noting that ocrelizumab is the only DMT shown to alter disease progression in ambulatory PPMS patients. The guideline also lists ocrelizumab (amongst other high-efficacy DMTs) as an option to consider when switching treatment in MS patients who have breakthrough disease activity while on a DMT.

The European Committee of Treatment and Research in Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) guideline on the pharmacological treatment of people with MS recommends early treatment with DMTs (including ocrelizumab) in patients with active RRMS as defined by clinical relapses and/or magnetic resonance imaging (MRI) activity, with the choice of DMT being based on patient characteristics and comorbidities, disease severity/activity, and the safety profile and accessibility of the drug. Ocrelizumab is also recommended for patients with PPMS and, along with other anti-CD20 mAbs, for SPMS. The guidelines also recommend considering a higher-efficacy DMT (such as ocrelizumab) early on, according to disease activity and patient particulars (84,85).

In addition, the Multiple Sclerosis Therapy Consensus Group guideline recommends ocrelizumab as first-line treatment for clinically isolated syndrome (CIS) and highly active RMS (amongst other options), and as first-line treatment for progressive MS, including secondary progressive MS (SPMS) and primary progressive MS (PPMS) (86).

9. Review of benefits: summary of evidence of comparative effectiveness

This section provides an overview of the current information on the effectiveness of ocrelizumab in MS. Section 9.1 summarizes evidence from the pivotal studies in relapsing forms of MS (RMS) and primary progressive MS (PPMS), which formed the basis of global approvals for ocrelizumab in these indications (more information on global regulatory approvals is provided in Section 12). Section 9.2 presents information from a recent literature survey. Finally, Section 9.3 provides an overview of the effectiveness of ocrelizumab in important patient subgroups.

9.1 Summary of available evidence for comparative effectiveness

This section provides an overview of the evidence for benefit of ocrelizumab from the pivotal phase 3 trials in RMS and PPMS. Section 9.1.1 provides an overview of the main clinical endpoints used in these studies. Section 9.1.2 summarizes the evidence by indication: for RMS in Section 9.1.2.1 (compared to the standard of care, interferon beta-1a [IFNβ1a]), and for PPMS in Section 9.1.2.2 (compared to placebo, as there is no other approved treatment for PPMS). Finally, Section 9.3 provides an overview of the effectiveness of ocrelizumab in important patient subgroups by indication (for RMS in Section 9.3.1, for PPMS in Section 9.3.2, and for across types in Section 9.3.3).

9.1.1 Important endpoints that support benefit

In the pivotal trials, the efficacy of ocrelizumab for the treatment of patients with RMS (Studies WA21092/ACT4181g [OPERA I] and WA21093/ACT4182g [OPERA II]) and PPMS (Study WA25046/ACT4619g [ORATORIO]) was characterized using valid and reliable measures of clinical benefit per the International Council of Harmonisation (ICH) E8 and E9 guidelines. The study endpoints are widely accepted as clinically relevant and have been used in numerous pivotal clinical trials in RMS and PPMS.

Prevention of relapses, as well as the prevention or delay of disability progression, are meaningful goals in the treatment of patients with RMS. The primary endpoint for the RMS studies is annualized relapse rate (ARR) over 96 weeks, based on protocol-defined relapses. Key secondary endpoints include changes to pre-specified magnetic resonance imaging (MRI) endpoints, as well as time to Confirmed Disability Progression (CDP). CDP is a standard definition based on increases in Expanded Disability Status Scale (EDSS) score that are subsequently confirmed at regularly scheduled visits at least 12 or 24 weeks after the initial event of neurological worsening (12-week and 24-week CDP respectively). Confirmation of sustained disability progression ensures that an observed increase in EDSS represents a persistent change in a patient's neurologic status, rather than a transient fluctuation in score because of a patient's fatigue or illness or inter-rater variability.

For the PPMS study, the primary endpoint is the time to 12-week CDP. Key secondary endpoints include time to 24-week CDP, as well as relative changes in Timed 25-Foot Walk (T25-FW), MRI T2 lesion volume, and total brain volume loss.

Trials also included measurement of patient-reported outcomes (PROs) assessed using validated instruments. Patient-reported outcomes provide the patient's perspective on clinical benefit.

9.1.2 Evidence of efficacy and effectiveness in approved indications

The characterization of benefits for ocrelizumab includes use in the approved indications. The Appendix A provides a description of all completed and ongoing clinical studies on ocrelizumab in MS.

The main sources of evidence for efficacy considered for the approved indications were the following pivotal studies:

- OPERA I (WA21092) and OPERA II (WA21093): In these identical active-controlled studies to evaluate the efficacy and safety of ocrelizumab in adults with RMS (5), patients were given ocrelizumab 600 mg (n=825) every six months (with the first dose administered as two 300 mg intravenous (IV) infusions separated by two weeks and all subsequent doses as a single 600-mg infusion), or subcutaneous (SC) interferon beta-1a (IFNβ1a) 44 mcg (n=826) three times per week. The controlled period of the studies lasted 96 weeks (four doses of ocrelizumab).
- ORATORIO (WA25046): In this placebo-controlled study to evaluate the efficacy and safety of ocrelizumab in adults with PPMS (6), patients were given ocrelizumab 600 mg (n=486) or placebo (n=239) every six months (administered as two 300-mg infusions separated by two weeks over the entire study).

At the time of preparation of this submission, the double-blinded control periods for all studies described above were complete, and patients were continuing in the open-label extension (OLE) phase.

A description of the key evidence of efficacy for each indication is presented below.

9.1.2.1 Relapsing forms of multiple sclerosis

Phase 3 pivotal trials

In the two identical randomized double-blind active comparator controlled pivotal phase 3 trials in RMS, OPERA I (WA21092; n=821) and OPERA II (WA21093; n=835), ocrelizumab was associated with lower rates of disease activity and progression than IFNβ1a over a period of 96 weeks (5). The ARR was lower with ocrelizumab than with IFNβ1a in OPERA I (0.16 vs. 0.29; 46% lower rate with ocrelizumab; P<0.001) and in OPERA II 2 (0.16 vs. 0.29; 47% lower rate; P<0.001).

The efficacy of ocrelizumab in RMS was demonstrated in two randomized, double-blind, double-dummy, active comparator controlled clinical trials with identical design, studies WA21092/ACT4181g (OPERA I) and WA21093/ACT4182g (OPERA II). The primary efficacy endpoint was ARR over 96 weeks. Key secondary efficacy endpoints included the time to onset of sustained disability progression, confirmed at scheduled clinic visits, for at least 12 and 24 weeks. The two trials used identical protocols but were conducted independently at non-overlapping trial sites (mainly in North America, Latin America, and Europe). OPERA I was conducted at 141 sites across 32 countries and OPERA II at 166 sites across 24 countries (5).

For studies WA21092/ACT4182g (OPERA I) and WA21093/ACT4182g (OPERA II), patients were randomized in a 1:1 ratio to the following treatment arms:

- Arm 1 (Investigational, N=410 for WA21092 and N=417 for WA21093): Ocrelizumab 600 mg regimen (given as dual infusions of 300 mg of ocrelizumab, 14 days apart for the first 24 weeks and single infusions of 600 mg every 24 weeks thereafter) and placebo IFNβ1a, same schedule as Arm 2.
- Arm 2 (Comparator, N=411 for WA21092 and N=418 for WA21093): IFNβ1a subcutaneous injections, 3x weekly, and placebo ocrelizumab, same schedule as Arm 1.

Patients who completed the 96-week double-blind, double-dummy treatment period, and who, in the opinion of the Treating Investigator, may benefit from treatment with ocrelizumab, were offered the opportunity to participate in the OLE phase of the study. Eligible patients who were not willing to participate in the OLE phase of the study were entered into the Safety Follow-Up Period.

Patient demographics (age, sex, and geographic region) and baseline disease characteristics (time since symptom onset, time since diagnosis, number of relapses in the past 12 months, number and type of previous DMTs, mean EDSS score, number of gadolinium-enhancing T1 MRI lesions, number and volume of T2 MRI lesions, and normalized brain volume) were well balanced between the two treatment arms.

Studies WA21092/ACT4182g (OPERA II) and WA21093/ACT4182g (OPERA II) demonstrated that the addition of ocrelizumab to control treatment resulted in a statistically significant and clinically meaningful improvement in ARR, compared with interferon control. In addition, results of several secondary endpoints supported the primary endpoint, demonstrating statistically significant efficacy of ocrelizumab when compared with interferon β1a (see Table 2).

Table 2: Studies WA21092 and WA21093: Key Efficacy Results

Endpoints	Study 1: WA21092 (OPERA I)		Study 2: WA21093 (OPERA II)	
	ocrelizumab 600 mg (n=410)	IFN 44 mcg (n=411)	ocrelizumab 600 mg (n=417)	IFN 44 mcg (n=418)
Clinical Endpoints				
Annualized Relapse Rate (primary endpoint)	0.156	0.292	0.155	0.290
Relative Reduction	46% (p<0.0001)		47% (p<0.0001)	
Proportion of patients with 12-week Confirmed Disability Progression[a] Risk Reduction (Pooled Analysis[b])	9.8% ocrelizumab vs. 15.2% IFN 40% (p=0.0006)			
Risk Reduction (Individual Studies[c])	43% (p=0.0139)		37% (p=0.0169)	
Proportion of patients with 24-week Confirmed Disability Progression[a] Risk Reduction (Pooled Analysis[b])	7.6% ocrelizumab vs. 12.0% IFN 40% (p=0.0025)			
Risk Reduction (Individual Studies[c])	43% (p=0.0278)		37% (p=0.0370)	
Proportion of patients with at least 12-weeks Confirmed Disability Improvement[d] (Pooled)	20.7% ocrelizumab vs. 15.6% IFN			
Relative Increase (Pooled Analysis[b])	33% (p=0.0194)			
Relative Increase (Individual Studies[c])	61% (p=0.0106)		14% (p=0.4019)	
Mean change from baseline in Multiple Sclerosis Functional Composite (MSFC)	0.213	0.174	0.276	0.169
Difference	0.039 (p=0.3261)		0.107 (p=0.0040)	

Endpoints	Study 1: WA21092 (OPERA I)		Study 2: WA21093 (OPERA II)	
	ocrelizumab 600 mg (n=410)	IFN 44 mcg (n=411)	ocrelizumab 600 mg (n=417)	IFN 44 mcg (n=418)
Proportion of patients with No Evidence of Disease Activity (NEDA)[e]	48%	29%	48%	25%
Relative Increase[c]	64% (p<0.0001)		89% (p<0.0001)	
MRI Endpoints				
Mean number of T1 Gd-enhancing lesions per MRI scan	0.016	0.286	0.021	0.416
Relative reduction	94% (p<0.0001)		95% (p<0.0001)	
Mean number of new and/or enlarging T2 hyperintense lesions per MRI scan	0.323	1.413	0.325	1.904
Relative reduction	77% (p<0.0001)		83% (p<0.0001)	
Mean number of new T1-hypo-intense lesions (chronic black holes) per MRI scan	0.420	0.982	0.449	1.255
Relative reduction	57% (p<0.0001)		64% (p<0.0001)	
Percentage change in brain volume from Week 24 to Week 96	-0.572	-0.741	-0.638	-0.750
Relative reduction in brain volume loss	22.8% (p=0.0042)[f]		14.9% (p=0.0900)	
Quality of Life				
Mean change from baseline in SF-36 Physical Component Summary	0.036	-0.657	0.326	-0.833
Difference	0.693 (p=0.2193)		1.159 (p=0.0404)[f]	

IFN=Interferon; MRI=Magnetic resonance imagining; MSFC=Multiple Sclerosis Functional Composite; NEDA=No Evidence of Disease Activity

[a] Defined as an increase of ≥ 1.0 point from the baseline Expanded Disability Status Scale (EDSS) score for patients with baseline score of 5.5 or less, or ≥ 0.5 when the baseline score is > 5.5, Kaplan-Meier estimates at Week 96.

[b] Data prospectively pooled from Study 1 & 2.

[c] Non-confirmatory p-value; analysis not part of the pre-specified testing hierarchy.

[d] Defined as decrease of ≥ 1.0 point from the baseline EDSS score for patients with baseline EDSS score ≥ 2 and ≤ 5.5, or ≥ 0.5 when the baseline score is > 5.5. Patients with baseline score < 2 were not included in analysis.

[e] NEDA defined as absence of protocol-defined relapses, Confirmed Disability Progression (CDP), and any MRI activity (either Gd-enhancing T1 lesions, or new or enlarging T2 lesions) during the whole 96-week treatment. Exploratory result based on complete ITT population.

[f] Non-confirmatory p-value; hierarchical testing procedure terminated before reaching endpoint.

Studies WA21092/ACT4181g (OPERA I) and WA21093/ACT4182g (OPERA II) were well-designed and conducted trials that met their primary endpoints and demonstrated that treatment with ocrelizumab resulted in statistically significant and clinically meaningful improvement in ARR, as well as in key efficacy endpoints, such as time to onset of 12-week and 24-week CDP.

Clinical outcomes

As described above, treatment with ocrelizumab reduced the ARR by 46% in Study WA21092/ACT4181g (OPERA I) and 47% in Study WA21093/ACT4181g (OPERA I) at Week 96, compared with interferon β−1a (adjusted ARR ratio 0.536 [95% CI: 0.400, 0.719], p<0.0001 for WA21092; adjusted ARR ratio 0.532 [95% CI: 0.397, 0.714], p<0.0001 for WA21093). Sensitivity analyses confirmed the robustness of the primary outcomes for both studies. The reduction in relapse frequency was observed early and sustained over time in both studies. Furthermore, more patients remained free of protocol-defined relapses on ocrelizumab (80.4% patients in WA21092 and 78.9% in WA21093) compared with IFNβ1a (66.7% patients in WA21092 and 64.3% in WA21093) (p<0.0001).

The benefit of ocrelizumab was also demonstrated by meeting both endpoints of 12-week and 24-week CDP, with risk reductions of 40% (p=0.0006 and p=0.0025, respectively). These endpoints were pre-specified to be analyzed based on pooled data from both studies WA21092 and WA21093 in order to provide sufficient statistical power to detect relevant treatment differences against IFNβ1a. The individual study-level analyses and sensitivity analyses of these endpoints were also highly consistent. These robust CDP results therefore show a significant effect of ocrelizumab in comparison with IFNβ1a on disability progression, a clinically meaningful and important measure in RMS trials. Treatment with ocrelizumab also resulted in a significant 33% relative increase in the proportion of patients with 12-week Confirmed Disability Improvement in the pre-specified pooled analysis (p=0.0194). Finally, the proportion of patients with NEDA was significantly higher after ocrelizumab treatment (48% vs. 29%, ocrelizumab vs. IFNβ1a, respectively, in WA21092 and 48% vs. 25%, ocrelizumab vs. IFNβ1a, respectively, in WA21093, both p<0.0001). Both p-values are non-confirmatory since in both studies, the NEDA test result follows a non-significant test result within the hierarchy structure.

Magnetic resonance imaging outcomes

Ocrelizumab markedly reduced inflammatory lesion activity on brain MRI, further supporting the relapse and disability clinical effects. This was demonstrated by reductions in the number of T1 Gd-enhancing lesions (94% and 95% reduction in studies WA21092 and WA21093, respectively, p<0.0001) and new and/or enlarging T2 lesions (77% and 83% reduction in studies WA21092 and WA21093, respectively, p<0.0001) over two years, compared with IFNβ1a. Relative reductions were observed as early as Week 24, and were maintained throughout the 96-week double-blind, double-dummy treatment period.

Ocrelizumab also demonstrated efficacy on MRI measures of degenerative tissue loss. Treatment with ocrelizumab resulted in significantly fewer new T1 hypointense lesions compared with IFNβ1a (57% and 64% in studies WA21092 and WA21093, respectively, p<0.0001). T1 hypointense lesions may represent evolution of MS lesions into permanent brain parenchymal loss. Consistent with these findings, in Study WA21092, treatment with ocrelizumab resulted in less brain atrophy compared with IFNβ1a, as measured by the change in whole brain volume from Week 24 to 96 (relative reduction of 22.8% in mean percent brain volume loss, non-confirmatory p=0.0042). Although treatment with ocrelizumab in Study WA21093 resulted in a 14.9% reduction in the rate of whole brain volume loss from Week 24 to Week 96 compared with IFNβ1a, this difference was not significant (p=0.0900). Brain volume at 24 weeks had been chosen as a reference point to account for a potential pseudoatrophy effect that might theoretically occur early after the initiation of an anti-inflammatory treatment. Discounting the potential effects of pseudoatrophy, ocrelizumab showed a greater degree of protection from brain atrophy (relative reduction of 23.5% and 23.8% in mean percent brain volume loss in Study WA21092 and Study WA21093, respectively, p<0.0001) in

an analysis of the change in brain volume from baseline to Week 96. Treatment with ocrelizumab was also associated with less reduction in cortical gray matter volume than IFNβ1a (p=0.0005 for Study WA21092 and p<0.0001 for Study WA21093). These data, therefore, strongly suggest a potential positive impact of ocrelizumab on MS-related neurodegenerative processes in addition to a marked reduction in MS-related inflammation.

Efficacy of the active comparator IFNβ1a during the study was in line with expectations and contemporary clinical trials with IFNβ1a44 mcg in MS (87,88). Low levels of neutralizing antibodies against IFNβ1a observed during the study were also in line with prior studies (89,87). This indicates that the observed treatment effects of ocrelizumab in the current studies were due to its superior efficacy compared with IFNβ1a.

Overall, both studies provided robust evidence that ocrelizumab demonstrated consistent efficacy on clinical and subclinical measures of inflammation (ARR, T1-Gd-enhancing lesions and T2 hyperintense lesions) and on measures of disease progression (CDP, new T1 hypointense lesions, and brain volume) against the active comparator INFβ1a at 96 weeks.

Evidence of efficacy from the OLE phase of OPERA I and II

Periodic analyses of efficacy data from patients in the OPERA trials who continued on into the OLE phase have been published. The key publications are summarized in this section; additional publications based on these studies are summarized in Section 9.2.

Hauser et al. (90) assessed the efficacy of switching to or maintaining ocrelizumab therapy on disease activity and progression after four years of follow-up in the OLE period of OPERA I and OPERA II in RMS. The results showed that, after six years of total follow-up, the proportion of patients with 24-week confirmed disability progression (CDP) remained lower in patients who initiated ocrelizumab treatment earlier (ocrelizumab - ocrelizumab), compared with patients who received initial interferon treatment (interferon - ocrelizumab), demonstrating that the benefits of earlier initiation of ocrelizumab were maintained compared with patients switching from interferon. Switching from interferon to ocrelizumab after two years at the start of the OLE period was associated with a reduction in ARR. Both ocrelizumab - ocrelizumab and interferon- ocrelizumab patients maintained their reduction in ARR through the four-year follow-up of the OLE period.

Giovannoni et al. (8) assessed the efficacy of switching to or maintaining ocrelizumab therapy on disease activity and progression after four years of follow-up in the OLE period of OPERA I and OPERA II in RMS. At the start of the OLE period, patients who completed the double-blind period (DBP) either continued ocrelizumab (ocrelizumab-ocrelizumab) or were switched from IFNβ1a to ocrelizumab (interferon-ocrelizumab). Adjusted ARR, time to onset of 24-week CDP, and change in adjusted mean EDSS score from the DBP baseline were analyzed. This study showed that after six years of total follow-up, the proportion of patients with 24-week CDP remained lower in patients who initiated ocrelizumab treatment earlier (ocrelizumab-ocrelizumab), compared with patients who received initial interferon treatment (interferon-ocrelizumab), demonstrating that the benefits of earlier initiation of ocrelizumab were maintained, compared with patients switching from interferon. Switching from interferon to ocrelizumab after two years (at the start of the OLE period) was associated with a reduction in ARR. Both ocrelizumab-ocrelizumab and interferon-ocrelizumab patients maintained their reduction in ARR through the four-year follow-up of the OLE period.

Hauser et al. (9) assessed the efficacy of switching to or maintaining ocrelizumab therapy on disease activity and progression after four years of follow-up in the OLE period of OPERA I and OPERA II in RMS. At the start of the OLE period, patients who completed the DBP either continued ocrelizumab (ocrelizumab-ocrelizumab) or were switched from IFNβ1a to ocrelizumab (interferon-ocrelizumab). ARR, time to onset of 24-week CDP, and change in adjusted mean EDSS score from the DBP baseline were analyzed. After six years of total follow-up, the proportion of patients with 24-week CDP remained lower in patients who initiated ocrelizumab treatment earlier (ocrelizumab-ocrelizumab), compared with patients who received initial interferon treatment (interferon-ocrelizumab), demonstrating that the benefits of earlier initiation of ocrelizumab were maintained, compared with patients switching from interferon. Switching from interferon to ocrelizumab after two years at the start of the OLE period was associated with a reduction in ARR. Both ocrelizumab-ocrelizumab and interferon-ocrelizumab patients maintained their reduction in ARR through the four-year follow-up of the OLE period.

Giovannoni et al. (91) assessed the efficacy of switching from IFNβ-1a or maintaining ocrelizumab therapy on disease activity and CDP after 5.5 years of follow-up in the OLE of OPERA I and OPERA II. The results showed that switching from IFNβ1a to ocrelizumab at the start of the OLE period was associated with a rapid and robust reduction in ARR that was maintained through the 5.5-year follow- up of the interferon - ocrelizumab period. Compared with patients switching to ocrelizumab at the OLE, patients initiating ocrelizumab two years earlier had a significantly reduced risk of requiring a walking aid and 48-week CDP.

Giovannoni et al. (92) assessed the effect of ocrelizumab on time to EDSS score ≥6.0 in relapsing MS. The results showed time to reach EDSS score ≥6.0 was significantly delayed in those initially randomized to ocrelizumab versus interferon. Over 6.5 years, the risk of requiring a walking aid confirmed for ≥24 weeks was 34% lower among those who initiated ocrelizumab earlier versus delayed treatment (average HR DBP + OLE 0.66, 95% CI 0.45–0.95; p = 0.024); the risk of requiring a walking aid confirmed for ≥48 weeks was 46% lower (average HR DBP+OLE 0.54, 95% CI 0.35–0.83; p = 0.004). The reduced risk of requiring a walking aid in earlier initiators of ocrelizumab demonstrates the long-term implications of earlier highly effective treatment.

Kappos et al. (93) analyzed disease activity based on repeated, 48-week CDP on EDSS, relapses, and new MRI activity in patients with RRMS in OPERA I and II over eight years (including their ongoing OLEs). Overall, the analyses confirm the benefit of earlier and sustained treatment with ocrelizumab in patients with RMS. Over eight years, the rate of repeated disability progression across measures of overall and upper- and lower-limb disability was lower among patients who initiated ocrelizumab earlier vs. those with delayed treatment. Patients who switched from comparator to ocrelizumab subsequently experienced rates of repeated events similar to those continuously treated with ocrelizumab across measures of overall and upper- and lower-limb disability.

Evidence of efficacy with early treatment in RMS

In the Phase 3b ENSEMBLE study (N=1,225), most treatment-naïve patients with early-stage RRMS treated with ocrelizumab over two years showed minimal disease activity based on clinical and MRI measures (86.5% [n=959] had no evidence of clinical activity and 88.9% [n=986] had no evidence of MRI activity). The EDSS score remained stable or showed improvements in most patients (87.4% [n=994]), and safety results were consistent with prior ocrelizumab experience, with no new safety signals (68).

In an analysis of seven-year OLE data from the OPERA I and OPERA II studies, 81% of treatment-naive patients with early MS had no disability progression over seven years on treatment with ocrelizumab. Over seven years, AE rates in the ocrelizumab early RMS population remained consistent with those in the double-blind period and with the known ocrelizumab safety profile (see Section 10.3). These findings support first-line use of ocrelizumab in newly diagnosed patients with early RMS (94).

Overall conclusion for RMS

On the basis of the clinical trial data from the controlled treatment and OLE periods of the OPERA I and II studies, the benefit profile of ocrelizumab for the treatment of RMS continues to favor treatment with ocrelizumab.

9.1.2.2 Primary progressive multiple sclerosis

In the randomized, double-blind, parallel-group, multicenter, placebo-controlled pivotal phase 3 clinical trial in PPMS, ORATORIO (WA25046), ocrelizumab was associated with lower rates of clinical and MRI progression than placebo (6). The percentage of patients with 12-week CDP was 32.9% with ocrelizumab versus 39.3% with placebo (HR, 0.76; 95% CI, 0.59 to 0.98; P = 0.03). The percentage of patients with 24-week CDP was 29.6% with ocrelizumab versus 35.7% with placebo (HR, 0.75; 95% CI, 0.58 to 0.98; P = 0.04). By Week 120, performance on the Timed 25-Foot Walk worsened by 38.9% with ocrelizumab versus 55.1% with placebo (P = 0.04); the total volume of brain lesions on T2-weighted MRI decreased by 3.4% with ocrelizumab and increased by 7.4% with placebo (P<0.001); and the percentage of brain volume loss was 0.90% with ocrelizumab versus 1.09% with placebo (P = 0.02).

The efficacy of ocrelizumab, as treatment of patients with PPMS, was demonstrated in a phase 3, randomized, double-blind, parallel-group, multicenter, placebo-controlled clinical trial (Study WA25046/ACT4619g [ORATORIO]). The primary efficacy endpoint was the proportion of patients with 12-week CDP. Key secondary efficacy endpoints included 24-week CDP, T25-FW, T2 lesion volume, and total brain volume loss. The study was conducted globally, with centers primarily in North America, Europe, and Latin America (6).

Patients in Study WA25046/ACT4619g (ORATORIO) were randomized in a 2:1 ratio to the following treatment arms:

- Arm 1 (Investigational, n=488): Ocrelizumab 600 mg regimen (given as dual infusions of 300 mg of ocrelizumab, 14 days apart for the double-blind treatment duration)
- Arm 2 (Placebo, n=244): Placebo of ocrelizumab (same schedule as Arm 1)

Following the primary analysis, patients who, in the opinion of the investigator, could benefit from further treatment could receive open-label ocrelizumab until discontinuation of the program. For patients in the placebo arm, the investigator could elect to commence treatment with ocrelizumab at the next scheduled visit following communication from the Sponsor on the start of the OLE after the primary analysis. The first treatment cycle of the OLE phase consisted of two 300 mg IV infusions of ocrelizumab, separated by 14 days. Subsequent cycles of the OLE phase consisted of single 600 mg IV infusions of ocrelizumab at a scheduled interval of every 24 weeks.

Patient demographics (age and sex) and baseline disease characteristics (time since onset of MS symptoms, time since diagnosis of PPMS, previous DMT use, EDSS score, number of Gd-enhancing T1 MRI lesions, number and volume of T2 MRI lesions, and normalized brain volume) were well balanced between the two treatment arms.

Overall, Study WA25046/ACT4619g (ORATORIO) provided robust evidence that ocrelizumab demonstrated consistent efficacy on clinical measures of disease progression (12-week CDP, 24-week CDP, and T25-FW) and on subclinical measures of disease progression (T2 hyperintense lesion volume and whole brain volume) against a placebo comparator, and treatment effects achieved were clinically relevant (see Table 3).

Table 3: Study WA25046/ACT4619g (ORATORIO): Key Efficacy Results

Endpoints	Study 3	
	WA25046 (Oratorio)	
	Ocrelizumab 600 mg (n=488)	Placebo (n=244)
Clinical Endpoints		
Primary efficacy endpoint	30.2%	34.0%
Proportion of patients with 12 weeks - Confirmed Disability Progression[a] (primary endpoint) Risk reduction	24% (p=0.0321)	
Proportion of patients with 24 weeks - Confirmed Disability Progression[a]	28.3%	32.7%
Risk reduction	25% (p=0.0365)	
Percentage change in Timed 25-Foot Walk from baseline to Week 120	38.9	55.1
Relative reduction in progression rate of walking time	29.4% (p=0.0404)	
MRI Endpoints		
Percentage change in T2 hyperintense lesion volume, from baseline to Week 120	-3.4	7.4
	(p< 0.0001)	
Percentage change in brain volume from Week 24 to Week 120	-0.902	-1.093
Relative reduction in rate of brain volume loss	17.5% (p=0.0206)	
Quality of Life		
Mean change from baseline in SF-36 Physical Component Summary	-0.731	-1.108
Difference	0.377 (p=0.6034)	

[a] Defined as an increase of ≥ 1.0 point from the baseline EDSS score for patients with baseline score of 5.5 or less, or ≥ 0.5 when the baseline score is > 5.5, Kaplan-Meier estimates at Week 120.

Overall, the study provided robust evidence that ocrelizumab demonstrated consistent efficacy on clinical measures of disease progression (12-week CDP, 24-week CDP, and T25FW) and on subclinical measures of disease progression (T2 hyperintense lesion volume and whole brain volume) against a placebo comparator. The result of the primary endpoint was confirmed by the secondary endpoints (except for Short Form-36 Physical Component Summary [SF-36 PCS]) and the treatment effects achieved were clinically relevant.

Clinical outcomes

The study met its primary endpoint. Treatment with ocrelizumab reduced the risk of 12-week CDP by 24% in the ocrelizumab group compared with placebo (HR: 0.76 [95% CI: 0.59, 0.98], p=0.0321). Sensitivity analyses confirmed the robustness of the primary outcome.

The benefit of treatment with ocrelizumab was further shown in a 25% reduction in the risk of 24-week CDP in the ocrelizumab group compared with placebo (HR 0.75 [95% CI: 0.58, 0.98], p=0.0365), demonstrating consistency of effect with the 12-week CDP endpoint and further confirming the impact of ocrelizumab in delaying disease progression. Furthermore, ocrelizumab treatment resulted in a 29% relative reduction in the percent progression in Timed 25-Foot Walk (T25FW) over 120 weeks (p=0.0404), a component of the MSFC. T25FW is a clinically meaningful measure of disease activity, especially since lower extremity motor dysfunction is a key hallmark of PPMS (95). This result was further supported by exploratory analysis of proportion of patients with a 20% increase in the T25FW confirmed for at least 12 weeks (HR 0.75 [95% CI 0.61, 0.92]; p=0.0053) and 24 weeks (HR 0.73 [95% CI 0.59, 0.91]; p=0.0055).

Exploratory analyses of time to confirmed CDP were measured by the 12-week composite endpoint (CDP by EDSS or a 20% increase in T25FW or 20% increase in 9-Hole Peg Test, all confirmed for 12 weeks), which has been more recently used as a clinically meaningful and more sensitive measure of disability progression (96,97). This analysis showed a 26% relative reduction in patients treated with ocrelizumab versus placebo (HR 0.74 [95% CI: 0.61, 0.89], p=0.0014). Results were similar for the 24-week CDP composite endpoint, with a 29% relative reduction (HR 0.71 [95% CI: 0.58, 0.87], p=0.0008). The relative contribution of the three components of the composite endpoint was analyzed and the effect seen in the composite was found to be maintained in an analysis with the EDSS component removed and in further analyses with all components analyzed alone. This effect was consistent for both the 12-week and 24-week composite endpoint.

Magnetic resonance imaging outcomes

Efficacy was shown in key secondary endpoints on brain MRI. Ocrelizumab decreased the percentage change in total volume of T2 hyperintense lesions from baseline to Week 120 (decrease of 3.4%) compared with an increase for patients on placebo (increase of 7.4%; p<0.0001). Treatment with ocrelizumab also reduced the relative rate of brain volume loss by 17.5% (p=0.0206) measured from Week 24 to Week 120, when compared with placebo.

Exploratory MRI endpoints examined the rate of whole brain volume loss, cortical gray matter volume loss, and white matter compartment volume loss from baseline to Week 120. Treatment with ocrelizumab was associated with a numerical reduction in the relative rate of whole brain volume loss compared with placebo from baseline to Week 120 by 11.4% (p=0.0883). Cortical gray matter volume and white matter compartment volume are highly exploratory brain volumetric measures without definite clinical correlates. Treatment with ocrelizumab reduced the relative rate of cortical gray matter volume loss compared with placebo by 20.6% (p=0.0170). The reduction in the cortical gray matter volume loss is conceptually relevant

for PPMS, where it is known that pathology occurs to a greater extent in the gray matter (30). Treatment with ocrelizumab was associated with a numerically greater loss of volume in the white matter compartment compared with placebo by 73.6% (p=0.0974). The observed difference between ocrelizumab and placebo on the white matter compartment might possibly be explained by the potent anti-inflammatory effect of ocrelizumab and the known diffuse inflammatory white matter injury that occurs in PPMS (30). Similar results for gray and white matter volume were confirmed following analysis from Week 24 to Week 120.

Patient-reported outcomes

In the secondary endpoint analyzing the change in quality of life as measured by SF-36 PCS, patients in the ocrelizumab group experienced less worsening (-0.73 points) from baseline to Week 120 compared with placebo (-1.11 points; p=0.6034), although not statistically significant. However, ocrelizumab did show significant improvement in the exploratory endpoint of change in Short Form-36 Mental Component Summary (SF-36 MCS) score from baseline to Week 120, with an increase of 1.65 points on ocrelizumab compared with a decrease of -1.67 on placebo (p=0.0007). This is a relative improvement of 3.32 points with ocrelizumab. A clinically meaningful difference is considered to be ≥3 points (98).

Ocrelizumab also showed significantly greater improvement in the exploratory endpoint of fatigue compared with placebo as measured by the Modified Fatigue Impact Scale (MFIS). Patients treated with ocrelizumab showed an improvement in the mean MFIS score from baseline to Week 120 of 0.462 points, whereas there was a worsening of 2.994 points with placebo (p=0.0091). A reduction in MFIS score was also observed consistently in all of the subscale components (physical, cognitive, and psychosocial). Fatigue is a significant and clinically meaningful aspect of MS symptomology (99).

Evidence of efficacy from the OLE phase of ORATORIO

Wolinsky et al. (100) assessed the efficacy of switching to or maintaining ocrelizumab therapy on 48-week CDP (48W CDP), in the ORATORIO OLE over eight years (408 weeks). Overall, 72% of patients entered the OLE phase. Rates of 48W CDP-EDSS were lower in the ocrelizumab - ocrelizumab vs. placebo - ocrelizumab group at Week 168 (W168 [12 weeks after the first patients entered the OLE]; 30.5% vs. 44.4%; p<0.001) and Week 408 (55.9% vs. 67.5%; p=0.005). Rates of 48W CDP-9HPT (9-Hole Peg Test) were lower in the ocrelizumab - ocrelizumab vs. placebo - ocrelizumab group at W168 (15.8% vs. 27.9%; p<0.001) and W408 (34.1% vs. 45.9%; p=0.009). Rates of 48W EDSS≥7 were numerically lower in the ocrelizumab - ocrelizumab vs. placebo - ocrelizumab group at W168 (4.8% vs. 9.1%; p=0.054) and W408 (14.9% vs. 21.0%; p=0.096). Mean cumulative number of recurrent 48W CDP-EDSS was lower in the ocrelizumab - ocrelizumab vs. placebo - ocrelizumab group at W168 (0.40 vs. 0.60; p=0.002) and W408 (0.94 vs. 1.21; p=0.013). After eight years, continuous ocrelizumab treatment reduced the risk of the first 48W CDP-EDSS by 29% (HR [95% CI]: 0.71 [0.57-0.87]; p=0.001), the first 48W CDP-9HPT by 34% (HR [95% CI]: 0.66 [0.50-0.86]; p=0.002), the first 48W EDSS≥7 by 33% (HR [95% CI]: 0.67 [0.45-1.01]; p=0.057), and the rate of recurrent 48W CDPEDSS by 24% (RR [95% CI]: 0.76 [0.62-0.92]; p=0.005), vs. placebo - ocrelizumab. After eight years, 48W CDP outcomes still favored earlier, continuous ocrelizumab treatment. Patients with PPMS initiating ocrelizumab three to five years earlier had a significantly reduced risk of the first CDP-EDSS and rate of recurrent CDP-EDSS vs. those switching from placebo.

Kappos et al. (93) analyzed repeated 48-week CDP events for the 9HPT, T25FW, and composite CDP in patients with PPMS ORATORIO over eight years (including the ongoing OLE). Overall, the analyses confirm the benefit of earlier and sustained treatment with ocrelizumab in patients with PPMS. Over eight years, the

rate of repeated disability progression across measures of overall and upper- and lower-limb disability was lower among patients who initiated ocrelizumab earlier vs. those with delayed treatment. Patients who switched from comparator to ocrelizumab subsequently experienced rates of repeated events similar to those continuously treated with ocrelizumab across measures of overall and upper- and lower-limb disability.

Evidence of efficacy with early treatment of PPMS patients in ORATORIO

A post-hoc analysis of PPMS patients in the ORATORIO study provided evidence of ocrelizumab's superior efficacy versus placebo on clinical measures of disease progression to EDSS ≥ 7.0 (24W-CDP, 48W-CDP) during the extended controlled period (ECP) in a PPMS population. In addition, the data from the combined ECP+OLE period highlights the benefit of early vs. delayed treatment of ocrelizumab on clinical measures of disease progression to EDSS ≥ 7.0 (24W-CDP, 48W-CDP). Extrapolation analyses on potential long-term impact of ocrelizumab treatment through Weibull regression analysis using this data predict a delay in the progression to these milestones by several years. Overall, early treatment with ocrelizumab has shown superior efficacy versus delayed treatment with ocrelizumab during long-term assessment in ECP+OLE phase (11).

Overall conclusion for PPMS

On the basis of the clinical trial data from the controlled treatment and OLE periods of ORATORIO, the benefit profile of ocrelizumab for the treatment of PPMS continues to favor treatment with ocrelizumab.

Evidence of efficacy after treatment switch from other DMTs

Vermersch et al. (101) assessed the efficacy of ocrelizumab in patients with RRMS with a prior suboptimal response, defined by MRI or relapse criteria, to one or two DMTs. A total of 680 patients were enrolled, 167 (24.6%) based on MRI activity only. At Week 96, 74.8% (95% CI, 71.3-78.0; n/N=492/658) of patients had NEDA. NEDA was highest among patients enrolled due to MRI activity alone (80.6% [68.6-89.6] n/N=50/62) versus for relapse (75.1% [69.0-80.6] n/N=172/229) or relapse with MRI (70.5% [60.0-79.0] n/N=74/105). NEDA across subgroups was highest in patients with baseline EDSS score < 2.5 (77.2% [72.8-81.2] n/N=315/408). NEDA was higher in patients receiving one prior DMT (77.6% [73.2-81.6] n/N=312/402) versus two (70.3% [64.3-75.8] n/N=180/256). In patients switching therapy due to suboptimal disease control, treatment with ocrelizumab led to an overall high NEDA rate across a wide range of disease-related and demographic subgroups, regardless of prior treatment background, with no new safety signals detected.

Weinstock-Guttman et al. (102) reported the two-year findings from the Phase 3b CHORDS study (NCT02637856) investigating ocrelizumab in patients with RRMS who had a suboptimal response with previous DMT. The primary endpoint was the proportion of patients free of any protocol-defined event (i.e., relapse, T1 Gd-enhancing lesion, new/enlarging T2 lesion, 24-week CDP on the EDSS). The ITT population included 608 patients with a mean (SD) time since diagnosis of 4.2 (3.03) years. The most frequently used DMTs prior to enrollment included glatiramer acetate (49.3%), dimethyl fumarate (35.4%), and fingolimod (20.1%). In the modified ITT population (576 [94.7%]), 48.1% of patients were free of all protocol-defined events, and most experienced freedom from individual events (relapse, 89.6%; T1 Gd-enhancing lesions, 95.5%; new/enlarging T2 lesions, 59.5%; 24-week CDP, 89.6%) over 96 weeks. This analysis demonstrated the potential benefits of ocrelizumab treatment over two years in patients with RRMS who are relatively early in the disease course and have experienced suboptimal response on prior DMTs.

Evidence of societal impact of ocrelizumab treatment

In an analysis of cognitive function of ocrelizumab-treated RRMS patients in the Phase3b CASTING study, there was a significant improvement in Symbol Digit Modalities Test (SDMT) score over 96 weeks in patients with RRMS treated with ocrelizumab, mainly observed in the lower-cognitive-functioning subgroup (103).

In a separate analysis from the same study, unemployment was found to be higher in RRMS patients who were younger and female and was associated with higher baseline EDSS score and lower cognitive functioning. Over the two years of the CASTING study, patients treated with ocrelizumab showed a greater shift towards employment (32.2%) than towards unemployment (12.9%). By comparison, prospective data gathered over the same or similar periods in persons with MS, largely treated with DMTs, indicated employment status deteriorated between 12.5% to 22.0% (104).

9.1.2.3 Progressive multiple sclerosis

The ongoing CONSONANCE trial (NCT03523858), a single arm phase 3b trial, was designed to evaluate the effectiveness and safety of ocrelizumab across the spectrum of progressive MS (i.e., in patients with either PPMS or SPMS). Comprehensive phenotyping of patients is carried out using clinical assessments, including disability outcomes such as EDSS, T25FW, 9HPT, and low contrast visual acuity (LCVA), relapses, and cognition outcomes (SDMT and Brief Visuospatial Memory Test - Revised [BVMT-R]). A comprehensive battery of disease and symptom-specific PROs is also used, along with biomarkers including conventional and advanced MRI measures, fluid biomarkers (e.g., neurofilament light chain [NfL]), and electrophysiological measures (optical coherence tomography [OCT] and motor evoked potentials), as well as novel digital measures (the FLOODLIGHT™ smartphone test battery). Primary outcomes are (1) proportion of patients with no evidence of progression (NEP), defined as no progression confirmed for ≥ 24 weeks on EDSS, no ≥ 20% increase in T25FW, no ≥ 20% increase in 9HPT time, and no MS-related death or treatment discontinuation due to efficacy failure; (2) proportion of patients with no evidence of progression and no active disease (NEPAD), defined as NEP plus no protocol-defined relapse, no new/enlarging T2 lesions, and no T1 gadolinium-enhanced lesions. In the two-year interim analysis, treatment with ocrelizumab was associated with comparable rates of NEP and NEPAD in patients with SPMS and PPMS and with functional improvement in around one third of patients. Safety outcomes were consistent with known safety profile (69). Future updates from this study will continue to be reported.

9.2 Systematic literature search

This section lists articles identified in systematic literature searches periodically conducted by the applicant. Appendix B contains a description of the search methodology used, followed by a summary of the main findings from these reviews from 2018 to January 2022.

In the Table 4 below, each entry is linked to a summary of the publication in Appendix B.

Table 4: List of Articles Providing Evidence of Benefit with Ocrelizumab Treatment, Identified in Literature Searches from 2018 to January 2022

No.	Author, year	Publication title
1.	Fox et al. (105), 2018	Ocrelizumab reduces progression of upper extremity impairment in patients with primary progressive multiple sclerosis: Findings from the phase 3 randomized ORATORIO trial
2.	Wolinsky et al. (106), 2018	Evaluation of no evidence of progression or active disease (NEPAD) in patients with primary progressive multiple sclerosis in the ORATORIO trial
3.	Barkhof et al. (107), 2019	Onset of clinical and MRI efficacy of ocrelizumab in relapsing multiple sclerosis
4.	Elliott et al. (108), 2019	Chronic white matter lesion activity predicts clinical progression in primary progressive multiple sclerosis
5.	Turner et al. (109), 2019	Ocrelizumab efficacy in subgroups of patients with relapsing multiple sclerosis
6.	Leist et al. (110), 2019	One-year interim analysis results of the phase 3b CHORDS study evaluating ocrelizumab effectiveness and safety in patients with relapsing-remitting multiple sclerosis who had suboptimal response with prior disease-modifying treatments
7.	Vermersch et al. (111), 2020	Efficacy/safety of ocrelizumab in relapsing-remitting MS patients with suboptimal response to prior disease-modifying therapies (1-year interim results)
8.	Wolinsky et al. (10), 2020	Long-term follow-up from the ORATORIO trial of ocrelizumab for primary progressive multiple sclerosis: a post-hoc analysis from the ongoing open-label extension of the randomised, placebo-controlled, phase 3 trial
9.	Arnold et al. (112), 2020	Reduced thalamic atrophy in patients initiating earlier versus delayed ocrelizumab therapy: results from the OLE of OPERA I/II and ORATORIO
10.	Bar-Or et al. (113), 2020	Blood neurofilament light chain levels and association with brain volume change in patients with PPMS and RMS before and under treatment with ocrelizumab
11.	Bar-Or et al. (114), 2020	Ocrelizumab reduces thalamic volume loss and clinical progression in PPMS and RMS independent of baseline NfL and other measures of disease severity
12.	Jia et al. (115), 2020	Blood Neurofilament Light Chain Levels and Association with Brain Volume Change in Patients with Primary Progressive Multiple Sclerosis and Relapsing Multiple Sclerosis Before and During Ocrelizumab Treatment
13.	Wiendl et al. (116), 2020	Ocrelizumab phase 3b efficacy from CASTING: 2-year NEDA (MRI re-baselined) subgroup rates in RRMS patients with a suboptimal response to prior DMTs
14.	Arnold et al. (117), 2021	Effect of ocrelizumab on cerebellar atrophy in RMS and PPMS: Results from OPERA I/OPERA II and ORATORIO
15.	Bhattacharyya et al. (118), 2021	Recurrent MRI activity after treatment with ocrelizumab for multiple sclerosis
16.	Bigaut et al. (119), 2022	Ocrelizumab versus fingolimod after natalizumab cessation in multiple sclerosis: an observational study
17.	Braune et al. (15), 2021	Real world experience with ocrelizumab in patients with primary progressive multiple sclerosis: Insights from the German Neuro Trans Data Registry

No.	Author, year	Publication title
18.	Buttmann et al. (120), 2021	The effectiveness of ocrelizumab in real-world patients with relapsing multiple sclerosis over 18 months-interim analysis of the CONFIDENCE study
19.	Butzkueven et al. (11), 2021	Risk of requiring a wheelchair in primary progressive multiple sclerosis: Data from the ORATORIO trial and the MSBase registry
20.	Butzkueven et al. (16), 2021	Real-world experience with ocrelizumab in relapsing multiple sclerosis: Insights from the MSOCR-R cohort, an MS Base registry sub-study
21.	Cellerino et al. (121), 2021	Predictors of Ocrelizumab Effectiveness in Patients with Multiple Sclerosis
22.	Cellerino et al. (17), 2021	Ocrelizumab treatment in patients with relapsing-remitting and progressive MS: A real-world experience
23.	Cellerino et al. (18), 2021	Ocrelizumab treatment in patients with progressive multiple sclerosis: A single-center real-world experience
24.	Coban et al. (71), 2021	Real-world experience of ocrelizumab initiation in a diverse multiple sclerosis population
25.	Epstein et al. (122), 2021	Evaluation of ocrelizumab in older progressive multiple sclerosis patients
26.	Glanz et al. (123), 2021	The impact of ocrelizumab on health-related quality of life in individuals with multiple sclerosis
27.	Hersh et al. (124), 2021	Comparison of time to clinically meaningful improvement in Neuro-QoL in patients treated with natalizumab versus ocrelizumab
28.	Jungquist et al. (125), 2021	Is there 'wearing off' with Ocrelizumab? Preliminary results of symptom burden on ocrelizumab, a longitudinal study (SymBOLS)
29.	Lanzillo et al. (126), 2021	Ocrelizumab treatment in multiple sclerosis: Prospective real world observational multi-center study in Campania, Italy
30.	Lanzillo et al. (19), 2021	Ocrelizumab treatment in multiple sclerosis: A real world observational multi-center study to confirm efficacy on disability accrual and explore prognostic factors of response to treatment
31.	Laplaud et al. (127), 2021	Assessing efficacy and safety of ocrelizumab in active relapsing multiple sclerosis: PRO-MSACTIVE study interim analysis
32.	Lapucci et al. (128), 2021	Short-term evaluation of alemtuzumab to ocrelizumab switch in MS patients with disease activity after alemtuzumab: An Italian multicentric study
33.	Manchon et al. (129), 2021	Ocrelizumab impact on patient-reported outcomes in active relapsing multiple sclerosis: PRO-MSACTIVE interim analysis
34.	Nicholas et al. (130), 2021	Claims-based relapse and hospitalization rates in patients with multiple sclerosis treated with natalizumab or ocrelizumab
35.	Ozakbas et al. (131), 2021	Comparison of early treatment response of ocrelizumab in relapsing and progressive multiple sclerosis patients on the basis of cognitive functions
36.	Ozakbas et al. (132), 2021	Early treatment response of ocrelizumab in persons with multiple sclerosis: Six-month results
37.	Pereira et al. (133), 2021	Ocrelizumab-time to expand borders?
38.	Pontieri et al. (134), 2022	Ocrelizumab treatment in multiple sclerosis: A Danish population-based cohort study
39.	Rojas et al. (20), 2021	Real-world experience of ocrelizumab in multiple sclerosis patients in Latin America
40.	Roos et al. (135), 2021	Comparison of the effectiveness of ocrelizumab vs. interferons, fingolimod and natalizumab on relapses in relapsing-remitting multiple sclerosis
41.	Signoriello et al. (136), 2022	Switch from sequestering to anti-CD20 depleting treatment: disease activity outcomes during wash-out and in the first 6 months of ocrelizumab therapy
42.	Smoot et al. (137), 2021	Clinical outcomes of patients with multiple sclerosis treated with ocrelizumab in a US community MS center: An observational study
43.	Smoot et al. (138), 2021	Utilization, safety, and tolerability of ocrelizumab: Year 4 data from the Providence Ocrelizumab Registry
44.	Toorop et al. (139), 2021	The wearing-off phenomenon of ocrelizumab in patients with multiple sclerosis
45.	Treffts et al. (140), 2021	Short term relapse risk after switching from natalizumab to ocrelizumab or cladribine-An international cohort study

No.	Author, year	Publication title
46.	Van Lierop et al. (141), 2021	Ocrelizumab after natalizumab in JC-virus positive relapsing remitting multiple sclerosis patients
47.	Van Wijmeersch et al. (142), 2021	Efficacy and safety of ocrelizumab in patients with RRMS with suboptimal response to prior disease-modifying therapies: 3-year data from CASTING and LIBERTO 1-year interim results
48.	Vollmer et al. (143), 2021	Two-year real-world experience with ocrelizumab in the treatment of patients with multiple sclerosis
49.	Weinstock-Guttman et al. (144), 2022	Ocrelizumab treatment for relapsing-remitting multiple sclerosis after a suboptimal response to previous disease-modifying therapy: A nonrandomized controlled trial
50.	Yousuf et al. (21), 2021	Real-world experience with ocrelizumab in multiple sclerosis patients: Two years follow up in Qatar
51.	Zhong et al. (145), 2021	Prediction of multiple sclerosis outcomes when switching to ocrelizumab
52.	Bigaut et al. (146), 2021	How to switch disease-modifying treatments in multiple sclerosis: Guidelines from the French Multiple Sclerosis Society (SFSEP)
53.	Samjoo et al. (147), 2021	Efficacy classification of modern therapies in multiple sclerosis
54.	Mohammad et al. (148), 2021	The comparative efficacy and safety of anti-CD20 monoclonal antibodies for relapsing. -remitting multiple sclerosis: A network meta-analysis
55.	Liu et al. (149), 2021	Disease modifying therapies in relapsing-remitting multiple sclerosis: A systematic review and network meta-analysis
56.	Zanghì et al. (150), 2021	Exit strategies in natalizumab-treated RRMS at high risk of progressive multifocal leukoencephalopathy: a multicentre comparison study
57.	Bigaut et al. (119), 2022	Ocrelizumab versus fingolimod after natalizumab cessation in multiple sclerosis: an observational study
58.	Guerra et al. (22), 2021	Effectiveness and safety of ocrelizumab in a real-world setting: A single center experience from southern Italy
59.	Trojano et al. (151), 2022	The real-world effectiveness of ocrelizumab for treating patients with MS: 1-year Data from the MuSicalE study

9.3 Assessment of applicability of the available evidence across diverse populations and settings

This section summarizes available evidence for the benefit of ocrelizumab treatment in population subgroups in RMS (Section 9.3.1), PPMS (Section 9.3.2), and across MS subtypes (Section 9.3.3). Finally, ongoing studies to evaluate benefit in other subgroups are described (Section 9.3.4).

9.3.1 Subgroups in RMS

The effect of ocrelizumab vs. IFNβ1a on ARR in subgroups of the pooled OPERA studies has been assessed in different studies.

In Turner et al. (152), between-group hazard ratios (HRs) and p-values were based on Cox proportional hazards models with study, region, and baseline EDSS score (<4.0 vs. ≥4.0) as factors. If the subgroup was one of the key covariates, that covariate was not included in the model.

Patient characteristics were comparable between treatments and within subgroup strata. The risk reduction (RR; ocrelizumab vs. IFNβ1a) for 12-and 24-week CDP in the overall pooled population was 40% (p<0.001 and p=0.003, respectively) and was maintained across most subgroups and strata. No significant treatment-by-subgroup interactions were observed for either endpoint. The reduction rate results for 12-week CDP by subgroup are shown in Table 5. Similar results were observed for 24-week CDP.

Table 5: OPERA I and II: Subgroup Analyses of Risk Reduction in 12-Week CDP

Subgroup	RR in 12-week CDP OCR vs. IFNβ1a	p-value
Age		
<40 years	41%	0.019
≥40 years	39%	0.018
Sex		
Male	44%	0.019
Female	36%	0.019
Prior DMT use in the last 2 years		
Yes	39%	0.080
No	40%	0.004
Baseline EDSS score		
<2.5:	18%	0.4
≥2.5	52%	<0.001
<4.0	34%	0.014
≥4.0	61%	0.010
Prior relapses in the last 12 months		
≤1	42%	0.002
≥2	33%	0.2
T1 Gd+ lesions at baseline		
None	40%	0.010
≥1	40%	0.029

CDP=confirmed disability progression; DMT=disease-modifying therapy; EDSS=Expanded Disability Status Scale; Gd+=gadolinium-enhancing; IFNβ1a= interferon beta-1a; OCR=ocrelizumab; RR=risk reduction.

These subgroup analyses were consistent with the overall pooled population on ocrelizumab reducing the risk of CDP vs. IFNβ1a.

Turner et al. (109) demonstrated the treatment effects of ocrelizumab, versus IFNβ1a, for the treatment of RMS, across subgroups of patients with different baseline characteristics; the efficacy of ocrelizumab in patient subgroups relating to disability and clinical and MRI disease activity; and the efficacy of ocrelizumab in both treatment-naïve patients and those previously treated with DMT. The study showed the substantial reductions in both the average number of Gd-enhancing T1 lesions (94% [$p < 0.001$]) and the average number of new or newly enlarged hyperintense T2 lesions per scan (80% [$p < 0.001$]), of ocrelizumab relative to IFNβ1a, observed in the overall pooled analysis of the ITT population were maintained across all subgroup-levels ($p < 0.001$ for both endpoints and all comparisons). The significant reductions in disease progression with 12-week confirmation (40% [$p < 0.001$]) and 24-week confirmation (40% [p=0.003]), relative to IFNβ1a and observed in the overall pooled analysis of the ITT population, were maintained across most subgroup-levels. The significant reduction in ARR observed in the overall pooled analysis of the ITT population with ocrelizumab, relative to IFNβ1a (47% [p<0.001]), was maintained across the majority of subgroup-levels, including study, region, age, sex, baseline BMI, prior DMT use and prior relapse, baseline EDSS, normalized brain volume, and Gd-enhancing T1 lesions; a numerical trend favoring ocrelizumab was observed for the specific subgroup strata of patients aged ≥ 40 years.

Cree et al. (70) performed a post-hoc subgroup analysis of participants of African descent with relapsing forms of MS who were enrolled in the Phase 3 OPERA I or OPERA II clinical trials to evaluate the efficacy and safety of ocrelizumab vs. IFNβ1a. A trend for reduction in ARR was observed in participants of African descent, with an ≈50% reduction with ocrelizumab vs. IFNβ1a. The relative rate of the mean number of Gd-enhancing lesions on MRI was 0.04 (95% CI, 0.01–0.22; p=0.001) in participants of African descent treated with ocrelizumab compared with IFNβ1a. Similarly, the relative rate of the number of new or enlarging T2 lesions on MRI was 0.14 (95% CI, 0.06–0.32; p<0.001). In participants of African descent, those treated with ocrelizumab were 2.61 times more likely than those who received IFNβ1a to be classified as having NEDA (95% CI, 1.24–5.49; p=0.003) and 4.17 times more likely to be classified as having NEDA or progression (95% CI, 1.27–13.65; p=0.006). African-descent participants tended to have a greater radiographic burden of disease at baseline, develop more brain lesions when treated with IFNβ1a, and be at greater risk of disability progression than non-African-descent participants. Participants of African descent experienced slightly more AEs, SAEs, and hypersensitivity reactions than non-African-descent participants. The author concluded that in this small sample of participants of African descent with relapsing MS from the OPERA studies, ocrelizumab demonstrated treatment benefits in clinical, MRI, and composite efficacy outcomes vs. IFNβ1a, consistent with what was observed in the complete OPERA intention-to-treat cohorts.

In addition, the ongoing open-label, single-arm, phase 4 CHIMES trial (NCT04377555) is the first MS trial designed to investigate the efficacy and safety of ocrelizumab in Black and Hispanic patients with RMS. Preliminary data indicates some differences in demographics and baseline disease characteristics between Black and/or Hispanic and White patients. Findings from this trial may improve the current understanding of MS disease biology, treatment response, and clinical trial participation (153).

Finally, findings from an analysis of seven-year OLE data for treatment-naive patients with early MS from the OPERA I and OPERA II studies (described in Section 9.1.2.1) supports first-line use of ocrelizumab in newly diagnosed patients with early RMS (94).

9.3.2 Subgroups in PPMS

The treatment effect of ocrelizumab was explored in subgroups in the ORATORIO study, including age, sex, region, body mass index (BMI), body weight, baseline EDSS, presence of T1 Gd-enhancing lesions, prior MS DMT, and duration of MS symptom onset, for the primary endpoint, all secondary endpoints and the following exploratory endpoints: CDP 12-week and 24-week composite endpoint, cortical gray matter volume, WMV, MFIS, and SF-36 MCS.

Considering the primary endpoint of 12-week CDP and all secondary endpoints, except for SF36 PCS, there was a directionally consistent treatment effect favoring ocrelizumab in all subgroups (HR or ratio of adjusted geometric means <1). Numerical differences in treatment effect were observed for the primary endpoint within some subgroups including sex, baseline T1 Gd-enhancing lesions, and age. Univariate and multivariate analysis of the primary endpoint showed a trend towards a greater risk reduction for 12-week CDP in the ocrelizumab group versus placebo in males compared with females, in patients with T1 Gd-enhancing lesions at baseline compared to patients without T1 Gd-enhancing lesions, and in patients ≤45 years of age compared to patients >45 years of age. Based on these results and similar findings for the univariate and multivariate analysis of the secondary endpoint 24-week CDP, secondary and exploratory endpoints were further analyzed to explore the influence of sex, T1 Gd-enhancing lesions and age on these endpoints. Treatment effects within subgroups were consistent, with no pattern across endpoints for a single subgroup.

Overall, these data support the benefit of ocrelizumab in the overall study population, as well as in all investigated subgroups. Numerical differences were observed for some subgroups on some of the endpoints (e.g., 12-week and 24-week CDP); however, it should be recognized that the study was not powered to demonstrate efficacy differences between subgroups.

9.3.3 Subgroups across MS types

Coban et al. (71) performed a retrospective observational analysis of MS (RRMS and PPMS) patients who were treated with ocrelizumab from 31 March 2017 to 30 April 2020. Ocrelizumab was found to be effective among all racial/ethnic groups (18 [22%] African American, 50 [61%] Caucasian, and 14 [17%] Hispanic patients) in this cohort.

9.3.4 Other patient subgroups

As described in Section 7.2, studies are underway to assess the use of ocrelizumab in pregnant and lactating women (studies MINORE and SOPRANINO) and in pediatric MS patients (studies OPERETTA 1 and 2). Details of these studies are available in Appendix A.

10. Review of harms and toxicity: summary of evidence of comparative safety

This section summarizes topics relevant to the safety of ocrelizumab, including information on total patient exposure (10.1); information from systematic literature searches (10.2); available clinical evidence on safety of ocrelizumab (10.3); information on adverse events (10.4); discussion of the safety of ocrelizumab versus other relevant comparators (10.5); information on inappropriate use (10.6); information on variations in safety relating to health systems and patient factors (10.7); as well as information on warnings or safety issues identified by regulatory authorities (10.8).

10.1 Total patient exposure

Section 10.1 summarizes total patient exposure, including cumulative exposure on clinical trials (10.1.1) and cumulative patient exposure from marketing experience (10.1.2).

10.1.1 Cumulative exposure in clinical trials

As of 31 March 2022, an estimated 9,417 patients with MS across multiple clinical trials had received ocrelizumab (unblinded and blinded). Approximately 3000 patients had received eight doses or more of ocrelizumab, approximately 2000 had received ten doses or more, and more than 1000 had received 17 doses. Demographic characteristics for the exposed population (unblinded patients only) reflect the regional demographics of sites where the clinical trials have been conducted to date (predominantly North America and Europe); the majority of patients were white and aged between 18 and 65 years, and approximately 64% were female.

10.1.2 Cumulative patient exposure from marketing experience

10.1.2.1 Methodology

The market exposure data presented below for the European Economic Area (EEA) and the rest of the world (RoW) are estimated based on total number of ocrelizumab vials sold. In the US, patient estimates are based on a combination of Symphony Health claims data (for April 2017 – December 2021) and shipment data from distributors. Overall exposure is calculated in patient years (PYs) on ocrelizumab. Calculation of the estimated total patient exposure numbers and total patient years in each region is based on specific assumptions for each region.

10.1.2.2 Cumulative exposure

From the international birth date (IBD, i.e., the date of the first marketing approval worldwide, 28 March 2017) till 31 March 2022, an estimated cumulative total of 250,428 MS patients had received ocrelizumab from marketing experience (Table 6). This is equivalent to an estimated 510,060 patient years of exposure.

Table 6: Cumulative Exposure from Marketing Experience in European Economic Area, Rest of the World, and United States of America

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

F=female; M=male; Unk=unknown; EEA=European Economic Area; PPMS=primary progressive multiple sclerosis; RMS=relapsing forms of multiple sclerosis; RoW=rest of world; US=United States of America.
Note: RMS includes RRMS and all forms of secondary-progressive multiple sclerosis (SPMS).
Rounding errors may be introduced in the total figures.

10.2 Systematic literature search

Section 10.2 provides information from systematic literature searches.

Literature searches are a part of routine pharmacovigilance, with results presented in periodic benefit-risk evaluation reports (PBRERs) and evaluated by health authorities. These results contribute to the overall safety characterization of ocrelizumab.

A recent search of the medical literature from 28 March 2021 to 27 March 2022 was conducted in the MEDLINE®, Biosis®, and Embase® databases, using the following search terms (terms for other anti-CD20 mAbs were included so as not to miss any signals related to class effects):

- *Ocrelizumab* including synonyms (i.e., Ocrevus)
- Terms for drugs in the same class or with the same method of action (i.e., anti-CD20 mAbs): *ofatumumab, ibritumomab tiuxetan, obinutuzumab, tositumomab, ublituximab, veltuzumab, ocaratuzumab, pro131921, lymphomun, rituximab and its biosimilars*
- The search identified the co-occurrence of the above with relevant search terms that encompass the following medical concepts (including synonyms): interaction, efficacy and effectiveness, lack of therapeutic efficacy, overdose, contraindications, drug abuse or misuse, normal and abnormal pregnancies, lactation, usage in children, usage in elderly patient, usage in organ-impaired (hepatic, renal, cardiac) patient, genetic polymorphism(s), long-term treatment, epidemiological studies, clinical studies, meta-analyses, compassionate use, registries, animal and in-vitro studies, medication errors, suspected transmission of infectious agents, patient compliance, counterfeit drugs, falsified drugs, occupational exposure, meeting abstracts, risk-benefit balance, off-label use, quality defect, practice guidelines, and case reports of suspected adverse drug reactions
- Date restrictions were applied to exclude the receipt of large numbers of old revised articles from Medline which have already been received and reviewed by Roche (i.e., records that were created in the database before the year 2016).
- No exclusion criteria were applied.

The search identified two articles providing information on patients > 55 years treated with ocrelizumab and 22 articles providing significant data on COVID-19 and ocrelizumab:

- The small sample sizes of the two studies analyzing the effects of ocrelizumab in MS patients aged > 55 years limit interpretation of results. Safety in patients over 55 years old (including elderly) is currently categorized as missing information for ocrelizumab. This population was not included in ocrelizumab clinical trials.
- Analysis of ocrelizumab use during the COVID-19 pandemic, which includes data on immune response to SARS-CoV-2 vaccines and infections in patients receiving ocrelizumab, did not indicate any new safety signals.

10.3 Summary of available evidence

Section 10.3 summarizes the available clinical evidence on safety of ocrelizumab, with a description of clinical trials (10.3.1), an overview of safety information from clinical trials (10.3.2), and a description of post-marketing data sources (10.3.3).

10.3.1 Description of clinical trials used to characterize the ocrelizumab safety profile

The safety of ocrelizumab in patients with MS has been evaluated in phase 1-3 trials (see the Appendix A for a listing of all ocrelizumab clinical studies in MS indications). As described in Section 9.2.2, the pivotal phase 3 clinical program in MS consisted of OPERA I (WA21092) and OPERA II (WA21093) in adults with RMS (5) and ORATORIO (WA25046) in adults with PPMS (6).

In addition, one phase 2 study in relapsing-remitting multiple sclerosis (RRMS), WA21493/ACT4422g (154), also provided safety data.

At the time of preparation of this submission, the double-blinded control periods for all four studies described above (WA21092, WA21093, WA25046, and WA21493) were complete, and patients were continuing in the open-label extension (OLE) phase to assess long-term benefit-risk.

Other phase 3b studies that provide supporting safety evidence are:

- VELOCE (BN29739; n=102), evaluating the effects of ocrelizumab on the immune response of RMS patients to vaccines (completed).
- CASTING (MA30005; n=681) and CHORDS (MN30035; n=608), assessing the efficacy and safety of ocrelizumab in RRMS patients who have a suboptimal response to an adequate course of DMTs (completed).
- ENSEMBLE (MA30143; n=1225), assessing the efficacy and safety of ocrelizumab in patients with early RRMS (ongoing).
- OBOE (ML29966; n=132), a biomarker study in RMS and PPMS patients (ongoing).
- CONSONANCE (MN39159; n=900), assessing the efficacy and safety of ocrelizumab in patients with progressive MS (ongoing).
- LIBERTO (MN39158; as this is an extension study where eligible patients are enrolled from ongoing ocrelizumab trials, there is no formal sample size), assessing the tolerability and effectiveness in patients with long-term exposure (ongoing).

Periodic analyses of safety, conducted annually since ocrelizumab approval, have shown consistent results and have been presented at scientific conferences. One such analysis of long-term safety of ocrelizumab over more than seven years of follow-up in patients with RMS and PPMS, based on integrated data from all patients with MS who received ocrelizumab during the controlled treatment and associated OLE periods of the phase 2 and 3 clinical trials, plus seven phase 3b trials (the All-Exposure Population), has been recently published (12). An overview of pooled safety data is presented in Section 10.3.2.4.

A number of other studies, ranging from phase 1b to phase 4, have been initiated in both relapsing and progressive forms of MS, including a dose-finding study for the subcutaneous formulation (OCARINA 1), two studies in pediatric RRMS patients (OPERETTA 1 and OPERETTA 2), two phase 3b studies testing higher doses of ocrelizumab in patients with RMS (MUSETTE) and PPMS (GAVOTTE), a phase 4 open-label placental study to evaluate B-cell levels in infants potentially exposed to ocrelizumab during pregnancy (MINORE), and a

phase 4 open-label lactation study to evaluate B cell levels over the first year of life in infants of lactating women receiving ocrelizumab postpartum (SOPRANINO). These studies are expected to further establish the benefit-risk profile of ocrelizumab in MS patients.

Further details on all studies are available in Appendix A.

10.3.2 Overview of safety in clinical trials

10.3.2.1 Pivotal phase 3 studies in RMS

An overview of the Adverse Events (AEs) profile during the controlled treatment period of the pivotal phase 3 studies in RMS, WA21092 (OPERA I) and WA21093 (OPERA II), is presented in Table 7 (individually and pooled). Overall, the AE profile was consistent between the two studies. Ocrelizumab was well tolerated with lower rates of treatment discontinuations for AEs in patients treated with ocrelizumab 600 mg (3.5%, pooled results) than in patients receiving interferon β-1a (6.2%, pooled results). In both phase 3 studies, percentages of patients (83.3% in both groups, pooled results), as well as total number of AEs, were similar in the ocrelizumab and the interferon β-1a treatment groups over the 96-week treatment period. The proportion of patients with serious adverse events (SAEs) was lower in the ocrelizumab treatment group than in the interferon β-1a treatment group (6.9% in the ocrelizumab treatment group versus 8.7% in the interferon β-1a treatment group, pooled results). Three deaths occurred in Studies WA21092 and WA21093: two patients (suicide and mechanical ileus) in the interferon β-1a treatment group and one patient (suicide) in the ocrelizumab treatment group. A total of six malignancies were observed, with four malignancies (two breast cancers, one renal cancer and one melanoma) occurring in patients treated with ocrelizumab 600 mg and two malignancies (one mantle cell carcinoma and one squamous cell carcinoma) occurring in the interferon β-1a treatment groups. In the ocrelizumab group, the most frequently reported AE was infusion-related reaction (IRR), and as expected, the percentage of patients experiencing IRRs was higher in the ocrelizumab group compared with the IFNβ1a group who received placebo infusions to maintain blinding (approximately 3.5-fold, pooled results).

Table 7: Adverse Events Profile in RMS Phase 3 Studies (Pooled Studies WA21092 and WA21093) in the Controlled Treatment Period (Safety Population)

	WA21092		WA21093		WA21092/3 Pooled	
	IFNβ1a	OCR 600 mg	IFNβ1a	OCR 600 mg	IFNβ1a	OCR 600 mg
	N = 409	N = 408	N = 417	N = 417	N = 826	N = 825
Total No. of patients with at least one adverse event	331 (80.9%)	327 (80.1%)	357 (85.6%)	360 (86.3%)	688 (83.3%)	687 (83.3%)
Total number of events	1825	1837	2316	2357	4141	4194
Total number of deaths	1 (0.2%)	0	1 (0.2%)	1 (0.2%)	2 (0.2%)	1 (0.1%)
Total number of patients with at least one:						
-Fatal AE	1 (0.2%)	0	1 (0.2%)	1 (0.2%)	2 (0.2%)	1 (0.1%)
-SAE	32 (7.8%)	28 (6.9%)	40 (9.6%)	29 (7.0%)	72 (8.7%)	57 (6.9%)
-SAE leading to trt discont.	4 (1.0%)	3 (0.7%)	5 (1.2%)	3 (0.7%)	9 (1.1%)	6 (0.7%)
-AEs leading to trt discont.	26 (6.4%)	13 (3.2%)	25 (6.0%)	16 (3.8%)	51 (6.2%)	29 (3.5%)
No. of pts with malignancies	1 (0.2%)	3 (0.7%)	1 (0.2%)	1 (0.2%)	2 (0.2%)	4 (0.5%)
No. of pts with infections[a]	216 (52.8%)	231 (56.6%)	217 (52.0%)	251 (60.2%)	433 (52.4%)	482 (58.4%)
No. of pts with serious infections[a]	12 (2.9%)	5 (1.2%)	12 (2.9%)	6 (1.4%)	24 (2.9%)	11 (1.3%)
No. of pts with IRRs	30 (7.3%)	126 (30.9%)	50 (12%)	157 (37.6%)	80 (9.7%)	283 (34.3%)

AE=adverse event; discont=discontinuation; IFNβ1a=interferon beta-1a; IRR=infusion-related reaction; No.=number; OCR=ocrelizumab; pts=patients; SAE=serious adverse event; trt=treatment

[a] Infections are defined using adverse events falling into the MedDRA System Organ Class "Infections and Infestations"

10.3.2.2 Pivotal phase 3 study in PPMS

An overview of the AE profile during the controlled treatment period of Study WA25046 (ORATORIO) is provided in Table 8. The proportion of patients who experienced at least one AE was 90% in the placebo group, compared with 95% in the ocrelizumab group. During the double-blind period, the most frequently reported AEs by system organ class (SOC) were Infections and Infestations, which occurred with a similar frequency in both the placebo and ocrelizumab groups, followed by Injury, Poisoning and Procedural Complications, where a higher proportion was observed in the ocrelizumab group compared with placebo, mostly driven by IRRs in patients receiving ocrelizumab (IRRs: placebo 26% vs. ocrelizumab 40%). The percentage of patients experiencing an IRR was greatest after the first infusion; thereafter, the incidence was lower.

Table 8: Adverse Event Profile in Study WA25046 (Safety Population)

	Placebo (N=239)	OCR 600mg (N=486)
Total number of patients with at least one adverse event	215 (90.0%)	462 (95.1%)
Total number of events	1762	3690
Total number of deaths	1 (0.4%)	4 (0.8%)
Total number of patients with at least one:		
-AE with fatal outcome	1 (0.4%)	4 (0.8%)
-Serious AE	53 (22.2%)	99 (20.4%)
-Serious Infection*	14 (5.9%)	30 (6.2%)
-Serious AE leading to withdrawal from treatment	6 (2.5%)	13 (2.7%)
-Serious AE leading to dose modification/interruption	4 (1.7%)	8 (1.6%)
-AE leading to withdrawal from treatment	8 (3.3%)	20 (4.1%)
-AE leading to dose modification/interruption	12 (5.0%)	47 (9.7%)
-IRRs leading to withdrawal at first infusion	0	1 (0.2%)
Medical concepts: patients with		
-Malignancies+	2 (0.8%)	11 (2.3%)
-Infections*	162 (67.8%)	339 (69.8%)

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; SMQ=Standardized MedDRA Query.
Investigator text for AEs encoded using MedDRA version MedDRA v18.0. Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
* Identified by MedDRA System Organ Class "Infections and Infestations".
+ Identified using the "Malignant tumors (SMQ)". Non-Serious Relapses are excluded.

10.3.2.3 Phase 2 study in RRMS

Treatment with 300 mg x 2 and 1000 mg x 2 of ocrelizumab was generally well tolerated in Study WA21493. The AE profile of ocrelizumab during the open-label treatment period up to Week 96 and during follow-up and monitoring/observation periods up to Week 144 was consistent with observations during the first 24 weeks. The single most common AE was IRRs, reported more often in ocrelizumab-treated patients compared to placebo. The proportion of patients reporting IRRs was higher in ocrelizumab-treated patients after the first infusion on Day 1 of the study (9.3% in placebo arm, 34.5% in the 300-mg x 2 arm, and 43.6% in the 1000-mg x 2 arm).

10.3.2.4 Pooled safety analyses

Pooled safety data up to a clinical cutoff date (CCOD) of November 2020 from the phase 2 study and three pivotal phase 3 studies alongside pooled safety data for the same CCOD for a total of 5688 patients exposed to ocrelizumab in the eleven phase 2, phase 3, and phase 3b studies (WA21092, WA21093, WA25046, WA21493, BN29739, MA30005, ML29966, MN30035, MN39158, MN39159, and MA30143), and accruing for 21674.6 patient years (referred to as the All-Exposure Population), are presented in Table 9. There were no relevant differences in the safety profile between the pooled pivotal studies and the MS All-Exposure Population. Safety findings, excluding COVID-19 infections, remain generally consistent with the controlled treatment period in the pooled RMS/PPMS population from the phase 2 and pivotal phase 3 studies. There were no meaningful changes in type, rate, or severity of AEs observed and no new safety concerns were identified in the All-Exposure Population.

A recent analysis of COVID-19 in ocrelizumab-treated MS patients is presented separately in Section 10.4.3.

Table 9: Overview of Adverse Events

	Pooled Pivotal Phase 2 and Phase 3 studies[a] CCOD Nov 2020 (N=2305; PY=14036.5)		All-Exposure Population[b] CCOD Nov 2020 (N=5688; PY=21674.6)	
Safety Endpoint	**AEs [c,d]**	**AEs per 100 PY (95% CI)**	**AEs [c,d]**	**AEs per 100 PY (95% CI)**
Overall total number of events	28670	204.25 (201.90, 206.63)	51677	238.42 (236.37, 240.49)
Death	29	0.21 (0.14, 0.30)	45	0.21 (0.15, 0.28)
Serious AE	1134	8.08 (7.62, 8.56)	1583	7.30 (6.95, 7.67)
Serious Infection	357	2.54 (2.29, 2.82)	488	2.25 (2.06, 2.46)
Serious AE leading to withdrawal from treatment	76	0.54 (0.43, 0.68)	101	0.47 (0.38, 0.57)
AE leading to withdrawal from treatment	156	1.11 (0.94, 1.30)	210	0.97 (0.84, 1.11)

AE=adverse event; CCOD=clinical cutoff date; CI=confidence interval; IRR=infusion-related reaction; IV=intravenous; MS=multiple sclerosis; N=number of patients; PY=total patient years.
[a] Dataset limited to the phase 2 and pivotal phase 3 studies: WA21092, WA21093, WA25046, and WA21493.
[b] Comprehensive dataset, consisting of 11 phase 2, 3, and 3b studies: WA21092, WA21093, WA25046, WA21493, BN29739, MA30005, ML29966, MN30035, MN39158, MN39159, MA30143.
[c] 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. Non-serious MS relapses are excluded.
[d] Investigator text for AEs encoded using MedDRA version 23.1.

10.3.3 Description of post-marketing data sources

In addition to the clinical trial program, safety information is collected from post-marketing data sources, which include:

- Spontaneous reports, which include reports from healthcare professionals, consumers, health authorities worldwide, and scientific literature.
- Non-interventional programs/non-interventional studies.
- Post-authorization safety studies (PASS)/post-marketing requirement (PMR) studies (listed in Table 10).
- Market research programs and patient support programs.

Table 10: PASS/PMR Studies for Ocrelizumab

Study name (Study number)	Description[a]	PMRs/ PASS[b,c]	No of patients enrolled/planned
MANUSCRIPT (BA39730)	Long-term surveillance of ocrelizumab-treated patients with MS	EMA	Approx. 8500 patients (4500 from ML39632/ CONFIDENCE study) planned
VERISMO (BA39731)	Observational study of ocrelizumab-treated patients with MS to determine incidence and mortality of breast cancer and all malignancies	FDA	1366 patients from the US and 3767 from Germany (ML39632/CONFIDENCE study) planned
Pregnancy Registry (WA40063)	Ocrelizumab Pregnancy Registry	FDA	580 pregnant women with MS planned
MELODIC (BA39732)	Multisource surveillance study of pregnancy and infant outcomes in ocrelizumab-exposed women in MS	EMA/FDA	Approx. 7035 pregnancies (accrued from four data sources) planned.

MS=multiple sclerosis; PASS=post-authorization safety study; PMR=post-marketing requirement.
[a] Final study designs may be amended based on further discussions with regulatory authorities.
[b] United States FDA, Center for Drug Evaluation and Research (155)
[c] European Medicines Agency (EMA) (81)

10.4 Adverse effects

Section 10.4 summarizes information on adverse effects, including information on adverse events from clinical trials (10.4.1) and post-marketing sources (10.4.2), information on COVID-19 infection in ocrelizumab-treated MS patients (10.4.3), and detailed information on selected adverse effects (10.4.4).

10.4.1 Adverse effects in pivotal clinical trials

Table 11 summarizes the adverse drug reactions (ADRs) that have been reported in association with the use of ocrelizumab in the pivotal phase 3 studies (pooled data from Studies WA21092 and WA21093 for RMS and data from Study WA25046 for PPMS). Frequencies of ADRs, presented in decreasing order, are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000). During the controlled treatment periods of the pivotal phase 3 trials, the most common ADRs associated with ocrelizumab were IRRs (which were manageable using appropriate measures) and respiratory tract infections.

Table 11: Summary of Adverse Drug Reactions Associated with Ocrelizumab (in Patients with RMS or PPMS) with an Incidence of ≥ 2% and Higher than the Comparator [a]

ADR (MedDRA v18.0)	RMS Pooled WA21092 & WA21093		PPMS WA25046 [b]		Frequency Category for Ocrelizumab
	Ocrelizumab n=825	Interferon β-1a n=826	Ocrelizumab n=486	Placebo n=239	
Injury, Poisoning, and Procedural Complications SOC					
Infusion-related reaction [c]	283 (34.3%)	82 (9.9%)	195 (40.1%)	61 (25.5%)	Very common
Infections and Infestations SOC					
Upper respiratory tract infection	125 (15.2%)	88 (10.7%)	59 (12.1%)	14 (5.9%)	Very common
Nasopharyngitis	123 (14.9%)	84 (10.2%)	117 (24.1%)	67 (28.0%)	Very common
Sinusitis	46 (5.6%)	45 (5.4%)	19 (3.9%)	7 (2.9%)	Common
Bronchitis	42 (5.1%)	29 (3.5%)	31 (6.4%)	15 (6.3%)	Common
Influenza	38 (4.6%)	39 (4.7%)	57 (11.7%)	20 (8.4%)	Very common
Gastroenteritis	25 (3.0%)	19 (2.3%)	22 (4.5%)	12 (5.0%)	Common
Oral herpes	25 (3.0%	18 (2.2%)	13 (2.7%)	2 (0.8%)	Common
Respiratory tract infection	19 (2.3%)	17 (2.1%)	13 (2.7%)	2 (0.8%)	Common
Viral infection	18 (2.2%)	23 (2.8%)	15 (3.1%)	4 (1.7%)	Common
Herpes zoster	17 (2.1%)	8 (1.0%)	8 (1.6%)	4 (1.7%)	Common
Conjunctivitis	9 (1.1%)	5 (0.6%)	10 (2.1%)	1 (0.4%)	Common
Cellulitis	7 (0.8%)	5 (0.6%)	11 (2.3%)	1 (0.4%)	Common
Respiratory, Thoracic, and Mediastinal Disorders SOC					
Cough	25 (3.0%)	12 (1.5%)	34 (7.0%)	8 (3.3%)	Common
Catarrh	0	0	10 (2.1%)	2 (0.8%)	Common

ADR=adverse drug reaction; OCR=ocrelizumab; MedDRA=Medical Dictionary for Regulatory Activities; PPMS=primary progressive multiple sclerosis; RMS=relapsing multiple sclerosis.
[a] Interferon beta-1a 44 mcg (subcutaneous) or placebo
[b] PPMS patients were randomized 2:1 (ocrelizumab:placebo).
[c] Symptoms reported as infusion-related reactions within 24 hours of infusion are described in more detail in Section 10.4.4.

10.4.2 Adverse effects from post-marketing data sources

A cumulative summary of the most common AEs by MedDRA SOC from post-marketing sources, from the IBD of 28 March 2017 to 10 January 2022, is shown in Table 12. In line with the known safety profile of ocrelizumab (described in the product labelling), the most common AEs by SOC were general disorders and administration site conditions; injury, poisoning and procedural complications; infections and infestations and nervous system disorders.

Table 12: Total Numbers of Adverse Events and SOCs of the Most Frequently Reported Adverse Events from Post-Marketing Sources

SOC	Spontaneous, including health authority (worldwide) and literature		Non-interventional post-marketing study and reports from other solicited sources
	Serious	Non-serious	Serious
Total no. of AEs (all SOCs)	8,361	28,804	28,563
SOCs of the most frequently reported AEs			
-General disorders and administration site conditions	652	6,645	2,306
-Injury, poisoning and procedural complications	386	4,532	2,546
-Infections and infestations	1,836	2,127	5,886
-Nervous system disorders	1,676	2,945	8,046

AE=adverse event; SOC=System Organ Class.
Note: Cumulative interval is from 28 March 2017 to 10 January 2022.
Sources include non-interventional studies (including post-authorization safety studies), reports from other solicited sources, and spontaneous Individual Case Safety Reports (ICSRs) (i.e., reports from healthcare professionals, consumers, health authorities [worldwide], and scientific literature).

10.4.3 COVID-19 in ocrelizumab-treated MS patients

To better understand COVID-19 in ocrelizumab-treated MS patients, suspected or confirmed COVID-19 cases were identified from ten ongoing Roche/Genentech clinical trials, as of 28 May 2021. The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE v5.0) grading system (156) was used, which categorizes cases into mild, moderate, severe, life-threatening, or fatal. Outcome was captured as recovered/recovering, not recovered/not resolved, or fatal. Where no information was provided for a given parameter, this was noted as "missing." Seriousness criteria defined in the study protocols were aligned with the definitions of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

The reference population refers to patients with MS who were receiving ongoing ocrelizumab treatment at the beginning of January 2020 and newly enrolled patients thereafter; patients withdrawing from treatment between January 2020 and May 2021 are also included.

Symptomatic COVID-19 was reported in 406 (9.9%) of 4,089 ocrelizumab-treated patients across ten clinical trials. Most cases were non-serious (274/406, 67.5%) and most patients had recovered or were recovering at the time of the analysis (347/406, 85.5%). Eighteen patients (out of 406; 4.4%) had not recovered, and in 32 cases (out of 406; 7.9%) the event had a fatal outcome. Most of the symptomatic COVID-19 cases (265/406, 65.3%) had a mild/moderate presentation, with 86 (21.2%) being classified as severe, 13 (3.2%) life-threatening, 32 (7.9%) fatal, and information on severity was missing for ten patients (2.5%).

Overall, 132 (32.5%) cases were serious. Most of serious cases (n = 76, 57.6%) were classified as severe, ten (7.6%) were mild/moderate, 13 (9.8%) life-threatening, and 32 (24.2%) fatal. Information on severity was missing for one patient (0.8%).

Comorbidities known to be associated with severe COVID-19 (e.g., hypertension, diabetes, obesity) were more prevalent in patients who suffered from serious COVID-19. The proportion of male patients and older patients increased with COVID-19 disease severity. The proportion of patients with fatal COVID-19 disease increased with greater EDSS score.

In addition to the cases of COVID-19 from clinical trials, 1,568 cases from post-marketing use of ocrelizumab until 30 May 2021 were identified and assessed.

Based on the latest assessment of cases from ongoing Roche/Genentech clinical trials and post-marketing use, the experience of ocrelizumab-treated patients with MS with COVID-19 appears in line with the reported data from the general population and MS datasets. Most of ocrelizumab-treated patients experience non-serious COVID-19 and recover.

The factors that affect COVID-19 disease severity in the general population or in the MS population are also observed in ocrelizumab-treated patients.

Reference safety information for ocrelizumab and the conduct of studies with ocrelizumab are not affected by these findings.

10.4.4 Description of selected adverse effects

The adverse effects and their descriptions provided in this section are as per the ocrelizumab risk management plan (RMP) for the EU (endorsed by the EMA's Pharmacovigilance Risk Assessment Committee [PRAC]). Table 13 presents the identified risks (i.e., risks for which there is sufficient evidence of a relationship with ocrelizumab) and potential risks (i.e., risks for which there is insufficient evidence of a relationship with ocrelizumab). Each risk is described in detail in the sections that follow the table.

Table 13: Identified Risks and Potential Risks with Ocrelizumab in MS

Risk Category	Risk	Description
Identified risk	Infusion-related reaction (IRR)	See Section 10.4.4.1
	Infections	See Section 10.4.4.2
	Decrease in immunoglobulins	See Section 10.4.4.3
	Delayed return of peripheral B cells	See Section 10.4.4.4
	Impaired immunization response	See Section 10.4.4.5
	Serious infections related to decrease in immunoglobulins (particularly in patients previously exposed to immunosuppressive/immunomodulatory drugs or with pre-existing hypogammaglobulinemia)	See Section 10.4.4.6
Potential risk	Hypersensitivity reactions	See Section 10.4.4.7
	Malignancies	See Section 10.4.4.8
	Neutropenia	See Section 10.4.4.9
	Progressive multifocal leukoencephalopathy (PML)	See Section 10.4.4.10

10.4.4.1 Identified risk: infusion-related reactions

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, hypotension, and tachycardia. In PPMS patients, the symptoms included oropharyngeal pain, agitation, fatigue, flushing, throat irritation, rash, pyrexia, tachycardia, angioedema, and laryngeal edema. Electrocardiogram (ECG) QT prolongation was reported in one patient.

Some patients reported more than one symptom associated with their IRR.

IRRs were the most frequently reported AE in MS patients treated with ocrelizumab. In the controlled treatment period of the RMS phase 3 studies (OPERA I and II), 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 OLE).

In the PPMS phase 3 study (ORATORIO), the proportion of patients who reported an IRR was higher in the ocrelizumab group (39.9%) compared with placebo (25.5%). The proportion of patients who experienced an IRR was highest after the first infusion, with one patient withdrawing from ocrelizumab treatment at this time. The proportion of patients experiencing an IRR was lower at subsequent infusions. Overall, five patients (1.0%) experienced a serious IRR in the ocrelizumab group.

From the analysis of the MA30143 sub-study (ENSEMBLE PLUS, designed to characterize the safety profile of shorter [two-hour] ocrelizumab infusions in patients with RRMS), IRRs were the most frequently reported AEs in both the conventional and shorter infusion groups. At the first randomized dose, the incidence of IRRs between conventional infusion group (n=99 [26.5%]) and shorter infusion group (n=107 [28.8%]) was similar (2.4% [95% CI: -3.83, 8.71]). There were no patients with any serious IRRs in the conventional and shorter infusion groups.

There were no IRR symptoms that led to permanent discontinuation of ocrelizumab infusion in either infusion group. The proportion of patients who experienced an IRR leading to withdrawal at first infusion in the 11 phase 2, 3 and 3b studies was 0.14% (95% CI: 0.09, 0.20).

Most 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% (six 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 an 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 two 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).

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

At the time of the primary analysis of the MA30143 sub-study, most 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 sub-study.

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 two-fold lower incidence in IRRs compared with pretreatment with methylprednisolone alone (except for Dose 1, Infusion 2). The addition of analgesics/antipyretics to oral antihistamines did not appear to have additional benefit. Dosing intervals other than six-monthly have not been systematically studied in MS, and it is not known whether delaying dosing beyond the dosing schedule of six-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 antidrug antibodies (ADAs) did not allow for an evaluation of the impact of ADAs on rate and intensity of IRRs.

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 ADA 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). IRRs may be clinically indistinguishable from Type 1 (Immunoglobulin E/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 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.

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.

Information on reversibility via adjustments/interruption to the infusion in case of life-threating IRRs, severe

IRRs, and mild to moderate IRRs is available in Section 8.1.3. If a hypersensitivity reaction is suspected during infusion, the infusion must be stopped immediately and permanently.

Patients with known IgE-mediated hypersensitivity to ocrelizumab must not be treated.

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 on the label. 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.

10.4.4.2 Identified risk: infections

In the controlled treatment period of the RMS phase 3 studies WA21092 (OPERA I) and WA21093 (OPERA II), the percentage of patients experiencing an infection was higher in the pooled ocrelizumab treatment group (58.4%) compared with the pooled interferon β-1a treatment group (52.4%). This difference was primarily driven by more patients with upper respiratory tract infections in the ocrelizumab group, as well as bronchitis and herpes virus-associated infections.

In the PPMS phase 3 study (WA25046 [ORATORIO]), the proportion of patients who experienced an infection was 69.8% in the ocrelizumab group compared with 67.8% in the placebo group. The most frequently reported AEs of infection were nasopharyngitis and urinary tract infection (UTI). The proportion of patients who experienced a serious infection was 6.2% in the ocrelizumab group compared with 5.9% in the placebo group. All individual SAEs of infection were reported in less than one percent of patients in any group, except for pneumonia (placebo 0.8% vs. ocrelizumab 1.2%) and urosepsis (placebo 1.3% vs. ocrelizumab 0.4%).

In the MS All-Exposure Population treated with ocrelizumab for more than eight years (11 phase 2, 3 and 3b studies), no meaningful changes in incidence, rate, or type of infections were observed. Overall, the rate of serious infections in MS patients treated with ocrelizumab remained low. The rate of serious infections was 2.251 per 100PY, 95% CI: (2.06, 2.46) at the November 2020 cut-off. The rate of serious infection, after excluding COVID-19 infections, was 2.00 per 100PY (95% CI: 1.82, 2.20), which was like that reported previously (2.014 per 100PY, 95% CI: [1.814, 2.231]). There was no new or particular pattern of serious infection identified in MS patients treated with ocrelizumab, apart from COVID-19 type infections. COVID-19 pneumonia and COVID-19 are new and frequently observed serious infections in line with the pandemic.

Excluding serious COVID-19 infections, no new or particular pattern of serious infection was identified by year in RMS or PPMS patients treated with ocrelizumab during a period of more than eight years.

There was no increase of the same type of serious infections event over time. No specific risk factors have been identified (e.g., age, region, duration, latency) in any of the analyzed populations. Risk factors identified in patients who developed COVID-19 infections were consistent with the COVID-19 risk factors for the general and MS population. Most of serious infections were of Grade 3 or lower intensity, resolved without sequelae, within <2 weeks, and were not treatment-limiting.

The intensity (grades) of infections and serious infections was reported in clinical studies with ocrelizumab in MS. 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. Most serious infections (≥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 (ORATORIO), 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.

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 (157).

An increased risk of infection associated with previous exposure to other MS DMTs is possible. There is only limited experience from ocrelizumab clinical trials, because exposure in patients who switched from interferon to ocrelizumab is limited by the current treatment duration in the OLE, and because exposure to a range of other MS DMTs was not allowed in the pivotal clinical studies with ocrelizumab (e.g., any previous treatment with alemtuzumab or teriflunomide, treatment with natalizumab within 24 months prior to screening, treatment with fingolimod within six months prior to screening) and information on safety of ocrelizumab after DMTs other than beta interferons and glatiramer acetate is missing.

Previous or concomitant immunotherapy, and/or corticotherapy can be important contributing factors to infection risk. Exploratory analyses were conducted to identify prognostic and treatment-emergent risk factors for infections and serious infections. In pooled safety data including clinical trials from other indications, serious infections were observed more frequently in patients with other comorbidities, chronic use of immunosuppressants/steroids, or from Asia. 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 serious infections observed.

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.

Anti-CD20 antibody therapy may trigger Hepatitis B Virus (HBV) reactivation in patients with a history of HBV infection; however, no such reports in MS patients treated with ocrelizumab were reported. Similarly, immunomodulatory therapy may trigger reactivation of latent herpes virus in patients with a history of herpes infection (158). An increased risk of infection associated with an exposure to other MS DMTs is possible.

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, antigen presentation, and coordination of T-cell activity, patients may be at an increased risk of infection or infection reactivation following administration of ocrelizumab.

The majority of the serious infections were of CTCAE Grade 3 intensity, had resolved, and were not treatment-limiting (i.e., did not lead to treatment withdrawal).

Ocrelizumab administration must be delayed in patients with an active infection until the infection is resolved. Also see Section 8.2.7.

When initiating ocrelizumab after an immunosuppressive therapy or initiating an immunosuppressive therapy after ocrelizumab, the potential for overlapping pharmacodynamic (PD) effects should be taken into consideration. The prescriber should exercise caution when prescribing ocrelizumab, taking into consideration the PDs of other MS DMTs. Ocrelizumab has not been studied in combination with other MS DMTs. 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 [HB] surface antigen (HBsAg) and anti-hepatitis B testing) should not be treated with ocrelizumab. Patients with positive serology (i.e., negative for HBsAg and positive for 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.

Minimal public health impact is foreseen.

10.4.4.3 Identified risk: decrease in immunoglobulins

At the January 2020 data cut of the pooled studies WA21092, WA21093, and WA25046, an analysis showed that episodes of a single drop below lower limit of normal (LLN) continue to be infrequent for immunoglobulin (Ig)A and IgG, whereas they are observed in about 1/3 of the population for IgM. Mean levels of all three types of immunoglobulins showed a decline from baseline across the entire treatment period in both RMS and PPMS populations. Mean IgA decline was gradual and continued until seven years after ocrelizumab treatment initiation. Mean IgM decline was most pronounced at the beginning and gradually stabilized after three years. Mean IgG levels were seen declining gradually but did not stabilize by seven years of ocrelizumab treatment. Rates of decline of mean IgA, IgG and IgM depend on baseline concentrations of the respective immunoglobulin values, i.e., patients with higher baseline values decline faster compared to patients with lower baseline values.

10.4.4.4 Identified risk: delayed return of peripheral B cells

Treatment with ocrelizumab leads to rapid depletion of CD19+ B cells in blood by 14 days post treatment (first time point of assessment) as an expected pharmacologic effect. This was sustained throughout the treatment period. In the phase 3 studies, between each dose of ocrelizumab, up to five percent of patients showed B-cell repletion (>LLN or baseline) at least at one time point. The extent and duration of B-cell depletion was consistent in the PPMS and RMS trials. The longest follow-up time after the last ocrelizumab infusion from Phase 2 Study WA21493 in 51 patients indicates that the median time to repletion (return to baseline/LLN, whichever occurred first) of B cells was 72 weeks (range 27 - 175 weeks).

10.4.4.5 Identified risk: impaired immunization response

B cell depletion is expected (and desired) during therapy and is directly related to the mechanism of action of ocrelizumab. Ocrelizumab did not appear to influence specific humoral immunity to common bacterial and viral antigens over the 96-week study period in the pivotal phase 3 RMS studies (OPERA I/II). The

proportions of 106 ocrelizumab-treated patients with positive antibody titers against rubella, mumps, and Varicella Zoster Virus (VZV) at Week 96 were similar to the proportions at baseline.

Similarly, no effect on specific humoral immunity to common bacterial and viral antigens was observed with ocrelizumab at Week 120 in the pivotal phase 3 PPMS study (ORATORIO). The proportions of patients with positive antibody titers against rubella, mumps, and VZV at Week 120 were similar in both groups.
Patients with MS who had received immunomodulatory treatment had reduced protection after pandemic H1N1 vaccination in 2009 (31 [27%] vs. 94 [44%] in controls). The rates of protection were not influenced by interferon beta treatment (44.4% [16/36] of patients protected), but were reduced among patients receiving glatiramer acetate (21.6% [8/37]), natalizumab (23.5% [4/17]), and mitoxantrone (0% [0/11]). The authors observed similar patterns for seasonal influenza vaccination in 2010 (159).

Study BN29739/VELOCE (160) 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 neoantigen keyhole limpet hemocyanin (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. Based on these results, attenuated antibody response to certain vaccines is expected, but there is currently insufficient evidence to assess the impact of ocrelizumab treatment on the immune response (cellular or humoral) to the newly available SARSCoV-2 vaccines. New measures have been implemented to gather additional data on the response to COVID-19 vaccinations in patients treated with ocrelizumab.

Subpopulations at a greater risk of suffering from infectious diseases preventable by immunization include the elderly, immunocompromised, and young children. Also see Section 8.2.7.
Patients should complete local vaccination requirements six weeks prior to initiation of ocrelizumab in order to obtain full effectiveness of the vaccines. For seasonal influenza vaccines, it is still recommended to vaccinate patients on ocrelizumab, as a potentially protective humoral response to the vaccine, even if attenuated, can be expected. Physicians should review the immunization status of patients being considered for treatment with ocrelizumab.

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.

No available data regarding reversibility is reported in context with impaired immunization response.

Impaired response to vaccinations in the event of a pandemic, e.g., influenza, could potentially impact public health.

10.4.4.6 Identified risk: serious infections related to decrease in immunoglobulins (particularly in patients previously exposed to immunosuppressive/immunomodulatory drugs or with pre-existing hypogammaglobulinemia)

Decreased immunoglobulin levels are clinical-laboratory findings with varied causes and manifestations related to deficiencies of humoral immunity. A clinical feature of decreased immunoglobulin relates to predisposition toward infections, which normally are defended against by antibody responses. The severity depends on the type of infection that occurs.

For each immunoglobulin-related endpoint in WA21092 (OPERA 1) and WA21093 (OPERA II), decreases were gradual and declined steadily through Week 96. At Week 96, the number and proportion of patients with immunoglobulin concentration below LLN in the ocrelizumab treatment group was: 116 patients (16.5%) for IgM (LLN=0.4 g/L), 17 patients (2.4%) for IgA (LLN=0.7 g/L) and 11 patients (1.5%) for IgG (LLN=5.65 g/L). From WA25046 (ORATORIO), at Week 120 the number and proportion of patients with immunoglobulin concentration below LLN in the ocrelizumab treatment group was: 56 patients (15.5%) for IgM (LLN=0.4 g/L), 4 patients (1.1%) for IgG (LLN=5.65 g/L), and 2 patients (0.5%) for IgA (LLN=0.70 g/L).

The proportion of patients with immunoglobulin concentrations below the LLN in the ocrelizumab treatment group compared with placebo were similar for IgG and IgA. More patients in the ocrelizumab group had IgM concentrations below the LLN than patients in the placebo group.

From the study WA21493, serum IgM levels decreased by approximately 25% to 30% from baseline in both ocrelizumab groups over the placebo-controlled 24-week period. The proportion of patients with IgM levels below LLN increased to 30.2% in the ocrelizumab 1000 mg X 2 group in Dose 2 and remained stable throughout the study up to Week 144. Mean IgM levels did not return to baseline values in any treatment group at Week 144. There were no notable changes in IgG and IgA levels over the placebo-controlled treatment period.

The pooled data of the ocrelizumab pivotal clinical studies (RMS and PPMS) and their OLEs (over seven years of exposure, CCOD January 2020) have shown an apparent association between decreased levels of immunoglobulins and serious infection, and was most apparent for IgG (0.7% of 2092 patients had a serious infection during a period with IgG<LLN).

Patients with pre-existing hypogammaglobulinemia prior to the start of treatment with ocrelizumab may be at a greater risk of serious infection. Previous or concomitant treatment with immunosuppressive or other immunomodulatory drugs may also be a risk factor.

The prescriber is recommended by the product label to determine patient immunoglobulin levels before initiating treatment with ocrelizumab. After an immunosuppressive therapy or initiating an immunosuppressive therapy after ocrelizumab, the potential for overlapping PD effects should be taken into consideration, including pre-existing hypogammaglobulinemia. The prescriber should exercise caution when prescribing ocrelizumab, taking into consideration the PDs of other MS DMTs. Ocrelizumab has not been studied in combination with other MS DMTs.

Although an association was observed between a sustained decrease in IgG or IgM and the occurrence of a serious infection, these serious infections had no particular pattern and resolved with standard of care while patients were still on ocrelizumab treatment.

No specific dose adjustments are reported.

Ocrelizumab is thought to exert its therapeutic clinical effects in MS through the reduction of B cells. Since B cells play an important role in maintaining a normal immune response, patients may be at an increased risk of infection following administration of ocrelizumab. B cell depletion, as an expected pharmacologic effect of ocrelizumab, may result in Ab deficiency (161).

No data exits for reversibility in serious infections related to decrease in immunoglobulins.
Ocrelizumab administration must be delayed in patients with an active infection until the infection is resolved.

No public health impact in view of the population treated and the limitations placed upon administration of ocrelizumab by virtue of the warnings and precautions and its formulation. Use outside of controlled environments by non-healthcare professionals is not anticipated.

10.4.4.7 Potential risk: hypersensitivity reactions

Ocrelizumab is contraindicated in patients with a known hypersensitivity to ocrelizumab or to any of the excipients. Hypersensitivity may be difficult to distinguish from IRRs in terms of symptoms. A hypersensitivity reaction may present during any infusion, although typically would not present during the first infusion. For subsequent infusions, more severe symptoms than previously experienced, or new severe symptoms, should prompt consideration of a potential hypersensitivity reaction. Hypersensitivity could be a Type 1 (IgE-mediated) or Type 3 reaction. To date, no IgE titers have been measured in patients experiencing IRRs following ocrelizumab infusion. Based on currently available data, there is no evidence for the formation of mAb and antidrug antibody (ADA) complexes in patients exposed to ocrelizumab. In patients developing ADAs, there were no reports of hypersensitivity.

Patients with known IgE-mediated hypersensitivity to ocrelizumab must not be treated. If a hypersensitivity reaction is suspected during infusion, the infusion must be stopped immediately and permanently, and the patient should receive appropriate supportive treatment. Also see Section 8.2.7.

Risk factors for developing drug hypersensitivity include asthma, atopy, circulating lymphocyte counts of 25,000/mm^3 or higher (i.e., patients with lymphoma or leukemia), concomitant β-adrenergic blocker therapy, concurrent autoimmune disease, female sex, higher than standard drug doses, iodine or seafood allergies, newly diagnosed, untreated patients, older age, patients with hematologic malignancies (i.e., mantle cell lymphoma or chronic or small lymphocytic leukemia), personal history of drug allergy or previous immediate reaction to a medication, preexisting cardiac or pulmonary dysfunction, and previous exposure to the drug (162).

No available data regarding reversibility is reported in the context of hypersensitivity.

There were no reports of hypersensitivity reactions to ocrelizumab in clinical studies.

No impact on public health is anticipated. This is due to the limitations placed upon administration of ocrelizumab by virtue of the warnings. 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. Use outside of controlled environments by non-healthcare professionals is not anticipated.

10.4.4.8 Potential risk: malignancies

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.

Published studies on MS population have reported a similar or somewhat lower risk of any cancer compared to the general population (163,164).

As of November 2020, there was a total of 107 malignancies in 91 patients reported in MS patients treated with ocrelizumab in clinical studies, of which the most frequently reported type of malignancy was nonmelanoma skin cancer (NMSC, 32 patients) and breast cancer (24 patients), while the remaining malignancy types were reported in less than five patients each.

From Study WA25046, a total of 15 malignancies in 13 patients were reported. From WA21493 study, there was one malignancy (breast cancer) reported in the ocrelizumab group and from Study WA21092 during the OLE, there were two additional malignancies (one adenocarcinoma of the colon in a patient initially in the interferon β-1a group and one thyroid cancer in a patient initially in the ocrelizumab group).

The overall incidence rate of first malignancy was 0.423 per 100 PY (95% CI: 0.340, 0.519) (reported in 91 patients) for the All-Exposure Population and the incidence rate for female breast cancer was 0.182 per 100 PY, 95% CIs (0.116, 0.270) (reported in 24 patients) at the CCOD of November 2020.

Analysis of data at the most recent CCOD November 2020 showed no change in the incidence rates of all malignancies and female breast cancer compared with the previous CCOD January 2020.

Incidence rates of malignancies, including breast cancer, in patients treated with ocrelizumab remained within the range of placebo data from clinical trials in MS (0.50 per 100 PY [95% CI: 0.36, 0.67]) and epidemiological data (0.67 per 100 PY [95% CI: 0.63, 0.71] (163).

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 B cell-depleting anti-CD20 mAbs on tumor development, progression, and overall incidence. This is in contrast to the well-established positive role of T and NK cells in tumor surveillance (165,166). The specific biological plausibility of an increased risk of breast cancer remains unlikely.

No available data regarding reversibility is reported in the context of malignancy, including breast cancer.

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

The administration of ocrelizumab to patients with an active malignancy is contraindicated.

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

10.4.4.9 Potential risk: neutropenia

In the active-controlled (RMS) treatment period, decreased neutrophils were observed in 14.7% of ocrelizumab patients as compared to 40.9% of patients treated with interferon β-1a. In the placebo-controlled (PPMS) clinical trial, the proportion of ocrelizumab patients presenting decreased neutrophils was slightly higher (12.9%) than placebo patients (10.0%). Most of the decreased neutrophils were transient (only observed once for a given patient treated with ocrelizumab) and were Grade 1 and 2 in severity. Overall, approximately 1% of the patients in the ocrelizumab group had Grade 3 or 4 neutropenia that was not temporally associated with an infection.

10.4.4.10 Potential risk: progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a rare progressive subacute demyelinating disorder of the central nervous system (CNS), usually leading to death or severe disability. Primary infection with or reactivation of the JC virus, a polyoma virus that resides in latent form in approximately 50% of patients with MS (167), can lead to PML. Although no cases of PML were identified in clinical trials with ocrelizumab, John Cunningham virus infection resulting in PML has been observed in patients treated with other anti-CD20 antibodies and associated with risk factors (e.g., patient population such as HIV-infected, oncology and organ transplant patients, or polytherapy with immunosuppressants). To date, no specific risk factors with anti-CD20 mAbs have been identified (e.g., prolonged exposure) beside the known risk factors associated with immunosuppressive therapy described above.

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 took immunosuppressants before commencing natalizumab treatment, and who had received 25 to 48 months of natalizumab therapy (168–170). The risk of PML increases with the number of natalizumab infusions given (171). Natalizumab-treated patients with prior hematopoietic stem cell transplantation may also be at an increased risk (172). Recently, the EMA updated their recommendations on the minimization of the risk of PML with the use of natalizumab. The new advice outlines that in patients who have not been treated with immunosuppressants before starting natalizumab, the level of anti-JC virus Ab relates to the level of risk for PML. EMA's Pharmacovigilance Risk Assessment Committee (PRAC) concluded that patients with a high Ab index who have not used immunosuppressants before natalizumab and have been treated with natalizumab for more than two years are considered at higher risk of PML (173). 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 (174). A PML risk has also been associated with other MS DMTs, including fingolimod and dimethyl fumarate (175).

As of 10 January 2022, no cases of PML had been reported in the context of clinical trials. Twelve confirmed cases of PML were reported outside of clinical trials, of which ten were considered to be “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).

Ocrelizumab is thought to exert its therapeutic clinical effects in MS through the reduction in the number of B cells. Since B cells play an important role in maintaining a normal immune response, patients may be at an increased risk of infection following administration of ocrelizumab.

No available data regarding reversibility is reported in the context of PML.

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 PDs of other MS DMTs. Ocrelizumab has not been studied in combination with other MS DMTs.

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 MRI scan preferably with contrast (compared with pre-treatment MRI), confirmatory Cerebrospinal Fluid (CSF) testing for John Cunnigham viral DNA and repeat neurological assessments, should be considered. If PML is confirmed, treatment must be discontinued permanently. Also see Section 8.2.7.

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

10.5 Summary of Comparative Safety Versus Relevant Comparators

Section 10.5 discusses the safety of ocrelizumab versus relevant comparators in RMS (10.5.1) and PPMS (10.5.2), with a side-by-side comparison of risks between ocrelizumab and other DMTs (10.5.3). It should be noted that ocrelizumab has not been compared in head-to-head studies against comparators other than interferon β, which was used as the comparator in the OPERA I and II Phase III studies.

10.5.1 Important Alternative Therapies for patients with RMS

Long-standing injectable therapies in RMS include the interferon β class (INFβ1a intramuscular, INFβ1a SC, interferon β-1b SC) and glatiramer acetate, administered subcutaneously or intramuscularly at frequencies ranging from daily to once every other week. These treatments are generally considered safe but lack sufficient efficacy to impact the long-term disease course (176,177). In the real-world setting, suboptimal adherence to these therapies due to side effects, injection anxiety, and lack of perceived efficacy are also a recognized issues (178,179).

The approved oral therapies teriflunomide and dimethyl fumarate have established superiority in clinical trials versus placebo (180–182); however, these therapies are not considered to be more effective than injectable DMTs. Teriflunomide was not superior to INF β1a on time to relapse (183), and dimethyl fumarate data did not clearly establish effects in highly-active patients (three-month Sustained Disability Progression), and was therefore considered by the Scientific Advisory Group of the EMA's Committee for Medicinal Products for Human Use (CHMP) to be an alternative to interferon β for the treatment of patients with mildly active RRMS (184). Thus, these therapies do not offer an improvement in efficacy over injectable DMTs; their primary benefit might be considered to be convenience. Although generally considered to be safe and well tolerated, notable warnings include that teriflunomide is teratogenic (185) and patients treated with dimethyl fumarate may develop severe prolonged lymphopenia. Additionally, there have been reports of PML with the use of dimethyl fumarate (186).

Natalizumab, fingolimod, and alemtuzumab are therapies which have demonstrated more substantial reductions in relapse and disability progression (87,88,158,187), including versus active comparator in some cases. However, for fingolimod, more substantial efficacy is also accompanied by identified risks requiring risk minimization activities, including (but not limited to) cardiac side effects (bradyarrhythmia, QT prolongation, and atrioventricular block), macular edema, PML (three confirmed cases), and basal cell carcinoma (188). Natalizumab is associated with a risk of PML ranging from 0.1 to 10 per 1000 patients (173). Alemtuzumab is associated with secondary autoimmune disorders (thyroid disease, immune thrombocytopenic purpura, and nephropathies) (189).

Siponimod is a selective sphingosine-1-phosphate receptor modulator for oral use. Its efficacy on disease activity seems to be comparable to fingolimod, and side effects are also similar. As in its sole phase 3 trial (190), a beneficial effect on disability progression was only seen in patients with active signs of inflammation, and the drug received market authorization for active MS (RMS and SPMS) only.

Ozanimod is a sphingosine-1-phosphate receptor modulator, which was approved by the FDA and EMA in 2020 for adult patients with RRMS with active disease as defined by clinical or imaging features.
The FDA approved ozanimod for relapsing forms of MS, to include clinically isolated syndrome (CIS), relapsing-remitting disease, and active secondary progressive disease, in adults. Data from the randomized

active-controlled phase 3 SUNBEAM and RADIANCE Part B clinical trials of more than 2600 adults found ozanimod was efficacious in reducing ARR and the number and size of brain lesions. In both trials, ozanimod was compared with interferon β-1a. The oral treatment is the first and only approved sphingosine-1-phosphate receptor modulator with no genetic test or first dose observation at initiation. Because a transient decrease in heart rate and atrioventricular conduction delays may occur when taking ozanimod, an up-titration scheme is advised to reach the maintenance dosage in patients with RMS.

Cladribine is a purine analogue leading to depletion of B-cells, and, to a lower extent, also T-cells. This oral treatment for highly active MS had initially been rejected by both EMA and FDA for safety concerns, before finally being approved based on new data by both authorities in 2017 and 2019, respectively. Most common side effects are lymphopenia and infections with herpes zoster (191). The drug also carries a boxed warning for an increased risk of malignancies and fetal harm (192). Of the available treatment options, few have been studied head-to-head compared with INFβ1a 44 mg subcutaneous (SC), and none have demonstrated a significant reduction in risk of both 12- and 24-week disability progression in two separate pivotal trials against an active comparator, as has been shown with ocrelizumab by the WA21092 and WA21093 studies.

Ofatumumab is a subcutaneous anti-CD20 monoclonal antibody which selectively depletes B-cells. Ofatumumab received approval from the FDA and EMA in 2020 for the treatment of adult patients with relapsing forms of MS with active disease defined by clinical or imaging features. Approval was based on two phase 3 ASCLEPIOS studies demonstrating significant reductions in risk of relapses, confirmed disability progression (CDP), gadolinium-enhancing (Gd+ T1) brain lesions, and new/enlarging T2 lesions compared to teriflunomide (193). Ofatumumab may halt new disease activity in RMS patients as shown in a post-hoc analysis, with 47.0% and 87.8% of patients treated with ofatumumab achieving no evidence of disease activity (NEDA)-3 within the first (0–12 months) and second year (12–24 months) of treatment, respectively. The label requires hepatitis B virus screening and includes warnings around hepatitis B virus reactivation and PML (referring to ofatumumab at substantially higher doses in oncology indications and other anti-CD20 antibodies). The first dose needs to be administered under the guidance of a healthcare professional. IgG monitoring is a requirement on the US label.

Ponesimod is a once-daily oral selective sphingosine-1-phosphate receptor 1 modulator. In 2021, the US FDA approved ponesimod for the treatment of adults with relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease. The FDA approval is based, in part, on a two-year, head-to-head phase 3 clinical trial in which ponesimod 20 mg demonstrated superior efficacy in significantly reducing annual relapses by 30.5% compared to teriflunomide 14 mg in patients with relapsing MS. Over the study period, 71% of patients treated with ponesimod had no confirmed relapses, compared to 61% in the teriflunomide group. Ponesimod was also superior to teriflunomide in reducing the number of new Gd-enhancing T1 lesions and the number of new or enlarging T2 lesions by 59% and 56%, respectively (194).

The remaining unmet need in RMS resides in the physician's ability to offer earlier treatment to decrease the long-term consequences of accumulating disability and to improve quality of life. Ocrelizumab has a benefit-risk profile that supports initiation at any time during the course of disease, providing the opportunity to reduce relapses and slow disability progression in people living with RMS.

10.5.2 Important alternative therapies for patients with PPMS

At the time of preparation of this submission, there were no treatments other than ocrelizumab approved for PPMS. As noted earlier in clinical practice guidelines, no other treatments have been demonstrated to significantly slow the progression of disability in patients with PPMS, including therapies approved for the treatment of RMS (83). A large phase 3, randomized, controlled trial with glatiramer acetate (195) and smaller randomized, controlled clinical trials evaluating mitoxantrone (196), INFβ1a Intramuscular (197), and interferon β-1b (198) did not demonstrate significant impact on clinical progression in the PPMS population. Moreover, a phase 3 placebo-controlled trial of fingolimod in patients with PPMS failed to meet the primary endpoint (199).

Before the approval of ocrelizumab, a variety of unapproved agents, including mycophenolate mofetil, cyclophosphamide, and mitoxantrone, in addition to other therapies approved for the treatment of RMS (such as interferon β-1a or glatiramer acetate), were used in clinical practice with variable dosing regimens to treat PPMS. The use of these agents was not supported by Level 1 evidence (i.e., evidence from randomized controlled trials [RCTs] or SLRs of RCTs), exposing patients to risk without clearly defined and demonstrated benefits.

10.5.3 Comparison of risk between ocrelizumab and other MS DMTs

Safety data for ocrelizumab has been continuously collected via multiple data sources, including, but not limited to, the pivotal trials, long-term OLEs of clinical trials, phase 3b/4 trials, non-interventional studies and spontaneous AE reports to the post-marketing safety database. Together, this constitutes an adequate dataset to investigate and establish the safety profile of ocrelizumab. Since the IBD (28 March 2017) till 31 March 2022, an estimated cumulative total of 250,428MS patients had received ocrelizumab from marketing experience. This is equivalent to an estimated 510,060patient-years of exposure. Since the Developmental International Birth Date (DIBD; 23 September 2003), an estimated total of 9,542patients had received ocrelizumab in clinical trial settings. To date, no new safety concerns have been identified in MS patients treated with ocrelizumab. The favorable benefit-risk profile observed in the controlled periods of the pivotal clinical trials has been maintained with longer-term treatment, and in more heterogeneous populations. The safety dataset of ocrelizumab is the largest in the anti-CD20 class, with long-treatment data up to nine years duration in clinical trials and five years in real-world settings. This also emphasizes the fact that ocrelizumab is an anti-CD20 therapy with extensive benefit-risk evidence in MS.

A side-by-side comparison of the identified and potential risks reported for ocrelizumab and for other approved DMTs is presented in Table 14, taking into account the low frequency of reported events and the differences in identified risks (e.g., PML and idiopathic thrombocytopenic purpura are identified risks for natalizumab and alemtuzumab, respectively). This assessment is based on the SmPCs and summaries of risk management plans for the respective products available on the EMA website as of September 2022.

Serious infections, including PML and cytopenias, and their medical consequences, including purpuras, liver toxicity, and teratogenicity, are reported for the other DMTs, including interferon beta-1a (IFNβ1a), which has been directly compared with ocrelizumab in clinical trials (Table 14).

The safety profile of ocrelizumab is favorable when considering the identified risks associated with alemtuzumab (a DMT indicated for use in active RMS), which include an increased risk of permanent

autoimmune conditions affecting thyroid and kidney, stroke, serious infections such as herpes varicella zoster (HVZ) and tuberculosis, and serious infusion-associated reactions despite premedication (Table 14).

For those therapies approved for use in highly active RMS (Table 14), life-threatening risks with sometimes fatal outcome were identified in pivotal studies (such as cardiac rhythm disorders for fingolimod and hepatic failure for daclizumab); these have not been reported with ocrelizumab. PML was reported in patients treated with anti-CD20 agents, including ocrelizumab, but with a very low reporting rate (approximately 1 case per 100,000 patients) in comparison with the rate reported for natalizumab (ranging from 0.1 to 10 cases per 1000 patients). PML is categorized as an identified risk for both natalizumab and fingolimod, while for ocrelizumab, PML remains a potential risk as the evidence for causal association was weak. The application for cladribine was initially rejected by the EMA as well as the FDA due to safety concerns, before being finally approved based on new data by both authorities in 2017 and 2019, respectively. The most common side effects for cladribine are lymphopenia and infections with HZV (191).

Cladribine also carries a boxed warning for an increased risk of malignancies and fetal harm due to teratogenicity (192). In summary, the safety profile of ocrelizumab compares favorably with that of these approved therapies for active/highly active RMS/RRMS.

Ofatumumab, which currently has no identified risks, is another MS DMT targeting B cells (Table 14); however, it has a monthly administration regimen, compared to the six-monthly regimen for ocrelizumab.

Table 14: Qualitative Comparison of Safety Profiles of Ocrelizumab and Other MS DMTs

Category	Risks for approved DMTs by indication class									
	DMTS without restriction on disease activity				DMTs for active RMS	DMTs for highly active RMS				
	Teriflunomide[a]	Dimethyl Fumarate[b]	Glatiramer Acetate[c]	Interferon Beta[d]	Alemtuzumab[e]	Ocrelizumab[f]	Natalizumab[g]	Fingolimod[h]	Cladribine[i]	Ofatumumab[j]
Identified risks	• Hepatic effects • Hypertension • Hematologic effects • Infections • Acute pancreatitis	• PML • Decreases in leukocyte and lymphocyte counts • Drug-induced liver injury	Benign neoplasms of the skin and soft tissues	• Thrombotic microangiopathy • Thrombotic thrombocytopenic purpura or hemolytic uremic syndrome including fatal cases • Severe skin reactions • Systemic capillary leak syndrome with shock-like symptoms and fatal outcome • Pancreatitis	• Infusion associated reactions (IARs) • Stroke (including hemorrhagic stroke) • Dissection of the cervicocephalic arteries • Myocardial infarction and myocardial ischemia • Pulmonary alveolar hemorrhage • Thrombocytopenia • Thyroid disorders • Immune thrombocytopenic purpura • Nephropathies including anti-GBM disease • Autoimmune hepatitis • Serious infections • Hemophagocytic lymphohistiocytosis • Acquired Hemophilia A • Thrombotic Thrombocytopenic Purpura • Adult-Onset Still's disease • Autoimmune encephalitis • Acute acalculous cholecystitis	• IRR • Infections • Impaired immunization response	• PML • Serious herpes infections	• Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose • Liver transaminase elevation • Macular oedema • Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection • Reproductive toxicity • Skin cancer (basal cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell carcinoma, squamous cell carcinoma) • Convulsions • Lymphoma	• Severe (Grade ≥3) lymphopenia • Herpes zoster • Tuberculosis	None

Application for the addition of ocrelizumab on the WHO Model List of Essential Medicines

Category	Risks for approved DMTs by indication class									
	DMTS without restriction on disease activity				DMTs for active RMS	DMTs for highly active RMS				
	Teriflunomide[a]	Dimethyl Fumarate[b]	Glatiramer Acetate[c]	Interferon Beta[d]	Alemtuzumab[e]	Ocrelizumab[f]	Natalizumab[g]	Fingolimod[h]	Cladribine[i]	Ofatumumab[j]
Potential risks	• Teratogenicity • Serious opportunistic infections, including PML	• Serious and opportunistic infections (other than PML and herpes zoster) • Malignancies • Effects on pregnancy outcome • Interaction with nephrotoxic medications leading to renal toxicity.			• Other autoimmune disorders (i.e., cytopenia, including severe neutropenia, myasthenic syndrome, T1DM, GBS, sarcoidosis) • Malignancies • PML	• Malignancies including breast cancer • PML	• Malignancies	• Other malignant neoplasms	• PML • Opportunistic infections (other than tuberculosis and PML) • Malignancies • Teratogenicity/ adverse pregnancy outcomes. • Seizures	• Serious infections, including opportunistic infections (e.g., PML, HBV reactivation) • Malignancy • Impaired immunization response, including vaccination of newborns after exposure in utero.
Comparison with ocrelizumab	Teriflunomide has teratogenicity, which is absent from ocrelizumab labelling.	• Dimethyl fumarate may cause development of severe prolonged lymphopenia. • Additionally, there have been reports of PML with use. • PML is an identified risk. whereas PML is a potential risk for ocrelizumab, with weak evidence for causal association and a very low reporting rate (1 per 100,000 patients).		Interferon beta has been directly compared with ocrelizumab in the pivotal RMS trials.	Alemtuzumab carries increased risks for permanent autoimmune conditions affecting thyroid and kidney, stroke, serious infections such as herpes varicella zoster (HVZ) or tuberculosis, and serious infusion-associated reactions despite heavy premedication; hence the safety profile of ocrelizumab is clearly more favorable.	Late-onset neutropenia has been added to the ADR table and an association between decreased IgG level and serious infections is now mentioned in the ADR section of the SmPC.	Natalizumab is associated with a risk of PML ranging from 0.1 to 10 per 1000 patients, which is notably higher than the reporting rate in ocrelizumab-treated patients (1 per 100,000). The evidence for causal association between PML and ocrelizumab is weak, and PML remains a potential risk for ocrelizumab.	Fingolimod has identified risks requiring risk-minimization activities; including (but not limited to) cardiac side effects (bradyarrhythmia), macular oedema, PML (3 confirmed cases) and other opportunistic infections, basal cell carcinoma, and reproductive toxicity, all of which are not identified risks for ocrelizumab. PML remains a potential risk throughout ocrelizumab MS programs and the evidence of causal association is weak.	• Cladribine was initially rejected by both the EMA and the FDA due to safety concerns before final approval. • Most common side effects are lymphopenia and infections with herpes zoster. • The drug also carries a boxed warning for an increased risk of malignancies and fetal harm due to teratogenicity.	• Ofatumumab is injected monthly, vs. every six months for ocrelizumab. • Ocrelizumab has well-documented benefit-risk evidence, supported by a large safety dataset with various sources, including not only pivotal trials, but also long-term OLEs, phase 3b/4 trials, non-interventional studies and post-marketing data from >250,000 patients. Regular safety assessments have been made and the stability of the safety profile

Category	Risks for approved DMTs by indication class									
	DMTS without restriction on disease activity				DMTs for active RMS	DMTs for highly active RMS				
	Teriflunomide[a]	Dimethyl Fumarate[b]	Glatiramer Acetate[c]	Interferon Beta[d]	Alemtuzumab[e]	Ocrelizumab[f]	Natalizumab[g]	Fingolimod[h]	Cladribine[i]	Ofatumumab[j]
										after the initial approval has been verified. All relevant publications are included in the dossier.

ADR=adverse drug reaction; DMT=disease-modifying therapy; GBM=glomerular basement membrane; GBS=Guillain-Barré syndrome; HBV=hepatitis B virus; IRR=infusion-related reaction; MS=multiple sclerosis; OLE=open-label extension; PML=progressive multifocal encephalopathy; RMS=relapsing forms of multiple sclerosis; SmPC=summary of product characteristics; T1DM=type 1 diabetes mellitus; VZV=Varicella zoster virus.

[a] Aubagio® SmPC (185)

[b] Tecfidera® SmPC (186)

[c] Copaxone® SmPC (200)

[d] Rebif® SmPC (201)

[e] Lemtrada® SmPC (189)

[f] Ocrevus® SmPC (202)

[g] Tysabri® SmPC (203)

[h] Gilenya® SmPC (188)

[i] Mavenclad® SmPC (191); Mavenclad® Highlights of Prescribing Information (192)

[j] Kesimpta® SmPC (204)

10.6 Consideration of the potential for and consequences of inappropriate use or use outside the proposed indication

Section 10.6 discusses the potential for and consequences of inappropriate use, including off-label use (10.6.1), overdose (10.6.2), and misuse and abuse (10.6.3). This section also provides information on real-world use of ocrelizumab (10.6.4).

10.6.1 Off-label use

As of 10 January 2022, cumulatively, 4,775 events from 1,814 cases were flagged as off-label use of ocrelizumab. Other than the off-label indications, off-label use of ocrelizumab was also reported due to its use in unapproved frequency, unapproved dose, unapproved route of drug administration, unapproved age group, unlabeled combination therapy, and off-label use of drugs other than ocrelizumab. Based on the cases reported, no safety signal or safety concern regarding off-label use with ocrelizumab was identified that would warrant any changes to the label. Off-label use of ocrelizumab will continue to be reviewed.

10.6.2 Overdose cases

As of 10 January 2022, cumulatively, 412 events from 163 cases flagged as overdose with ocrelizumab were reported. Most of the cases reported overdose of a different medicinal product other than ocrelizumab or did not represent true cases of overdose pertaining to ocrelizumab. No trend in AE reporting due to overdose was observed. The review of the cases did not reveal any safety signal or safety concern regarding overdose cases reported for ocrelizumab that would warrant any changes to the label. Events of overdose will continue to be monitored for any potential safety concerns via routine assessments.

10.6.3 Misuse and abuse

As of 10 January 2022, cumulatively, 5042 events from 1,932 cases of misuse and abuse of ocrelizumab were reported. The review of the cases did not reveal any safety signal or safety concern regarding misuse or abuse with ocrelizumab that would warrant any changes to the label.

10.6.4 Evidence on real-world use of ocrelizumab

Analysis of use of ocrelizumab therapy in the real world reveal high persistence and adherence, indicating that the drug is being used appropriately in real-world situations. High persistence and adherence can be considered a surrogate for an acceptable safety profile. A recent analysis of data retrieved from the IBM MarketScan Commercial and Medicare Supplemental databases between April 2016 and December 2019 (205) measured persistence (continuing treatment for the prescribed length of time) and adherence (following the prescribed medication regimen with respect to dosage, frequency, and timing) in patients with MS initiating treatment with a new DMT. Both persistence and adherence at 24 months were higher in ocrelizumab-treated patients (75% and 80% respectively) than patients treated with other DMTs (persistence: 33% to 55%; adherence: 35% to 55%). These metrics correspond with adequate opportunities for the collection of safety data from patients in the post-marketing setting.

Additionally, the safety of ocrelizumab under real-world conditions is monitored in Study ML39632 (CONFIDENCE), a non-interventional post-authorization safety study in patients with MS. A recent publication on safety, adherence, and persistence in this study (206) reported that the overall frequency of

patients discontinuing ocrelizumab was low (RMS 4.7% [80/1702]; PPMS 4.8% [19/398]). Of these patients, few discontinued ocrelizumab due to an AE (RMS 0.8% [13/1702]; PPMS 1.0% [4/398]). Consequently, while acknowledging the potential for under-reporting (particularly spontaneous reports), Roche considers that together with high persistence in patients treated with ocrelizumab, sufficient pharmacovigilance measures are in place to enable the identification of AEs and new safety signals in the post-marketing setting.

10.7 Information on any variation in safety that may relate to health systems or patient factors

Section 10.7 provides information on variations in safety relating to health systems and patient factors, including women of childbearing potential, pregnancy, and breastfeeding.

Women of childbearing potential
Women of childbearing potential should use contraception while receiving ocrelizumab and for 12 months after the last infusion of ocrelizumab (202).

Pregnancy
Ocrelizumab is a humanized monoclonal antibody of an immunoglobulin G1 subtype, and immunoglobulins are known to cross the placental barrier.

Per the ocrelizumab EU SmPC (202), there is a limited amount of data from the use of ocrelizumab in pregnant women. Postponing vaccination with live or live-attenuated vaccines should be considered for neonates and infants born to mothers who have been exposed to ocrelizumab in utero. No B cell count data has been collected in neonates and infants exposed to ocrelizumab and the potential duration of B-cell depletion in neonates and infants is unknown.

Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy.

Ocrelizumab should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus.

Breastfeeding
It is unknown whether ocrelizumab/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of ocrelizumab in milk (202). A risk to neonates and infants cannot be excluded. Women should be advised to discontinue breast-feeding during ocrelizumab therapy.

Pharmacovigilance actions taken by Roche relating to risk in pregnancy and lactation include a global enhanced pregnancy pharmacovigilance and clinical development program. Efforts include the following (further information on these studies is available in Appendix A):

- A post-marketing study (BA39732/MELODIC) (75) to assess and characterize pregnancy and infant outcomes of women with MS exposed to ocrelizumab during the six months before the estimated date of conception or at any time during pregnancy

- A prospective observational pregnancy registry study (WA40063) (74) designed to assess and characterize frequency of maternal, fetal, and infant outcomes among women with MS exposed to ocrelizumab
- A phase 4 open-label placental study (MN42988/MINORE) (73)) to evaluate B cell levels and other outcomes in infants potentially exposed to ocrelizumab during pregnancy
- A phase 4 open-label breastfeeding study (MN42989/SOPRANINO) (73)) to evaluate B cell levels and other outcomes in infants potentially exposed to ocrelizumab through breastmilk.

10.8 Information on any warnings or safety issues identified by regulatory authorities

Section 10.8 provides a comprehensive list of special warnings or safety issues identified by regulatory authorities for use of ocrelizumab.

No new warnings or precautions have been added to the ocrelizumab label since registration. Existing warnings and precautions have been further characterized, and are summarized in Table 15.

Table 15: Special Warnings and Precautions for Use of Ocrelizumab

Warnings and Precautions	Description
Infusion-related reactions (IRR)F	See information in Section 10.4.4.1
Hypersensitivity reactions	See information in Section 10.4.4.7
Infections	See information in Section 10.4.4.2
Progressive multifocal leukoencephalopathy (PML)	See information in Section 10.4.4.10
Hepatitis B reactivation	Hepatitis B virus reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, has been reported in patients treated with anti-CD20 antibodies. See also information under *Infections* in Section 10.4.4.2
Late neutropenia	See information in Section 10.4.4.9
Malignancies	See information in Section 10.4.4.8
Treatment of severely immunocompromised patients	Patients in a severely immunocompromised state must not be treated until the condition resolves. See also information under *Delayed return of peripheral B cells* in Section 10.4.4.4
Vaccinations	The safety of immunization with live or live-attenuated vaccines following ocrelizumab therapy has not been studied, and vaccination with live-attenuated or live vaccines is not recommended during treatment and not until B-cell repletion. See also information under *Impaired immunization response* in Section 10.4.4.5
Source: Ocrevus® SmPC (202)	

11. Summary of available data on comparative cost and cost-effectiveness

11.1 Range of costs of the proposed medicine

11.1.1 Roche's pricing approach

Roche's pricing approach reflects the WHO definition of 'Fair Pricing', balancing the need for affordability to healthcare systems and patients, and sufficient market incentives for industry to invest in future innovation.

When setting product prices, Roche's pricing approach is based on three main factors:

1. the context of individual healthcare systems, factoring in different priorities and burdens of disease; varying abilities to pay; local regulatory environments and cost-effectiveness assessments when applicable
2. the health impact that a medicine brings to the patient, their family, and broader society
3. the possibility of Roche to invest year after year into high -risk and complex areas of medicines for developing future innovation

Together with healthcare system partners, Roche uses tailored pricing solutions and believes that this responsible approach to pricing enables broad, rapid, equitable and sustainable access for patients.

11.1.2 Europe and upper-middle, lower-middle, and low-income countries price ranges

In France, Germany, Italy, Spain, and the United Kingdom (UK), list ex-factory prices for ocrelizumab range from €5'125 – €6'250 per vial, or €20'500 – €25'000 per patient per year.

In upper-middle, lower-middle, and low-income countries, if we exclude countries with high foreign and exchange market rate fluctuation, the average ocrelizumab list price is €4'450 per vial with the lowest list price starting at €1'495 per vial.

11.1.3 Upper-middle, lower-middle, and low-income countries

At a global level, Roche is committed to broadening access for patients to its medicines in upper-middle, lower-middle, and low-income countries. To this end, Roche is developing comprehensive, scalable, and adapted solutions to ensure that people in these countries have affordable access to the healthcare they require and that Roche supports the journey towards Universal Health Coverage (UHC).

Non-communicable diseases (NCDs) have become a major disease burden globally, and Roche wants to continue to support the growing number of governments that are acting against NCDs, particularly in countries with more limited resources.

For more than a decade now, Roche has pioneered, promoted, and implemented International Differential Pricing (IDP), allowing our local organizations to adjust prices to reflect a country's relative income and ability to pay. This helps to ensure that Roche's innovations are fairly priced and therefore reach patients in need.

As part of a wider Roche commitment to doing more to address affordability challenges, Roche's IDP model has been strengthened with a broadened scope to make it more reflective of the local economic situation. As implemented for ocrelizumab, this model aligns innovative medicine prices to a purchasing parity-

adapted formula, factoring in gross domestic product (GDP) per capita, as well as public healthcare investment and the United Nations' Human Development Index (HDI), to ensure that the prices are as fair as possible.

Roche IDP model is applied in 75 upper-middle, lower-middle, and low-income countries worldwide, either through public funding or the Out-of-Pocket Paying (OoP) sector, where pricing is added to non-pricing support in the form of patient assistance programs. These programs include components such as medicine doses, donations, patient awareness educational campaigns involving healthcare practitioners, patient assistance to treatment adherence, and health service delivery improvements.

This comprehensive set of interventions has resulted in greater access to patients who otherwise could not afford ocrelizumab treatment for multiple sclerosis (MS). To date, and with the implementation of a greater price flexibility, as part of its IDP model, Roche was able to support governments and private institutions in over 30 upper-middle, lower-middle, and low-income countries in providing access to patients for ocrelizumab in MS, including Argentina, Armenia, Belarus, Bosnia and Herzegovina, Brazil, Bulgaria, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, Egypt, El Salvador, Georgia, Ghana, Guatemala, Honduras, Jordan, Kazakhstan, Kenya, Kosovo, Lebanon, Libya, Malaysia, Mexico, Montenegro, Morocco, Namibia, Nicaragua, Nigeria, North Macedonia, Pakistan, Paraguay, Peru, South Africa, Tunisia, Turkey, Ukraine, Uzbekistan, and Venezuela.

Due to its broadened scope and implementation in additional countries, Roche's new, strengthened IDP model will continue to allow access to ocrelizumab treatment for even more patients.

The two examples below illustrate such collaboration and the establishment of special price agreements.

Tunisia:
Ocrelizumab was granted marketing authorization by the Tunisian Regulatory Body *(Direction de la Pharmacie et du Médicament)* in June 2020 and was granted positive opinion for public reimbursement in May 2021 by the national health scheme revision commission (*Commission de revision du régime de base*) (207) for both indications, i.e., relapsing forms of MS (RMS) and primary progressive MS (PPMS). Broad national access was gained through the inclusion of Tunisian centers and patients in the OPERA I study, leading to strong clinical data through a tailored pricing strategy that answered payers' budget requirements and allocation.

Egypt:
Ocrelizumab in Egypt was registered in December 2018 and the product launch took place in January 2019. In the public sector (i.e., Health Insurance Organization [HIO] and Ministry of Health [MOH]), access was achieved in February 2019 with reimbursement granted to PPMS and relapsing-remitting MS (RRMS) patients (current restrictions: patients above an Expanded Disability Status Scale [EDSS] score of 4.5, 3rd line in active RRMS, Aggressive RRMS). Ocrelizumab is now included in the reimbursement list of all hospitals covered by the HIO and under the purview of the MOH.

11.2 Summary of available data on comparative cost and cost-effectiveness of the medicine

11.2.1 Real-world persistence

Treatment adherence is known to be associated with better clinical and economic outcomes (208–211). Many local real-world evidence studies, both comparative and non-comparative, investigated the adherence and persistence of ocrelizumab across different geographies (US, Germany, Australia, and Latin America). Findings from these studies consistently indicated that ocrelizumab is associated with high rates of adherence and persistence in treatment in either front or later line settings (20,205,206,212,213), including in low-resource settings (20), and that adherence and persistence profile of ocrelizumab compares favorably to that of other available disease modifying treatment options for MS, irrespectively of the mode of administration (e.g., oral versus injectable) (205,213). The high rates of persistence after one year of treatment with ocrelizumab observed in low resource settings (20) were associated with a greater likelihood of improved clinical outcomes compared to the year before starting ocrelizumab, thereby suggesting that treatment with ocrelizumab could play a role in reducing global inequalities in the treatment of MS.

11.2.2 Value for money and cost-effectiveness of ocrelizumab

The use of ocrelizumab in MS was supported by health technology assessment (HTA) recommendations (most of which factored in independent cost-effectiveness and/or budget impact assessments), and these eventually led to positive reimbursement decisions in several countries (including but not limited to UK (214), Ireland (215), France (216), Germany (217), Spain (218) and Canada (219)). This was further supported by Roche's pricing agreements tailored to country individual needs and affordability.

The cost-effectiveness of ocrelizumab, as well as of other DMTs for MS, has also been investigated in several published studies focusing on different high- or middle-income countries. It is important to note, however, that the breadth of studies used different parameters (such as treatment efficacy inputs, probabilities of transitioning across EDSS states, rates of treatment discontinuation, etc.) and different modelling assumptions (frequency of relapses across EDSS states, impact of a relapse on quality of life (QoL), patient health state and journey when experiencing a disease conversion from RRMS to SPMS, etc.). This may have a major impact on the comparability of the results across studies and on the generalizability of their conclusions. A similar situation applies to available budget impact studies, particularly with respect to market composition data and the assumptions used to model treatment uptake.

Furthermore, the application of cost-effectiveness analyses to DMTs for MS is inherently limited in its ability to effectively capture the consequences of the relative impact a DMT may have on all the aspects of a multifaceted disease such as MS. For instance, standard economic evaluations of MS treatments focus on quantifying the benefit of reducing the risk of relapses and slowing down the rate at which patients experience disability progression as measured by the EDSS, a disease severity scale which, although of widespread use, is known to be associated with many limitations (220,221). Consequently, the impact that a DMT may have on other functional domains which are not properly captured by the EDSS, such as upper limb function and cognition, is normally not accounted for in such analyses.

Finally, economic evaluations do not normally take a societal perspective in many countries (generally the perspective is that of a national health system or a health insurance plan), exception made for very few high-resource settings, which is a major limitation for a disease such as MS, where spillover effects on caregivers (56,57,222,223) and productivity losses (224–228,51–53,55) are known to have a substantial contribution to the overall disease burden (54), particularly as patients progress to higher levels of the EDSS. For the reasons

mentioned above, an in-depth review of all published economic evaluations of DMTs in MS, including ocrelizumab, is not presented in the context of this application.

12. Regulatory status, market availability, and pharmacopoeial standards

12.1 Summary of regulatory status

Ocrelizumab (Ocrevus®) was first granted a marketing approval in the United States of America (USA) on 28 March 2017, which marks the International Birth Date (IBD). Ocrelizumab was subsequently approved in the European Union on 8 January 2018. As of 27 March 2022, ocrelizumab was approved in over 100 countries worldwide. A list of the global marketing authorizations for ocrelizumab is provided in Appendix C. Ocrelizumab regulatory applications are currently being submitted in Asia.

In the European Union (and associated countries of the European Economic Area [EEA]), United States of America, and in many other countries worldwide, ocrelizumab is approved for relapsing forms of MS (RMS) and primary progressive MS (PPMS). The specific indications approved in the USA and Europe are as follows in Table 16.

Table 16: Ocrelizumab (Ocrevus®) indications approved in the USA and European Union

USA	Ocrelizumab is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults	Ocrelizumab is indicated for the treatment of primary progressive MS, in adults
European Union	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 adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity

12.2 Market availability

Ocrevus® is marketed by Roche in the vast majority of countries where a registration was granted. The exceptions are Algeria, Azerbaijan, Guyana, Jamaica, Serbia, and Sint Maarten.

12.3 Availability of pharmacopoeial standards

There are no pharmacopoeial standards specific for ocrelizumab. The drug product does comply with the European Pharmacopoeia monographs, “Pharmaceutical Preparations (2619)”, “Parenteral Preparations (0520)”, and “Substances for Pharmaceutical Use (2034)”.

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14. Appendix A

Table 17: Summary of Completed and Ongoing Clinical Studies on Ocrelizumab in Multiple Sclerosis

Protocol No. (Study Name)	Study Design	Diagnosis, Inclusion Criteria	Criteria for Evaluation	Dose, Duration	No. Patients	Study Status
Relapsing Forms of Multiple Sclerosis						
WA21493/ ACT4422g	Placebo-controlled, double-blind, multicenter, dose-finding Phase 2 study.	Patients with relapsing-remitting multiple sclerosis with evidence of recent activity.	Effect on gadolinium-enhancing T1 lesions in the brain; relapse rate; safety and tolerability; pharmacokinetics and pharmacodynamics.	First dose: A: OCR 1000 mg (x2) B: OCR 300 mg (x2) C: placebo (x2) D: IFN 30 mcg IM every week Second dose: A: OCR 1000 mg (x1) B: OCR 600 mg (x1) C: OCR 300 mg (x2) D: OCR 300 mg (x2) Third and fourth doses: A: OCR 1000 mg (Dose 3), 600 mg (Dose 4) (x1) B: OCR 600 mg (x1) C: OCR 600 mg (x1) D: OCR 600 mg (x1) doses separated by 24 weeks.	220 patients enrolled.	Double-blind treatment period complete; open-label extension is ongoing.
MN30035 (CHORDS)	Open-label study to evaluate the effectiveness and safety of ocrelizumab in patients with RRMS who have had a suboptimal response to an adequate course of disease modifying treatment, Phase 3b study.	Patients with RRMS who have had a suboptimal response to an adequate course of a disease modifying treatment.	Effectiveness of ocrelizumab 600 mg IV every 24 weeks over 96 weeks. Safety and tolerability. Patient-reported outcomes related to quality of life and treatment satisfaction.	First dose of ocrelizumab 600 mg given as dual IV infusions of 300 mg x2 separated by 14 days followed by one 600 mg infusion every 24 weeks for the study duration of 96 weeks (last dose administered at Week 72).	608 patients enrolled.	Complete

Protocol No. (Study Name)	Study Design	Diagnosis, Inclusion Criteria	Criteria for Evaluation	Dose, Duration	No. Patients	Study Status
MA30005 (CASTING)	Open-label study to evaluate the efficacy and safety of ocrelizumab, Phase 3b study.	Patients with RRMS who have a suboptimal response to an adequate course of a disease modifying treatment.	Effect on annualized relapse rate; time to onset of sustained disability progression; number of T1 lesions and change in T2 lesion; change in EDSS; brain volume; and cognitive performance safety and tolerability.	First dose of ocrelizumab 600 mg given as dual IV infusions of 300 mg x2 separated by 14 days followed by one 600 mg infusion every 24 weeks for the study duration of 96 weeks (last dose administered at Week 72).	681 patients enrolled.	Complete
MA30143 (ENSEMBLE and ENSEMBLE PLUS sub- study)	Phase 3b, prospective, multicenter, open-label, single-arm effectiveness and safety study in patients with early stage RRMS.	Patient with definite diagnosis of RRMS, confirmed as per the revised McDonald 2010 criteria.	Effect on annualized relapse rate; time to onset of sustained disability progression; effect on T1 gadolinium-enhancing lesions and new/enlarging T2 lesions in the brain; safety and tolerability. ENSEMBLE PLUS: Proportion of patients with IRRs* following shorter duration infusions of ocrelizumab as compared to conventional infusions.	Each ocrelizumab infusion given as a slow IV infusion over approximately 150 minutes (2.5 hours) for the 300 mg dose and approximately 215 minutes (3.6 hours) for the 600 mg dose.	1225 patients enrolled.	Ongoing
WA21092 (OPERA I)	Double-blinded, double-dummy, multicenter Phase 3 study to evaluate the efficacy and safety of ocrelizumab in comparison to IFN.	Patients with relapsing-remitting multiple sclerosis with evidence of recent activity.	Effect on annualized relapse rate; time to onset of sustained disability progression; effect on T1 gadolinium-enhancing lesions and new/enlarging T2 lesions in the brain; safety and tolerability.	Ocrelizumab IV 600 mg every 24 weeks; IFN 44 mcg given SC 3 times per week for 96 weeks. Patients who finish Week 96 visit have the possibility of entering open-label extension of study and receive ocrelizumab IV 600 mg every 24 weeks.	821 patients enrolled.	Double-blind treatment period complete. Open-label extension is ongoing.

Protocol No. (Study Name)	Study Design	Diagnosis, Inclusion Criteria	Criteria for Evaluation	Dose, Duration	No. Patients	Study Status
WA21093 (OPERA II)	Double-blinded, double-dummy, multicenter Phase 3 study to evaluate the efficacy and safety of ocrelizumab in comparison to IFN.	Patients with relapsing-remitting multiple sclerosis with evidence of recent activity.	Effect on annualized relapse rate; time to onset of sustained disability progression; effect on T1 gadolinium-enhancing lesions and new/enlarging T2 lesion in the brain; safety and tolerability.	Ocrelizumab IV 600 mg every 24 weeks; IFN 44 mcg given SC three times per week for 96 weeks. Patients who finish Week 96 visit have the possibility of entering open-label extension of study and receive ocrelizumab IV 600 mg every 24 weeks.	835 patients enrolled.	Double-blind treatment period complete. Open-label extension is ongoing.
BN42082 (MUSETTE)	Controlled, double-blind, multicenter study to evaluate the efficacy, safety, and pharmacokinetics of a higher dose of ocrelizumab Phase 3b study.	Patients with relapsing multiple sclerosis.	Difference in time to cCDP12; time to onset of sustained cCDP; percent change in total brain volume; safety.	2:1 randomization to a higher dose of ocrelizumab 1200/1800 mg and approved dose 600 mg, respectively; at least 120 weeks of treatment.	786 patients planned.	Ongoing
BN29739 (VELOCE)	Phase 3b, multicenter, randomized, open-label study.	Patients with relapsing-remitting multiple sclerosis.	Characterize the humoral immune response (immunoglobulin G [IgG]) to TT adsorbed Vaccine.	Dual infusion of OCR 300 mg x 2 on Day 1 and Day 15 during immunization study period (12-24 weeks, depending on assigned group). Followed by Optional OCR Extension with single infusions of 600 mg OCR every 24 weeks (split of first dose depending on assigned group) until 4 years after end study immunization period.	102 patients randomized.	Completed

Protocol No. (Study Name)	Study Design	Diagnosis, Inclusion Criteria	Criteria for Evaluation	Dose, Duration	No. Patients	Study Status
WA39085 (OPERETTA 1)	Phase 2, open-label, multicenter, PK-PD study.	Children and adolescents with relapsing-remitting multiple sclerosis.	To characterize the PK and PD profiles of ocrelizumab.	Cohort 1: 300 mg OCR for patients with a body weight ≥25 kg and <40kg Cohort 2: 600 mg OCR in patients with a body weight >40 kg 24-week dose exploration period followed by an optional OCR extension period of 72 weeks.	12 to 24 patients planned.	Ongoing
ML42071 (CHIMES)	Phase 4, open- label, multicenter study.	Self-identified Black and Hispanic patients aged 18–65 years with a diagnosis of RMS in accordance with the revised 2017 McDonald Criteria, EDSS 0–5.5 inclusive at enrollment.	To assess disease activity and biomarkers of neuronal damage.	Ocrelizumab 600 mg IV six-monthly over 48 weeks (optional 96 weeks extension).	150 patients planned.	Ongoing
ML29966 (OBOE)	Phase 3b, open-label, multicenter, biomarker study.	Patients with relapsing multiple sclerosis and primary progressive multiple sclerosis.	To assess neurofilament light on neuronal damage in CSF, CD19+ B cells in CSF, CD3+ T cells in CSF.	For RMS: OCR 300 mg IV infusions Day 1 and Day 15. For PPMS: OCR 600 mg will be administered as two 300 mg IV infusions separated by 14 days at a scheduled interval of every 24 weeks.	132 patients Randomized.	Ongoing Patients are in long-term extension phase.

Protocol No. (Study Name)	Study Design	Diagnosis, Inclusion Criteria	Criteria for Evaluation	Dose, Duration	No. Patients	Study Status
WN42086 (OPERETTA 2)	Multicenter, randomized, double-blind, double-dummy phase 3 study.	Children and adolescents with relapsing-remitting multiple sclerosis.	To evaluate safety and efficacy of OCR administered by IV infusion every 24 weeks compared with fingolimod taken orally daily.	Experimental arm: ● OCR will be administered at 600 mg by IV infusion on Day 1 and Day 15 (half the dose, 2 weeks apart) and every 24 weeks thereafter. ● Other: Fingolimod placebo will be administered daily as a capsule. Active control arm: ● OCR placebo will be administered by IV infusion on Day 1 and Day 15 and every 24 weeks thereafter. ● Fingolimod will be administered daily as 0.5 mg capsule.	233 planned.	Ongoing
Primary Progressive Multiple Sclerosis						
WA25046 (ORATORIO)	Placebo-controlled, double-blinded, multicenter, Phase 3 study.	Patients with primary progressive multiple sclerosis.	Effect on time to onset of sustained disability progression; total volume of T2 lesions in the brain; safety and tolerability.	Ocrelizumab 600 mg given as dual IV infusions of 300 mg x2 separated by 14 days for all treatment doses; at least 120 weeks of treatment.	732 patients enrolled.	Double-blind treatment period complete. Open-label extension is ongoing.
WA40404 (ORATORIO-HAND)	Placebo-controlled, double-blinded, multicenter, Phase 3b study.	Patients with primary progressive multiple sclerosis,	Effect on upper extremity disability progression; time to onset of sustained disability progression; total	First dose of ocrelizumab 600 mg given as dual IV infusions of 300 mg x2 separated by 14 days	Approx. 1000 patients planned.	Ongoing

Protocol No. (Study Name)	Study Design	Diagnosis, Inclusion Criteria	Criteria for Evaluation	Dose, Duration	No. Patients	Study Status
		including patients later in their disease course.	volume of T2 lesions in the brain; and safety.	followed by one 600 mg infusion every 24 weeks; at least 120 weeks of treatment.		
BN42083 (GAVOTTE)	Controlled, double-blind, multicenter study to evaluate the efficacy, safety, and pharmacokinetics of a higher dose of ocrelizumab, Phase 3b study.	Patients with primary progressive multiple sclerosis.	Difference in time to cCDP12; time to onset of sustained cCDP; percent change in total brain volume; safety.	2:1 randomization to a higher dose of ocrelizumab 1200/1800 mg and approved dose 600 mg, respectively; at least 120 weeks of treatment.	699 patients planned.	Ongoing
MN39159 (CONSONANCE)	Prospective, multicenter, open-label, single-arm Phase 3b effectiveness and safety study.	Patients with PMS (as per the revised McDonald 2010 criteria for PPMS or Lublin et al. (26) criteria for PMS).	To evaluate the effectiveness and safety of ocrelizumab in PMS patients.	First dose of ocrelizumab 600 mg given as dual IV infusions of 300 mg x2 separated by 14 days followed by one 600 mg infusion every 24 weeks.	900 patients planned.	Ongoing
Multiple Sclerosis (progressive or relapsing)						
MN39158 (LIBERTO)	Single-arm, open-label, multicenter, Phase 3b/4 extension study.	Patients with multiple sclerosis who have previously completed treatment in a Roche- sponsored ocrelizumab trial.	Tolerability and effectiveness information from patients with long- term exposure.	Ocrelizumab 600 mg given as single IV infusions every 24 weeks, up to Week 72.	No formal sample size.	Ongoing

Protocol No. (Study Name)	Study Design	Diagnosis, Inclusion Criteria	Criteria for Evaluation	Dose, Duration	No. Patients	Study Status
CN41144 (OCARINA 1)	Phase Ib, open- label, multicenter, pharmacokinetics study.	Patients with relapsing multiple sclerosis and primary progressive multiple sclerosis.	To investigate the pharmacokinetics, safety, and tolerability of subcutaneous ocrelizumab being equivalent to administration 600 mg IV dose.	During dose escalation phase: single dose of SC ocrelizumab in a dose-escalating manner until the SC dose is identified. One group then receiving a single 600 mg dose of IV ocrelizumab or the identified SC dose (randomized in 1:1 ratio). During dose continuation phase: identified SC dose every 24 weeks.	135 patients recruited.	Ongoing
BA39730 (MANUSCRIPT)	PASS. Multisource, multi-country, noninterventional, longitudinal cohort study (secondary use of data).	Patients with MS after initiation of ocrelizumab or another DMT during the study period, or not on DMT therapy in routine clinical practice.	To characterize the long-term safety data from the use of ocrelizumab in patients with MS, including serious infections and malignancies.	Follow-up of patients on ocrelizumab or other DMT as per standard of care for up to 10 years.	Approx. 8500 patients (4500 from ML39632 / CONFIDENCE study) planned.	Ongoing

Protocol No. (Study Name)	Study Design	Diagnosis, Inclusion Criteria	Criteria for Evaluation	Dose, Duration	No. Patients	Study Status
ML40638 (SaROD)	Open-label, nonrandomized study.	Patients with PPMS and RMS.	To evaluate the safety and tolerability of shorter infusions of ocrelizumab.	Cohort 1: One or two doses of 600 mg ocrelizumab according to the approved infusion protocol (US label). Dose 2 or 3: 600 mg IV ocrelizumab per a shorter infusion protocol. Cohort 2: Dose 1 of ocrelizumab as two split 300 mg IV infusions 14 days apart. The first infusion will be administered per the US label; the second infusion will be administered per a shorter infusion protocol.	141 patients enrolled.	Complete
ML39632 (CONFIDENCE)	Prospective, multicenter, noninterventional, long-term study (primary data collection in Germany).	RMS and PPMS patients newly treated with ocrelizumab, or other selected MS DMTs in routine clinical practice.	Long-term safety and effectiveness data of ocrelizumab in the real-world setting.	Observational study, all treatments received as per standard of care; up to 10 years, once the initial dose of ocrelizumab (dosing as per label), or other selected MS DMTs, has/have been administered to the patient.	3767 MS patients planned.	Ongoing
BA39731 (VERISMO)	Prospective, noninterventional, longitudinal, observational study (primary data collection).	MS patients who have newly initiated treatment with ocrelizumab or other DMTs according to the local routine clinical practice.	Incidence and mortality rates of all malignancies, including breast cancer, and the long-term safety regarding SAEs.	Observational study: all treatment received as per standard of care. Follow-up of a minimum of 6.5 years or until death (whichever comes first).	1366 MS patients from the United States and 3767 from Germany (ML39632/ CONFIDENCE study) planned.	Ongoing

Protocol No. (Study Name)	Study Design	Diagnosis, Inclusion Criteria	Criteria for Evaluation	Dose, Duration	No. Patients	Study Status
WA40063 (Pregnancy Registry)	Prospective non-interventional observational registry (primary data collection).	Pregnant women with MS who have been exposed to ocrelizumab (during the 6 months prior to their last menstrual period) or who have not been exposed to ocrelizumab.	To assess and characterize frequency of maternal, fetal, and infant outcomes among women with MS exposed to ocrelizumab during the 6 months before the estimated date of conception or at any time during pregnancy.	Observational study with total duration of participation up to 21 months, and the expected total duration of the study is approx. 10 years.	580 pregnant women with MS planned.	Ongoing
BA39732 (MELODIC)	Observational cohort study, (secondary data use from US and Danish data sources).	Ocrelizumab-exposed pregnancies in women with MS, pregnancies not exposed to ocrelizumab in women with MS, and pregnancies not exposed to ocrelizumab in women without MS.	To assess and characterize pregnancy and infant outcomes of women with MS exposed to ocrelizumab during the 6 months before the estimated date of conception or at any time during pregnancy.	Observational study, monitored annually for a maximum of 11 years.	Approx. 7035 pregnancies (accrued from four data sources) planned.	Ongoing

Protocol No. (Study Name)	Study Design	Diagnosis, Inclusion Criteria	Criteria for Evaluation	Dose, Duration	No. Patients	Study Status
MN42988 (MINORE)	Global, prospective, multicenter, open-label study.	Women with MS/CIS and a singleton pregnancy at ≤gestational week 30, whose last OCR infusion was ≤6 months before the LMP, or in the first trimester.	To assess whether placental transfer of OCR occurs, and its impact on B cell development and other outcomes in infants potentially exposed during pregnancy.	As per local labeling (initial split dose of two 300 mg infusions or as a single 600 mg infusion; with pre-treatment with methylprednisolone (or equivalent).	44 planned.	Ongoing
MN42989 (SOPRANINO)	Global, prospective, multicenter, open-label study.	Women with MS/CIS willing to breastfeed after OCR infusion whose infants are 2-24 weeks old at the first postpartum OCR dose.	To assess whether OCR is transferred into breastmilk, and its impact on infant B cell development and other outcomes in infants potentially exposed via breastfeeding.	As per local labeling (initial split dose of two 300 mg infusions or as a single 600 mg infusion; with pre-treatment with methylprednisolone (or equivalent).	22 planned (along with their infants).	Ongoing

15. Appendix B

Appendix B outlines the search methodology used from systematic literature review searches periodically conducted by the applicant, and the summarized main findings from these reviews from 2018 to January 2022. The final results were reviewed for relevance.

Literature search methodology

Since the first approval of ocrelizumab, systematic literature searches have been conducted periodically (at least annually) by the applicant to review publications reporting the benefit of ocrelizumab in MS on the electronic databases, including annual congress publication databases for ECTRIMS (European Committee for Treatment and Research in Multiple Sclerosis) and ACTRIMS (American Committee for Treatment and Research in Multiple Sclerosis), BIOSIS Previews®, Derwent Drug File, Embase®, Medline®, and Cochrane Library website, using the following terms:

- Ocrelizumab
- Ocrevus

Search data was then filtered through prospectively defined inclusion/exclusion criteria. Based on these criteria, publications presenting single-case studies (which would not affect the benefit-risk profile) were excluded. Reports of randomized controlled trials (RCTs) published in the form of a letter or editorial were also excluded. As the final steps, only reports of use in the approved indications and that included evaluation of standard important endpoints in RMS and PPMS (e.g., annualized relapse rate (ARR), confirmed disability progression (CDP), gadolinium-enhancing T1 lesion, T2 hyperintense lesion, T2 lesion volume, and T1 hypointense lesion) were included. The publications were then assessed to identify whether the importance of the evidence could significantly change the benefit-risk profile of ocrelizumab. For those considered to have the potential to affect the benefit-risk profile, the following prospectively defined rules were used to assess the weight of evidence:

- Sample size: >100 patients (strong evidence); 30-100 patients (moderate); <30 patients (weak)
- Study design: interventional RCT (strong); interventional non-RCT (moderate); observational trials (weak)
- Study design: prospective study (strong); retrospective study (moderate to weak)
- Statistical considerations
- Reported methodology (strong); not reported (weak)
- Prospective analysis (strong); retrospective analysis (moderate to weak)
- Powered analysis (strong); non-powered analysis (moderate to weak)
- Patients' baseline characteristics: reported

Literature search results

1. Fox et al. (105) performed an exploratory analysis to examine the effects of ocrelizumab on confirmed progression and confirmed improvement in upper extremity impairment in patients from ORATORIO. The results showed that ocrelizumab reduces the risk of upper extremity disability progression and may increase the possibility of improvement versus placebo in PPMS. Among intention-to-treat patients, ocrelizumab significantly reduced the change in Nine-Hole Peg Test time over 120 weeks, the risk of confirmed progression of ≥ 20% in Nine-Hole Peg Test time for both hands, and the risk of more severe Nine-Hole Peg Test progression vs. placebo. Numerical trends also favored ocrelizumab vs. placebo with respect to achieving confirmed improvement. Consistent directional trends were observed in subgroup analyses.

2. Wolinsky et al. (106) investigated the effect of ocrelizumab on no evidence of progression or active disease (NEPAD) comprehensive outcome and its components in a post-hoc analysis in patients with PPMS. The results showed that most ORATORIO study patients with PPMS experienced clinical progression or evidence of disease activity. From baseline to Week 120, 29.9% and 42.7% ocrelizumab-treated compared to 9.4% and 29.1% placebo-treated patients maintained NEPAD (relative risk [95% CI], 3.15 [2.07–4.79]; $p < 0.001$) and no evidence of progression (relative risk [95% CI], 1.47 [1.17–1.84]; $p < 0.001$), respectively. Effects on the individual components of both measures were consistent with the compound outcomes. Further, it was concluded that ocrelizumab enhanced the proportion of PPMS patients with no evidence of either progression or inflammatory disease activity three-fold, as compared to placebo. No evidence of progression or active disease may represent a sensitive and meaningful comprehensive measure of disease control in patients with PPMS.

3. Barkhof et al. (107) assessed the onset of ocrelizumab efficacy on brain MRI measures of disease activity in the phase 2 study in RRMS and relapse rate in the pooled phase 3 studies in RMS. Ocrelizumab reduced the number of new T1 Gd-enhancing lesions by Week 4 and Week 8 in RRMS patients. Ocrelizumab also reduced the number of new or enlarging T2 lesions appearing between weeks 4 and 8 vs. both placebo and IFNβ1a (both $p < 0.001$) in RRMS patients. Ocrelizumab significantly reduced Annualized Relapse Rate (ARR) ($p=0.005$) and the probability of time to first protocol-defined relapse ($p=0.014$) in RMS patients. This study reveals that for patients with RRMS and RMS, ocrelizumab suppressed MRI activity within four weeks and clinical disease activity within eight weeks.

4. Elliott et al. (108) assessed the effect of ocrelizumab vs. placebo on the accumulation of T1 hypointense lesion volume related to chronic lesion activity. There was a larger decrease in mean normalized T1 signal intensity and greater relative accumulation of T1 hypointense volume in slowly expanding/evolving lesions (SELs) compared with non-slowly expanding/evolving lesions (non-SELs). The study showed that ocrelizumab, which is highly effective in silencing acute new lesion formation in early RMS and PPMS, also reduced the relative volume of SELs and T1-weighted *in vivo* measures of chronic lesion activity in SELs and in non-SEL areas of pre-existing lesions in patients with PPMS.

5. Turner et al. (109) demonstrated the treatment effects of ocrelizumab, versus IFNβ1a, for the treatment of RMS, across subgroups of patients with different baseline characteristics; the efficacy of ocrelizumab in patient subgroups relating to disability and clinical and MRI disease activity; and the efficacy of ocrelizumab in both treatment-naïve patients and those previously treated with DMT. The significant reduction in ARR observed in the overall pooled analysis of the Intention-to-Treat (ITT) population with ocrelizumab relative to IFNβ1a was maintained across the majority of subgroup levels. This study is described in more detail in Section 0.

6. Leist et al. (110) reported one-year interim analysis results of the multicenter, open-label, Phase 3b CHORDS study (NCT02637856) evaluating ocrelizumab effectiveness and safety in patients with RRMS and a suboptimal treatment response to ≥6 months of DMT. Results of this interim analysis of patients with RRMS who had one year of follow-up in the CHORDS study suggest that ocrelizumab is effective and safe in patients with a suboptimal response to an adequate course of a prior DMT.
7. Vermersch et al. (111) reported one-year interim results of no evidence of disease activity (NEDA) (primary efficacy endpoint), assessed every 24 weeks, in CASTING study. The aim of this prospective,

multicenter, single arm phase 3b study (NCT02861014) was to evaluate the efficacy and safety of ocrelizumab in patients with RRMS who had a suboptimal response to an adequate course of one or two DMTs. The proportion of patients with NEDA was measured by an absence of protocol-defined relapses, 24-week CDP, T1 Gd-enhancing lesions, and new/enlarging T2 lesions, calculated using the modified ITT population. The results showed that most patients in CASTING had no evidence of MS disease activity. As future data becomes available and is reported, CASTING will describe additional data on the efficacy and safety of ocrelizumab treatment in patients who had ongoing disease activity while receiving another DMT.

8. Wolinsky et al. (10) assessed the effects of maintaining or switching to ocrelizumab therapy on measures of disease progression and safety in the OLE phase of the randomized, placebo-controlled, phase 3 trial of ocrelizumab for PPMS (ORATORIO). The post-hoc analysis from the ongoing OLE of ORATORIO showed that the proportion of patients with 24-week CDP on individual and composite measures of disability from the double-blind baseline remained lower in patients receiving continuous ocrelizumab compared with those switching from placebo to ocrelizumab at the end of the double-blind period (DBP). Compared with patients switching from placebo, earlier and continuous ocrelizumab treatment provided sustained benefits on measures of disease progression over the six and a half (6.5) years of study follow-up.

9. Arnold et al. (112) assessed the efficacy of ocrelizumab on thalamic atrophy in patients with RMS and PPMS participating in the OPERA I/II and ORATORIO phase 3 trials switching to or maintaining ocrelizumab therapy, respectively. This study showed that in the OLE, patients with RMS and PPMS who were initially randomized to ocrelizumab experienced significantly less thalamic volume (TV) loss compared with those initiating ocrelizumab later.

10. Bar-Or et al. (113) examined the independent impact of ocrelizumab and baseline blood neurofilament light chain (NfL) on TV and clinical progression in patients with PPMS and RMS, including those with RMS without acute baseline activity (i.e., no Gd-enhancing lesions or relapse in the last three months) from week 24 until the end of the controlled treatment (ORATORIO Week 120, OPERA I/II Week 96). Ocrelizumab treatment remained associated with reduced thalamic atrophy and clinical progression after adjusting for baseline NfL and other factors. Higher baseline NfL was associated with increased rates of thalamic atrophy and clinical progression in patients with PPMS and those with RMS without acute disease activity.

11. Bar-Or et al. (114) assessed whether NfL levels measured before and during ocrelizumab treatment were associated with brain volume changes in patients with PPMS and RMS. Longitudinal blood NfL and brain MRI data from patients with PPMS (ORATORIO) and RMS (OPERA I) were analyzed in batches. Brain atrophy was calculated as percentage brain volume change from Week 24 to the end of the controlled treatment period (Week 120 in ORATORIO, Week 96 in OPERA I). Log-transformed NfL, normalized brain volume, log-transformed T2 lesion volume (T2LV), T1 Gd-enhancing lesion count, age, and Expanded Disability Status Scale (EDSS) at baseline were examined for associations with brain atrophy within each study. Lower baseline NfL levels and treatment with ocrelizumab were both associated with lesser brain volume loss in PPMS and RMS, independent of clinical and MRI measures of disease severity. During ocrelizumab treatment, blood NfL levels measured for up to 120 weeks in patients with PPMS and for the first 24 weeks in RMS correlate with brain atrophy.

12. Jia et al. (115) assessed whether NfL levels measured before and during ocrelizumab treatment were associated with brain volume changes in patients with PPMS or RMS. Longitudinal blood NfL and brain MRI data from patients with PPMS (ORATORIO; n=399) or RMS (OPERA I; n=477) were analyzed. Lower baseline NfL levels and treatment with ocrelizumab were both associated with lesser brain volume loss in PPMS and RMS, independent of measures of disease severity.

13. Wiendl et al. (116) reported results from the Phase 3b CASTING study (NCT02861014) of ocrelizumab that evaluated the efficacy/safety in patients with RRMS who had a prior suboptimal response to one or two DMTs (primary endpoint: two-year NEDA rate). The NEDA rate was high overall and across a wide range of disease-related and demographic subgroups, regardless of prior treatment background.

14. Arnold et al. (117) assessed ocrelizumab effect versus IFNβ1a/placebo on cerebellar atrophy in RMS/PPMS, in the phase 3 OPERA and ORATORIO trials, respectively. The results showed that ocrelizumab reduced cerebellar atrophy in RMS, compared with IFNβ1a. An analysis of the studies demonstrated that individuals initially treated with ocrelizumab maintained lower cerebellar volume loss relative to baseline in both RMS and PPMS during the OLE periods vs. those initially treated with comparators.

15. Bhattacharyya et al. (118) performed a retrospective review of MRI in patients with MS treated with ocrelizumab in the CLIMB cohort at Brigham and Women's Hospital. The results showed that there were 25 MRI relapses identified in 24 (6.2%) patients (23 new Gd-enhancing, one new restricted diffusion, one new T2 lesion). Patients with MRI activity were 63% female with mean age of 41.4 (SD 11.3) years, median EDSS of three, of whom 79% had RRMS and 21% had SPMS. There were two distinct patterns of relapse. The predominant pattern was gadolinium enhancement or restricted diffusion of an old T2 lesion present prior to start of ocrelizumab. This pattern occurred in 14 MRI scans (six brains, eight spinal cords) acquired a median of nine months after ocrelizumab start. The second pattern was new lesion formation, present in 11 MRI scans (eight brains, three spinal cords) obtained a median of five months after ocrelizumab start.

16. Bigaut et al. (119) performed an observational study to compare ocrelizumab to fingolimod after natalizumab cessation in patients with RRMS. The authors included 54 patients receiving fingolimod and 48 patients receiving ocrelizumab after natalizumab cessation. In multivariate analysis, ARR at one year was significantly lower in the ocrelizumab group than in the fingolimod group (0.12±0.39 versus 0.41±0.71, p=0.035), i.e., a 70.7% lower relapse rate. The cumulative probability of relapses at one year was 31.5% (17/54 patients) with fingolimod and 10.4% (5/48 patients) with ocrelizumab, corresponding to a hazard ratio (HR) of 3.4 (95%CI: 1.1-11, p=0.04). The study results suggest ocrelizumab is potentially a better exit strategy than fingolimod after natalizumab cessation.

17. Braune et al. (15) performed real-world data analysis using the NeuroTransData registry, a network of 66 neurology outpatient services across Germany. The analysis included 460 PPMS patients, of which 82 were treated with ocrelizumab. The ocrelizumab-treated patients were younger (mean age 51.5, SD 10.03 vs. 62.29, SD 11.35), had a shorter time from first PPMS symptoms (mean 8.69 years, SD 7.84 vs. 18.74, SD 10.98), and had similar EDSS levels (mean 4.44, SD 1.84 vs. 4.99, SD 2.13) compared to the overall PPMS cohort. The mean exposure time to ocrelizumab was 1.5 years (SD 0.73). During the

observation period, no significant change in EDSS was noted. Persistence at 12 and 24 months was 98.7% (76/77) and 94.8% (73/77) respectively, and administration of infusions followed the recommended schedule (median time interval between infusions 2-8: 5.82-6.32 months). Critical factors for achieving therapeutic goals (e.g., persistence and adherence to recommended dose regimes) were high. Longer observation times are needed to further expand real-world experience of ocrelizumab therapy on disability outcomes.

18. Buttmann et al. (120) performed analyses on ocrelizumab effectiveness in patients with RMS, patients who were treatment naïve (TN), and those with prior MS-specific therapies (PMST) in the CONFIDENCE study, over the course of 18 months. In total, 1510 ocrelizumab-treated patients with RMS were included in this analysis. In the ocrelizumab-treated RMS population with at least 18 months of follow-up, the mean change (SD) in EDSS was 0.06 (0.74; n=477). Patients with ≥3 PMST had a comparable EDSS change (0.08 [0.71; n=187]), while TN patients had a slight decrease in EDSS (-0.03 [0.93; n=64]). In the ocrelizumab-treated population with RMS, the proportion of patients that remained relapse-free was 88.90% within the first 6 months, 93.26% within 6-12 months, and 95.18% within 12-18 months. The proportions of relapse-free TN vs. ≥3 PMST patients were 91.82% vs. 85.08% within 6 months, 99.32% vs. 90.84% within 6-12 months, and 97.80% vs. 93.86% within 12-18 months, respectively. It was concluded that over 18 months, patients treated at an early line with ocrelizumab retained a low mean baseline Expanded Disability Status Scale. Most ocrelizumab-treated patients with RMS in CONFIDENCE remained relapse free, with the highest proportion in the TN population.

19. Butzkueven et al. (11) performed a post ad hoc analysis assessing time to 24-week confirmed EDSS ≥7.0 in two cohorts of patients with PPMS (baseline EDSS 3.0–6.5) in ORATORIO and MSBase. The results revealed that in the ORATORIO double-blind and extended controlled periods, ocrelizumab reduced the risk of 24-week confirmed EDSS ≥7.0 (HR = 0.54, 95% CI: 0.31–0.92; p = 0.022). Extrapolated median time to 24-week confirmed EDSS ≥7.0 was 12.1 and 19.2 years for placebo and ocrelizumab, respectively (7.1-year delay [95% CI: −4.3 to 18.4]). In MSBase, the median time to 24-week confirmed EDSS ≥7.0 was 12.4 years. The authors concluded that compared with placebo, ocrelizumab significantly delayed time to 24-week confirmed wheelchair requirement in ORATORIO. The plausibility of the extrapolated median time to reach this milestone in the placebo group was supported by observed real-world data from MSBase. Extrapolated benefits of ocrelizumab over placebo could represent a truly meaningful delay in loss of ambulation and independence.

20. Butzkueven et al. (16) assessed the long-term effectiveness of ocrelizumab in RMS patients in a real-world setting for clinical relapses and long-term disability accrual (progression or improvement), discontinuation rates, and persistence on ocrelizumab therapy. This real-world study confirms ocrelizumab as a high-efficacy DMT for relapsing MS, with very low discontinuation rates.

21. Cellerino et al. (121) reported short- to medium-term efficacy data in a real-world population of progressive multiple sclerosis (PMS) patients treated with ocrelizumab, including a relatively high proportion of patients without MRI activity at baseline assessment. The authors recorded data from 59 PMS patients (42 PPMS and 17 SPMS, 24 females, mean [SD] age 49.8 [8.2] years) with mean disease duration of 12.1 (10.1) years, median (interquartile range [IQR]) baseline EDSS: 5.5 (3.5-6.0) and median number of previous DMTs 1 (0-2). SPMS patients had longer disease duration (20.8 vs. 8.6; p=0.004) and had mean ARR of 0.24 (0.4). Twenty-one (36%) patients were TN. Mean follow-up was 2.0 (1.1) years.

Fourteen (24%) patients had an active MRI brain scan at baseline. At one-year follow up, MRI-inflammatory-activity-free survival was 87.3% (95% CI: 76.9-97.7%), relapse-free survival was 100%, and progression-free survival was 82.7% (72.3-93.1%). NEDA-3 status was achieved in 72.3% (59.0-85.5%) of patients. No differences were noted between PPMS and SPMS. The data suggests that ocrelizumab should be considered as a treatment option both in patients with PPMS and SPMS.

22. Cellerino et al. (17) conducted a study to provide effectiveness and safety data of ocrelizumab treatment in patients with RRMS and PMS and evaluated clinical and immunological predictors of early treatment response. The authors suggested that ocrelizumab is an effective treatment in real-world patients with RRMS and progressive MS, with a manageable safety profile. Better outcomes were observed in treatment-naïve patients and in patients with a low baseline disability level. Depletion of CD8 + cells could underlie early therapeutic effects of ocrelizumab.

23. Cellerino et al. (18) observed that ocrelizumab is a good and globally safe treatment option in patients with RRMS, PPMS, and SPMS, especially if initiating treatment in the early phases of the disease and for treatment-naïve patients. A total of 153 subjects were included in the analysis (93 RRMS, 43 PPMS, 17 SPMS; 60% females); baseline mean (SD) age was 41.9 (11.4) years, mean (SD) disease duration (DD) 10.3 (9.9) years, mean (SD) ARR 0.5 (0.7), and median (IQR) EDSS 3.5 (2-5.5). At two-year follow-up, percentage disability worsening-free patients was 90.5%, 64.7%, and 68.8%, of MRI-activity-free patients 67.1%, 72.7%, and 81.3%, and of NEDA-3 patients 62.1%, 54.6%, and 55.1% for RRMS, PPMS, and SPMS, respectively. Lower baseline EDSS, shorter disease duration, younger age, higher ARR, and baseline MRI activity were associated with reduced risk of disability worsening, while previous DMT exposure and baseline MRI activity were associated with increased risk of radiological activity. Treatment-naïve patients had higher probability of achieving NEDA-3. The data suggest that higher levels of CD8+ cells could be associated with early inflammatory activity.

24. Coban et al. (71) performed a retrospective observational analysis of MS patients who were treated with ocrelizumab from 31 March 2017 to 30 April 2020. The results revealed that 50% of patients had at least one adverse event (AE) while on ocrelizumab; 4.8% had AEs requiring ocrelizumab discontinuation, 36% had IRRs, and 7.3% had viral infections. The author found two cases of severe babesiosis, along with index cases of re-activation of lichen planus, agranulocytosis, severe lymphopenia, and ectopic pregnancy. There were no cases of malignancy, progressive multifocal leukoencephalopathy, or death within the cohort. The mean time after ocrelizumab initiation was 17.3 months in the RRMS group, 22.2 months in the PPMS group, and 28.2 months in the SPMS group. The annualized relapse rate reduced from 1.33 to 0.15 in the RRMS group. The mean EDSS scores did not worsen across MS phenotypes and ethnic groups while being treated with ocrelizumab.

25. Epstein et al. (122) performed retrospective chart review for patients older than 55 with PPMS or SPMS at the time of ocrelizumab initiation and found no difference in clinical endpoints for patients on ocrelizumab compared to the two years prior to anti-CD20 therapy; however, the authors could not exclude a modest effect given the sample size and noted that larger trials would be needed to evaluate ocrelizumab use in this understudied MS subpopulation.

26. Glanz et al. (123) examined the impact of ocrelizumab on health-related quality of life (HRQOL) in individuals with MS. The author observed significant improvements across multiple mental HRQOL

domains at 12 months in individuals treated with ocrelizumab. These findings support the use of HRQOL measures to provide a subjective measure of treatment impact that complements traditional outcomes.

27. Hersh et al. (124) compared time to improvement in each Quality of Life in Neurological Disorders domain in patients treated with natalizumab vs. ocrelizumab. The authors concluded that natalizumab treatment can shorten the time to clinically meaningful improvement in the Quality of Life in Neurological Disorders domains of cognition and satisfaction with social roles and activities compared with ocrelizumab. The results complement previous findings from MS PATHS indicating that natalizumab treatment can produce meaningful improvements in mental and social health, with overall annualized improvement rates higher than those observed with ocrelizumab.

28. Jungquist et al. (125) measured symptom burden using SymptoMScreen, Quality of Life in Neurological Disorders, and Work Productivity and Activity Impairment (WPAI):MS at three points in each infusion cycle over two infusion cycles and obtained ocrelizumab concentration (PK), NfL, B-cell subsets, and routine clinical labs prior to each infusion. SymBOLS, designed to assess the wearing-off effect in ocrelizumab-treated patients, had successfully enrolled 110 patients across two US sites. Preliminary data suggests there are no changes to symptom burden during the first half of the infusion cycle. Additional data regarding changes during the second half of the cycle, as well as Neuro-QoL (Neurology Quality of Life) and WPAI data, would be needed for further evaluation.

29. Lanzillo et al. (126) explored the potential impact of early ocrelizumab introduction and its efficacy on disability accrual in MS patients. The author included 89 relapsing and 294 progressive patients, with 217 patients following up for more than 12 months. Both relapsing and progressive patients showed an increased EDSS at baseline compared to the year before ocrelizumab start (coeff. = 0.18, 95%CI = 0.30–0.34, p = 0.02; coeff. = 0.28, 95%CI = 0.18–0.37, p < 0.001), while no further increase was observed after one year. Patients naïve to DMTs showed a decreased EDSS one year after ocrelizumab treatment compared with EDSS at baseline (relapsing: coeff. = −0.29, p = 0.02; progressive: coeff. = −0.33, p = 0.01). Patients with a time from conversion shorter than five years showed an increased EDSS between one year before ocrelizumab start and baseline (coeff. = 0.42, 95%CI = 0.12–0.72, p = 0.005), with no EDSS increase in the following year (p = 0.38). The author observed that naïve patients and those with a time-from-conversion shorter than five years were better responders to ocrelizumab; the study highlighted the need to treat patients as early as possible to be able to affect disease trajectory in the therapeutic window.

30. Lanzillo et al. (19) collected data for ocrelizumab from a real-world setting and explored potential impact of early treatment introduction and its efficacy on disability accrual. The authors observed that naïve patients and those with a time-from-conversion shorter than five years were better responders to ocrelizumab. The study highlighted the need to treat patients as early as possible to be able to affect disease trajectory in the therapeutic window. In addition, the study also highlights the need to tailor treatment according to patient characteristics to achieve the maximum effect from DMTs.

31. Laplaud et al. (127) reported the interim analysis findings from a phase 4 study evaluating the efficacy, safety, and impact of ocrelizumab on PROs in patients with active RMS. This interim analysis included data from 335 patients at Week 48. Most patients (65.1% [95%CI 59.7%-70.2%]) were free of all protocol-defined disease activity events. Regarding individual activity events, 87.2% of patients were

relapse-free at Week 48, 83.6% had no T1 Gd-enhancing lesions, and 76.1% had no new/enlarging T2 lesions. The adjusted ARR (0.13) was low. There were no deaths, and safety results were consistent with prior studies.

32. Lapucci et al. (128) evaluated efficacy and safety of MS patients who switched to ocrelizumab due to persistence of disease activity after two courses of alemtuzumab. The mean follow-up from ocrelizumab started: 7.9±7.4 months for 23 MS patients. Results showed that four (17.4%) patients had a relapse after ocrelizumab start (one during the interval between first and second ocrelizumab infusion and three patients after three, 11, and 15 months from ocrelizumab start. Four (17.4%) patients showed only radiological activity at three (n=2), four (n=1), and nine months (n=1). Infusion-associated reactions occurrence was lower than alemtuzumab courses ($p<0.05$); mild upper airways (n=1), urinary infections (n=1), appendicectomy (n=1), and fever due to probable Sars-Cov2 infection (n=1). No patients showed T CD4+ cell count <200 cell/mm^3 at three months, six months, or one year; B CD19+ cell depletion (<5 cell/mm^3) was confirmed at three months, six months, and one year, with the exception of one patient (B CD19+ count 12 cells/mm^3 at six-month follow-up [n=12 patients]). Ten (43.4%) patients developed hypogammaglobulinemia without infectious events and no alemtuzumab-related new complications occurred. This short-term follow-up suggests that the switch to ocrelizumab in MS after two alemtuzumab courses was characterized by a good safety and efficacy profile.

33. Manchon et al. (129) reported the interim analysis of PRO-MSACTIVE phase 4 study data. This interim analysis included data at Week 48 from 335 patients who had completed their treatment period before COVID-19 lockdown. Improvement from baseline total mean (SD) scores were observed for SymptoMScreen (-1.3 [8.8]), Modified Fatigue Impact Scale (MFIS) (-2.9 [13.47]), EQ-5D-5L with visual analogue scale (VAS) health state score (+4.07 [17.02]), WPAI:SHP activity impairment (-5.31 [23.65]), MusiQoL (+1.52 [11.0]), and TSQM-14 (+8.13 [21.39]). TSQM-14 total mean (SD) score improved from 59.7 (19.69) to 68.55 (20.03). The largest improvements from baseline were observed for MusiQoL on the psychological wellbeing, coping, and activities of daily living domains. EDSS score was improved (<-0.5) or stable (-0.5; +0.5) for 85.4% of patients. It was concluded that in PRO-MSACTIVE, patients with active RMS reported improvement in PROs from baseline to Week 48.

34. Nicholas et al. (130) compared claims-based relapses and relapse-related hospitalization rates for MS patients treated with natalizumab or ocrelizumab using data from a large insurance claims database. This analysis included 835 natalizumab and 3,497 ocrelizumab patients. After inverse probability weighting, natalizumab (n=4342) and ocrelizumab (n=4333) patients were well balanced with all standardized differences ≤0.1. Mean follow-up time was approximately 0.9 and 1.0 years for natalizumab and ocrelizumab patients, respectively. Natalizumab patients had longer time to first relapse vs. ocrelizumab, with HR significantly favoring natalizumab (0.70 [95%: 0.55-0.88]; $P<0.01$). The HR for time to first MS-related emergency room visit did not differ significantly between groups. Mean annualized rates were significantly lower with natalizumab than with ocrelizumab for any relapse (0.30 vs. 0.43; mean difference: -0.13 [95% CI: -0.25, -0.02]; P=0.02) and outpatient relapse (0.22 vs. 0.36; mean difference: -0.14 [95% CI: -0.24, -0.04]; P=0.01) but did not differ for MS-related emergency room visits (0.09 vs. 0.08; P=0.82) and relapse-related hospitalizations (0.07 vs. 0.07; P=0.83).The authors concluded that the rates of relapses overall were significantly lower with natalizumab than with ocrelizumab. Though relapses were insurance claims-based and not physician-reported, these results

provide a direct comparison of relapse-related outcomes and healthcare utilization in MS patients treated with natalizumab or ocrelizumab in real-world settings.

35. Ozakbas et al. (131) evaluated cognitive function changes with ocrelizumab as a part of treatment effectiveness. California Verbal Learning Test - Second Edition (CVLT-II) scores were significantly increased in PMS at month six according to baseline assessment ($p<0.05$), but no significant difference was observed in RMS. When two forms were compared to each other, the improvement in CVLT-II scores was significantly different in PMS over RMS. No significant differences were observed between the baseline and at month six in terms of Symbol Digit Modalities Test (SDMT) and Brief Visuospatial Memory Test - Revised (BVMT-R) scores in both forms ($p>0.05$). It was observed that ocrelizumab may improve verbal skills in PMS in the early phase of treatment. This finding is worth studying in detail and encourages further research to determine its causes. The data also confirms that there is no early cognitive impairment in RMS under ocrelizumab treatment.

36. Ozakbas et al. (132) presented six-month data for early treatment response of ocrelizumab in persons with multiple sclerosis. The average disease duration was approximately 17.7 years and average EDSS score was 5.29. Of the participants, 87 were RRMS, 175 SPMS, and 42 PPMS. The results showed that there was no discontinuation due to a cause related to ocrelizumab at the early stage. There was no significant difference between baseline and six-month EDSS scores for RRMS, PPMS, or SPMS patients (p:0.102, p:0.317 and 0.366, respectively). BVMT-R and CVLT-II scores were significantly increased at month six according to baseline (20.72±8.11 vs. 22.73±7.48, 46.50±12.99 vs. 49.91±12.78, respectively; $p< 0.05$). No significant difference was observed between baseline and month six in terms of SDMT (34.37±14.95 vs. 34.51±15.67), Timed 25-Foot Walk (T25FW) (12.95±10.30 vs. 16.28±14.75), or 9-HPT (35.45±22.35 vs. 35.34±20.23) scores ($p>0.05$). Between baseline and six-month assessments, there was no significant progression in physical disability scores, and increased cognitive performance based on visuospatial skills and verbal memory.

37. Pereira et al. (133) assessed all PPMS patients with at least two ocrelizumab cycles followed until December 2020 at two centers. Two groups were defined: a control group (aged 18-55 years, baseline EDSS 3-6.5, symptom duration <15 years for a baseline EDSS>5 or <10 years if baseline EDSS<5) and an expanded group (if any of the criteria were not met). No difference was observed in EDSS progression (31.2% control, 34.2% expanded, $p=0.831$), nor in time until EDSS progression (HR 0.931, CI 95% 0.324-2.683, $p=0.896$) between groups. Secondary outcomes (T-25FW, 9-Hole-Peg Test, MRI activity) were similar ($0.09<p<0.932$), just as incidence of any AE (31.3% control, 22.9% expanded, $p=0.523$). The author found no significant difference in efficacy and safety outcomes between groups and concluded that there would be a benefit to extending the indication of ocrelizumab beyond the ORATORIO trial's inclusion criteria.

38. Pontieri et al. (134) analyzed clinical and MRI data of MS patients enrolled prospectively in the Danish Multiple Sclerosis Registry who initiated ocrelizumab treatment between January 2018 and November 2020. A total of 1104 patients (85.7% RRMS, 8.8% SPMS, 5.5% PPMS) were included, with a median follow-up period of 1.3 years. At ocrelizumab initiation, the mean age was 41.4 years in the RRMS group, 44.5 years in the PPMS group, and 50.3 years in the SPMS group. Median EDSS score was 2.5, 3.5, and 5.5, respectively. Most RRMS and SPMS patients had received previous DMTs (87.5% and 91.8%, respectively), whereas PPMS patients were mostly treatment-naïve (78.7%). After ocrelizumab initiation,

9.3% of the patients experienced a relapse, and the ARR decreased from 0.58 in the year prior to initiation (95% CI 0.53 - 0.62) to 0.09 during follow-up (95% CI 0.07 - 0.11). Only 8.7% of the patients had a 24-week confirmed disability worsening. Conversely, 16.7% showed a 24-week confirmed disability improvement. After about one year of treatment, most patients (94.5%) were free of MRI activity. Ocrelizumab was generally well tolerated, as side effects were only reported for 10% of patients and mostly consisting of mild-to-moderate IRRs and infections. The author provides evidence that most MS patients treated with ocrelizumab are clinically stabilized and with an AE profile consistent with the experience from the pivotal clinical trials.

39. Rojas et al. (20) conducted a retrospective multicenter study in Argentina, Chile, and Mexico. A total of 81 patients who received ocrelizumab were included from medical record databases. The most frequent phenotype was RRMS, in 64.2% of the patients. The mean age at study entry was 41.3 ± 12.0 years and 51.8% were women. A total of 38% had had relapse activity during the 12 months before starting on ocrelizumab, with a mean relapse rate of 1.3 ± 0.6 during that period. Seventy-five percent were free from clinical relapses, and 91% were free from Gd-enhancing lesions in the relapsing-remitting course. Ocrelizumab discontinuation during the first 12 months was observed in three patients (3.7%). The mean persistence observed during the first-year follow-up was 338 ± 24 days. The authors concluded that the results were in line with previous randomized clinical trials and recent real-world studies describing patient profiles, effectiveness, and persistence regarding ocrelizumab treatment in MS patients in Latin America.

40. Roos et al. (135) compared the effectiveness of ocrelizumab with interferon-β, fingolimod, and natalizumab in RRMS. One hundred six patients treated with ocrelizumab were matched with 209 patients on interferon therapies with a mean age of 39 years, 0.8 relapses per year, and mean EDSS of 2.4-2.5. Over a pairwise-censored mean follow-up of 1.3 years, ocrelizumab was associated with lower relapse rates (ARR 0.08 vs. 0.27, p<0.001) and lower risk of relapse (HR 0.30, 95%CI 0.15-0.57) than interferon-β. Two hundred ninety-seven patients treated with ocrelizumab were matched with 811 fingolimod-treated patients with a mean age of 41 years, 0.6 relapses per year, and mean EDSS of 2.7-2.8. Over a pairwise-censored mean follow-up of 1.5 years, ocrelizumab was associated with lower relapse rates (ARR 0.03 vs. 0.14, p<0.001) and lower risk of relapse than fingolimod (HR 0.21, 0.13-0.32). Two hundred sixty-two ocrelizumab-treated patients were matched with 343 natalizumab-treated patients with a mean age of 39 years, 0.8 relapses per year, and mean EDSS of 2.7-2.8. Over a pairwise-censored mean follow-up of 1.6 years, ocrelizumab and natalizumab were associated with similar relapse rates (ARR 0.06 vs. 0.08, p=0.39) and risk of relapse (HR 0.77, 0.45-1.33). It was concluded that treatment with ocrelizumab provides superior control of relapses than interferon-β and fingolimod and the effects of ocrelizumab and natalizumab on relapse activity are similar. The authors noted that further evaluation of the comparative effectiveness of ocrelizumab on disability accumulation is warranted.

41. Signoriello et al. (136) performed a study to investigate the impact of switching from fingolimod or natalizumab to ocrelizumab on disease activity and observed withdrawal from sequestering agents as fingolimod increases the risk of relapses in the wash-out period. Nevertheless, starting ocrelizumab before achieving complete immune reconstitution could limit its effectiveness in the first six months, probably because trapped lymphocytes escape CD20-mediated depletion.

42. Smoot et al. (137) performed an observational study to evaluate safety and treatment outcomes of ocrelizumab in a community-based MS population. Of the 355 patients enrolled, respiratory infections occurred in 40.1% and urinary tract infections in 33.1% of patients. There was no difference in the percentage of infections among patients <55 (68.5%, n=122) and those ≥55 years of age (67.5%, n=104) (p=0.94). Twenty-five hospitalizations were due to infections; 69.2% of these patients were ≥55 with a mean EDSS of 5.7 (±1.86). Four patients died. Serum IgM and IgG levels did not predict infection risk. Annualized relapse rate was 0.34 for the patients with RMS in the preceding two years and 0.09 in patients who received ≥2 ocrelizumab 600 mg courses. The first on-treatment MRI was stable in 262 (90.0%) patients, 6.9% had new T2 lesions, 2.7% had enlarging T2 lesions, and 1.4% had Gd-enhancing lesions. Median EDSS at 12 months was unchanged. It was concluded that ocrelizumab effectively controlled relapse risk and disability worsening. Although only 12.1% of patients discontinued ocrelizumab, infections resulting in hospitalization were a concern, especially in older and disabled patients.

43. Smoot et al. (138) evaluated year 4 data from the Providence Ocrelizumab Registry for utilization, safety, and tolerability of ocrelizumab. The results showed that the RMS cohort had an ARR of 0.33 prior to starting ocrelizumab. Among all patients who had > one dose of ocrelizumab (n=407), ARR was 0.07. Median EDSS scores at 12 months were 3.0 [2.0, 4.5] (n=184) for RMS patients, 6.5 [6.5, 7.5] (n=32) for SPMS, and 6.5 [5.6, 7.5] (n=16) for PPMS. Infusion reactions occurred in 33.2% of patients during dose one, becoming less frequent with subsequent doses. Respiratory infections occurred in 40.5% of patients, followed by urinary tract infections (36.6%). Eight patients developed SARS-CoV-2 with no reported hospitalizations or deaths. Of 50 patients hospitalized, 19 had multiple hospitalizations. Over half of the hospitalizations were due to infections, and 69% (n=27) were 55 years or older. Of the 93 (21.3%) patients who stopped ocrelizumab, 47 patients stopped due to side effects, with recurrent infections being the main reason for stopping, followed by fatigue/malaise. The median time to discontinuation was 19.6 [IQR: 9.5, 30.2] months. There were seven deaths. Ninety-three patients who had baseline and 12-month MFIS had significant improvement at 12 months (mean difference -3.6 [±13.9], p=0.01). The study showed that ocrelizumab was effective in controlling relapse and disability worsening and reported similar rates of infusion reactions compared to earlier phase 3 clinical trials. A small number of patients developed SARS-CoV-2 with no adverse outcomes.

44. Toorop et al. (139) assessed the prevalence of the wearing-off phenomenon in patients with MS using ocrelizumab, to detect possible risk factors and to study possible changes in symptoms after ocrelizumab infusion. A total of 117 participants were included. Seventy-one (61%) patients reported the wearing-off effect during their treatment with ocrelizumab. The most frequently reported symptoms were fatigue, cognitive disability, and sensory symptoms. Wearing off symptoms started <1 week (11%), 1-4 weeks (49%), or more than 4 weeks (37%) before the ocrelizumab dose and disappeared in the first week after the ocrelizumab dose in most patients (44%). Fifty patients (43%) reported current wearing-off symptoms at the time of the first questionnaire. Higher BMI (≥ 25) increased the odds of reporting current wearing-off symptoms (OR 2.70, 95% CI 1.26 to 5.80, p=0.011). Infusion interval, EDSS score, clinical and radiological stability, CD19 B-cell counts, and NfL levels were not associated with current wearing-off symptoms. Patients with current wearing-off symptoms significantly improved in self-reported physical and psychological functioning after the ocrelizumab dose. Current wearing-off symptoms did not influence treatment satisfaction. Forty of 109 patients (37%) reported post-dose symptoms. It was concluded that the wearing-off effect is reported by more than half of patients with

MS using ocrelizumab. Only BMI was identified as a predicting factor. Wearing-off symptoms were not elicited by extending infusion intervals or higher B-cell counts. The ocrelizumab wearing-off effect therefore does not seem to reflect suboptimal efficacy of ocrelizumab.

45. Treffts et al. (140) assessed short-term relapse and disability risk after switching from natalizumab to ocrelizumab or cladribine in patients with RRMS. One hundred ninety-six patients (Denmark national registry [DMSR]: N=61, Germany national registry [GMSR]: N=79, academic centers [AC]: N=56) switched from natalizumab to ocrelizumab, 27 patients (DMSR: N=17, GMSR: N=8, AC: N=2) from natalizumab to cladribine. In the treatment-free switching interval, regardless of the following switch treatment, 11 (4.93%) patients had ≥1 relapse in 42.23 patient years (PYs) (DMSR: N=1 [1.28%] in 12.85PY, GMSR: N=5 [5.75%] in 17.47PY, AC: N=5 [8.62%] in 12.01PY). During the first six months after ocrelizumab/cladribine start, 20 (8.97%) had ≥1 relapse, regardless of the following switch treatment. Stratified by drug type, 16 (8.16%) of the ocrelizumab switchers had ≥1 relapse (DMSR: N=2 [3.28%], GMSR: N=6 [7.59%], AC: N=8 [14.29%]) and four (14.81%) of the cladribine switchers (DMSR: N=1 [5.88%], GMSR: N=2 [25%], AC: N=1 [50%]). The overall relapse risk during the treatment-free switching interval was low in this cohort but varied by data source.

46. Van Lierop et al. (141) assessed efficacy and safety of JC-virus-positive patients switching (either directly or indirectly) from natalizumab to ocrelizumab. Forty-two patients were included from an observational cohort (median follow-up 21 months). No evidence of disease activity was found in 83% of direct switchers and 50% of indirect switchers. Two direct switchers were diagnosed with carry-over progressive multifocal leukoencephalopathy (PML). The author's data supports a direct switch for adequate disease suppression, although carry-over PML illustrates the dilemma when choosing between a direct or indirect switch.

47. Van Wijmeersch et al. (142) assessed the efficacy and safety of ocrelizumab over three years in patients with RRMS who rolled over from the CASTING study to LIBERTO (LIBERTO one-year interim results). The results showed that as of 12 October 2020, 439/680 patients from CASTING rolled over to LIBERTO. Baseline demographics were consistent between CASTING and LIBERTO. In this cohort, NEDA was observed in 82.6% of patients from baseline to Year 1 (n/ N=549/665), 87.0% of patients from Year 1 to Year 2 (n/ N=571/656) and 82.5% of patients from Year 2 to Year 3 (n/ N=235/285). Over the three-year period (CASTING baseline to LIBERTO Week 48), 59.4% of patients had NEDA (n/N=190/320), 68.1% had no clinical activity (no CDP or relapse; n/N=218/320) and 86.6% had no MRI activity (no T1w-CEL or N/E T2w-L after CASTING Week 8; n/N=277/320). Over three years, AEs were reported in 92.3% of patients (n/N=405/439) and serious AEs in 8.4% of patients (n/N=37/439). Four patients from LIBERTO discontinued due to AEs (0.9%); no deaths occurred. The author concluded that patients with a suboptimal response to one or two prior DMTs who switched to ocrelizumab responded consistently well to ocrelizumab treatment over three years, based on clinical and MRI measures. No new safety signals were observed.

48. Vollmer et al. (143) described the two-year experience of MS patients treated with ocrelizumab. Of the sample group, 200 (81.6%), 37 (15.1%), and eight (3.3%) were RRMS, SPMS, and PPMS, respectively. Four (1.99%), one (0.5 %), and 20 (9.95%) patients experienced a clinical relapse, an enhancing lesion, and a new T2 lesion, respectively. Of 115 patients with available MRI data for re-baselining after initiation of ocrelizumab, three (2.6%) patients had a new T2 lesion. Fifty-one (20.8%) patients

discontinued ocrelizumab at <24 months. Twenty-two patients were lost to follow-up or relocated care, 17 patients discontinued due to issues with insurance, two patients discontinued due to AEs, specifically hypogammaglobulinemia and hair loss, and ten patients discontinued due to other reasons, such as family planning, concern for cancer, and preference for no treatment. During the first and second infusion course, 41 (16.9%) and 26 (10.0%) experienced an infusion reaction that interrupted the ocrelizumab infusion, respectively, and none experienced a life-threatening reaction or were hospitalized. Infections resulting in an emergency department visit or hospitalization occurred in 20 (8.2%) and seven (2.9%) patients, respectively. Twenty-five (10.2%) patients experienced lymphopenia ≤500/mm^3, and four (1.6%) experienced neutropenia ≤1000/mm^3. Eleven (5.3%) patients experienced IgG levels ≤500, and 77 (38.3%) experienced IgM levels ≤40. The data suggests ocrelizumab is safe and effective in the treatment of MS.

49. Weinstock-Guttman et al. (144) assessed the efficacy and safety of ocrelizumab in patients with RRMS and suboptimal response to prior DMTs. The results indicated the ITT population included 608 patients; NEDA was analyzed in a modified ITT (mITT) population (n = 576 [94.7%]). Over 96 weeks, 48.1% of mITT patients achieved NEDA, and most were free from protocol-defined relapse (89.6%), CDP (89.6%), and T1 Gd-enhancing lesions (95.5%); 59.5% had no new/enlarging T2 lesions. Safety observations were consistent with findings in the pivotal trials. The author concluded that consistent efficacy of ocrelizumab on clinical and MRI disease activity measures and progression was shown in patients with RRMS and a suboptimal response to prior DMTs; no new safety signals were observed.

50. Yousuf et al. (21) evaluated the generalizability of data on ocrelizumab from phase 3 clinical trials and its effectiveness in a real-world setting of an Arab population in a rapidly developing country such as Qatar. Of 83 patients, 65 met inclusion criteria. Mean age was 38.7, 58.5% were male, 31.7% were treatment-naïve, 52 had RRMS, five had PPMS, and three had SPMS. Average duration of disease and number of infusions was 7.75 years and 3.2 respectively. Average number of Gd-enhancing lesions on baseline MRI was 1.27 and 0.07 after treatment. Eleven patients had mild AEs (IRRs), 13 had upper respiratory tract infections (URTIs) (with one patient having COVID pneumonia), and one patient had urinary tract infection. Two patients developed cancer while on treatment. Compared to OPERA I/II, patients in Qatar were older (mean age of 38.7 vs. 37.1 and 37.2), mostly male (58.5% vs. 65.9% and 65.0%), and had similar mean EDSS score (2.57±2.67 vs. 2.86±1.24 and 2.78±1.30) but longer duration of disease (7.75±6.72 vs. 6.7±6.4 and 6.7±6.1). The authors concluded that ocrelizumab is highly effective for the treatment of MS, especially in this Arab population with a long follow-up period. Compared to previous clinical trials, patients in Qatar had different demographic characteristics, with longer disease durations and fewer enhancing lesions at baseline.

51. Zhong et al. (145) determined predictors of relapse and disability progression when switching from another DMT to ocrelizumab. The results indicated that after adjustment, relapse hazard when switching from fingolimod was greater than other prior DMTs, but only in the first three months of ocrelizumab therapy (HR = 3.98, 95% CI = 1.57-11.11, p = 0.004). The adjusted hazard for CDP was significantly higher with longer washout (2-6 m compared to <1 m: HR = 9.57, 95% CI = 1.92-47.64, p = 0.006). The author concluded that the risk of disability worsening during switch to ocrelizumab is reduced by short treatment gaps. Patients who cease fingolimod are at heightened relapse risk in the first three months on ocrelizumab. Prospective evaluation of strategies such as washout reduction may help optimize this switch.

52. Bigaut et al. (146), on behalf of the French Group for Recommendations in Multiple Sclerosis (France4MS) and the French Multiple Sclerosis Society (SFSEP), established guidelines on switching DMTs in MS. Switching from a first-line therapy to another first-line therapy or a second-line therapy could be done without a washout period. Switching from a second-line therapy to a first-line therapy could be done without a washout period with fingolimod or natalizumab, after three months with ocrelizumab or mitoxantrone, and, if disease activity occurs, with alemtuzumab or cladribine. The switch from a second-line therapy to another second-line therapy could be done after a washout period of one month with fingolimod or natalizumab, after three months with ocrelizumab, after six months with mitoxantrone, and, if disease activity occurs, with alemtuzumab or cladribine.

53. Samjoo et al. (145), in alignment with the 2015 guidelines for MS therapies classification of the Association of British Neurologists (ABN) based on the average relapse reduction, classified ocrelizumab and ozanimod (1.0 mg) as moderate- or high-efficacy, depending on the approach. Cladribine and ofatumumab were classified as high-efficacy.

54. Mohammad et al. (148) conducted a network meta-analysis and suggested that compared to INFβ1a, ocrelizumab reduced the risk of ARR (RR = 0.56, 95% CI, 0.50-0.64), serious adverse events (SAEs) (RR = 0.17, 95% CI, 0.09-0.30), and treatment discontinuation due to AEs (SAEs, RR = 0.60, 95% CI, 0.39-0.93), and was associated with higher odds of no relapses (OR = 2.47, 95% CI, 2.00-3.05). Ocrelizumab ranked best among all other treatments in terms of reducing ARR and SAEs. The quality of evidence was low for ocrelizumab, low to moderate for rituximab, and high for ofatumumab. Further large-sized, well-designed RCTs are needed to corroborate the efficacy and safety of ocrelizumab and other anti-CD20 Monoclonal Antibodies (MAbs) in RRMS.

55. Liu et al. (149) conducted a systematic review and network meta-analysis and suggested that the risk of relapses for most DMTs except Betaseron 50 µg was significantly lower compared to placebo. Non-compliance in patients treated with DMTs was not significantly increased compared to placebo. Dimethyl fumarate and ocrelizumab had superiority in improving MRI outcomes. Ocrelizumab and ofatumumab had the largest reduction of risk in disability progression at three months. By surface under the cumulative ranking curve (SUCRA), ofatumumab, alemtuzumab, and natalizumab showed the best efficacy and compliance. The study demonstrated the hierarchy of DMTs treating RRMS. Ofatumumab, alemtuzumab, and natalizumab have superiority with respect to effectiveness and compliance. The authors concluded that more studies are required to explore the long-term effect of DMTs.

56. Zanghì et al. (150) evaluated the efficacy and safety profile of ocrelizumab, rituximab, and cladribine, employed as natalizumab exit strategies in RRMS patients at high risk for PML. Patients from the three groups did not show differences for baseline characteristics, even after post-hoc analysis. The Inverse Probability Treatment Weighting propensity score-adjusted models revealed that patients on ocrelizumab had a lower risk for ARR than patients on cladribine ($ExpB_{ocrelizumab}$ 0.485, CI 95% 0.264–0.893, p = 0.020). This result was confirmed for 12-month MRI activity ($ExpB_{ocrelizumab}$ 0.248 CI 95% 0.065–0.948, p = 0.042). No differences were found in other pairwise comparisons (ocrelizumab vs. rituximab and rituximab vs. cladribine) for the investigated outcomes. AEs were similar among the three groups. Anti-CD20 drugs were revealed to be effective and safe options as natalizumab exit strategies. All investigated DMTs showed a good safety profile.

57. Bigaut et al. (119) conducted an observational study to compare ocrelizumab to fingolimod after natalizumab cessation in patients with RRMS. The author included 54 patients receiving fingolimod and 48 patients receiving ocrelizumab after natalizumab cessation. In multivariate analysis, ARR at one year was significantly lower in the ocrelizumab group than in the fingolimod group (0.12 ± 0.39 vs. 0.41 ± 0.71, p = 0.026), i.e., a 70.7% lower relapse rate. The cumulative probability of relapses at one year was 31.5% (17/54 patients) with fingolimod and 10.4% (5/48 patients) with ocrelizumab, corresponding to a HR of 3.4 (95%CI: 1.1-11, p = 0.04). The authors suggest ocrelizumab is potentially a better exit strategy than fingolimod after natalizumab cessation.

58. Guerra et al. (22) evaluated effectiveness and safety of ocrelizumab for PPMS, active SPMS, and RRMS patients recruited at the MS Center of Bari, Italy. The cohort of 133 patients included 35 PPMS, 22 SPMS, and 76 RRMS patients. The median (IQR) follow-up after the first DMT start were 2.09 (0.6-3.3), 1.8 (0.08–4.02), 1.63 (1.17–3.10) years for PPMS, RRMS, and SPMS patients, respectively. The last available EDSS after ocrelizumab start significantly increased compared to the baseline values only in the PPMS group (p = 0.01), but it remained stable in SPMS and RRMS groups. No clinical relapses and no evidence of radiological activity were found in RRMS patients during follow up. AEs reported were mostly IRRs in all groups, one dengue fever, and two *Herpes Zoster* infections. Seven cases reported COVID-19 infection during the pandemic, one of whom died. These real-world data indicate that ocrelizumab stabilized disability progression and disease activity in RRMS and SPMS patients. The safety profile was quite favorable in this cohort.

59. Trojano et al. (151) reported outcomes from the MuSicalE study, a large, global, real-world cohort using a comprehensive combination of participant-reported outcomes and conventional MS endpoints that measure clinical domains commonly affected by MS (e.g. fatigue, hand function, gait, cognition), and their impact on employment, activities of daily living, quality of life and healthcare resource utilization. 1-year treatment with ocrelizumab was associated with low levels of disease progression and activity. Stabilisation, as well as a potential improvement of functioning was observed in ocrelizumab-treated patients. No new safety signals emerged, and the safety profile matched that in clinical trials.

16. Appendix C

Table 18: Summary of Regulatory Status and Market Availability of Ocrevus®

	Country	Worldwide market approvals
	Albania	October 26, 2017
	Algeria	October 21, 2021
	Argentina	March 15, 2019
	Armenia	March 13, 2019
	Aruba	April 26, 2018
	Australia	July 3, 2017
	Austria	January 8, 2018
	Azerbaijan	June 24, 2019
	Bahrain	August 20, 2019
	Belarus	December 3, 2018
	Belgium	January 8, 2018
	Bolivia (Plurinational State of)	October 17, 2018
	Bosnia-Herzegovina	July 3, 2018
	Brazil	February 26, 2018
	Bulgaria	January 8, 2018
	Canada	August 14, 2017
	Chile	March 21, 2018
	Colombia	February 13, 2019
	Costa Rica	August 24, 2022
	Croatia	January 8, 2018
	Cuba	December 27, 2017
	Curacao	October 30, 2018
	Cyprus	January 8, 2018
	Czech Republic	January 8, 2018
	Denmark	January 8, 2018
	Dominican Republic	November 11, 2017
	Ecuador	April 26, 2018
	Egypt	December 20, 2018
	El Salvador	November 29, 2017
	Estonia	January 8, 2018
	Finland	January 8, 2018

	Country	Worldwide market approvals
	France	January 8, 2018
	Georgia	November 9, 2018
	Germany	January 8, 2018
	Ghana	October 9, 2020
	Greece	January 8, 2018
	Guatemala	March 16, 2018
	Guyana	May 10, 2021
	Honduras	January 11, 2018
	Hungary	January 8, 2018
	Iceland	January 8, 2018
	Iran, Islamic Republic Of	October 2, 2018
	Iraq	December 8, 2021
	Ireland	January 8, 2018
	Israel	August 13, 2017
	Italy	January 8, 2018
	Jamaica	January 3, 2019
	Jordan	July 25, 2018
	Kazakhstan	January 30, 2019
	Kosovo	October 30, 2017
	Kuwait	November 20, 2017
	Latvia	January 8, 2018
	Lebanon	October 18, 2018
	Libya	February 22, 2022
	Lithuania	January 8, 2018
	Luxembourg	January 8, 2018
	Macedonia	April 26, 2018
	Malta	January 8, 2018
	Mauritius	May 15, 2018
	Mexico	September 11, 2018
	Moldova, Republic of	May 18, 2018
	Montenegro	September 10, 2018
	Morocco	November 15, 2018
	Namibia	March 21, 2019

	Country	Worldwide market approvals
	Netherlands	January 8, 2018
	New Zealand	December 21, 2017
	Nicaragua	August 17, 2018
	Nigeria	August 25, 2022
	Northern Ireland (UK)	January 8, 2018
	Norway	January 8, 2018
	Oman	March 11, 2018
	Pakistan	January 23, 2019
	Palestine, State of	December 27, 2018
	Panama	August 16, 2018
	Paraguay	August 9, 2017
	Peru	March 19, 2019
	Philippines	16 October 2013
	Poland	January 8, 2018
	Portugal	January 8, 2018
	Qatar	October 15, 2017
	Romania	January 8, 2018
	Russian Federation	October 20, 2017
	Saudi Arabia	January 14, 2018
	Serbia	January 18, 2019
	Sint Maarten	January 29, 2020
	Slovakia	January 8, 2018
	Slovenia	January 8, 2018
	South Africa	July 14, 2020
	Spain	January 8, 2018
	Sweden	January 8, 2018
	Switzerland	September 20, 2017
	Syrian Arab Republic	December 2, 2020
	Taiwan	14 June 2013
	Thailand	24 January 2014
	Trinidad & Tobago	June 11, 2019
	Tunisia	June 12, 2020
	Turkey	March 7, 2018
	Turkmenistan	December 29, 2017

	Country	Worldwide market approvals
	Ukraine	September 4, 2017
	United Arab Emirates	August 10, 2017
	United Kingdom	January 8, 2018
	United States of America	March 28, 2017
	Uruguay	August 17, 2020

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