9 November 2017
EMA/790835/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ocrevus

International non-proprietary name: ocrelizumab

Procedure No. EMEA/H/C/004043/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

Quality

95/99 TI	95% confidence/99% probability tolerance interval
AC	Acceptance Criteria;
ADA	Anti-Drug Antibodies
ADCC	Antibody-Dependent Cellular Cytotoxicity
ADCP	Antibody-Dependent Cellular Phagocytosis
ADI	Acceptable Daily Intake
ADI/EDI	Acceptable And Estimated Daily Intake
AEX	anion-exchange
AGE	Advanced Glycation End product
AIM	Automatic Inspection Machine
AR	Acceptable Range
ATS	Attribute Testing Strategy
AUC	Analytical Ultracentrifugation
C	Constant Domain
CaM	Comparability and Monitoring
CCI	Container Closure Integrity
CDC	Complement-Dependent Cytotoxicity
CDR	Complementarity Determining Region
CE	Capillary Electrophoresis;
CE-LIF	Capillary Electrophoresis With Laser Induced Fluorescence Detection;
CE-SDS	Capillary Electrophoresis - Sodium Dodecylsulfate
CEX	Cation-Exchange
CFU	Colony-Forming Unit
CHO	Chinese hamster ovary
CHOP	Chinese Hamster Ovary Cell Protein
CI	Confidence Interval
CIP	Clean in place
CPA	Corrected Peak Area;
CPMF	Clinical Parenteral Manufacturing Facility
CPP	Critical Process Parameter;
CQA	Critical Quality Attribute
CQA-AC	Critical Quality Attribute Acceptance Criteria
CQA-TR	Critical Quality Attribute Target Range
CV	Column Volume
DNAF	DNA-Binding Fluorochrome
DP	Drug Product
DS	Drug Substance
DSC	Differential Scanning Calorimetry
DSp	Design Space
DV	Diafiltration Volume
EDTA	ethylenediaminetetraacetic acid
EPC	End-of-Production Cells
ESI-MS	Electrospray Ionization - Mass Spectrometry
EU	Endotoxin Units
F/T	Freeze/Thaw;

Fab	Antigen Binding Portion Of Immunoglobulin Molecule
FBS	Fetal Bovine Serum
Fc	Fragment crystallisable
FcγRIIIa	Fc gamma receptor IIIa
FcRn	neonatal Fc receptor
FTIR	Fourier Transform Infrared Spectroscopy
FVIP	filtered viral inactivation pool
GPMF	Genentech Production Manufacturing Facility
HC	Heavy Chain;
HCCF	Harvested Cell Culture Fluid
HCP	Host Cell Protein
HEPES	4-(2-hydroxyethyl)-1-piperazine ethane sulfonic acid
HMWS	High-Molecular-Weight Species
HTF	Heat Transfer Fluid;
HTIR	Historical Tolerance Interval Range
HTST	High-Temperature Short-Time
HVAC	Heating, ventilation, and air conditioning
ICH	International Conference on Harmonisation
IC-IEF	Imaged Capillary Isoelectric Focusing;
IdeS	Streptococcus pyogenes
IE-HPLC	Ion-Exchange High Performance Liquid Chromatography
IgG1	Immunoglobulin G1
IPCs	In-Process Controls
IV	Intravenous
JP	Japanese Pharmacopoeia
JP	Japanese Pharmacopoeia
KPI	Key Performance Indicator
LC	Light Chain
LC-MS	Liquid Chromatography - Mass Spectrometry;
LC-UV	Liquid Chromatography - Ultraviolet;
LMWS	Low-Molecular-Weight Species;
LPA	Leached Protein A
LPM	Liters Per Minute;.
LRV	Log Reduction Value
MAR	Multivariate Acceptable Range
MCB	Master Cell Bank
MMV	Murine Minute Virus
Mn2+	Manganese
MS	Multiple Sclerosis
MTX	methotrexate
NA	Not Applicable
NANA	N-acetylneuraminic acid;;
NEM	N-ethylmaleimide
NF	National Formulary
NGHC	Non-glycosylated Heavy Chain.
NGNA	N-glycolylneuraminic acid;
non-CPP	non- Critical Process Parameter
NOR	Normal Operating Range;
NR	Not Required
NT	not tested

OD	optical density
PALM	Post-Approval Lifecycle Management
PAR	Proven Acceptable Range
PBD	Polybutadiene
PC/PV	Process Characterization And Validation
PC/PV RRF	Process Characterization/Process Validation Risk Ranking and Filtering
pCCI	Physical Container Closure Integrity
PCR	Polymerase Chain Reaction
PCV	Packed Cell Volume
PD	Pharmacodynamics
PE	Polyethylene
PES	Polyethersulfone
PEU	Polyetherurethane
Ph. Eur.	European Pharmacopoeia
PHCCF	Preharvest Cell Culture Fluid
PK	Pharmacokinetics
PI	Isoelectric point;
PO	Polyolefin
PPMS	Primary Progressive Multiple Sclerosis
PPMS	Primary Progressive Multiple Sclerosis
PQA	product quality attribute
PQRA	product quality risk assessment
PQS	Pharmaceutical Quality System
PSB	Primary Seed Bank
PSU	Polysulfone
PVC	Polyvinyl Chloride
QbD	Quality By Design
Q-PCR	quantitative polymerase chain reaction
QS	quantity sufficient
QTPP	Quality Target Product Profile
RA	Rheumatoid Arthritis
RDG	Roche Diagnostics GmbH
RH	relative humidity
RMS	Relapsing Multiple Sclerosis
RP-UHPLC	Reversed-Phase Ultra High-Performance Liquid Chromatography;
RRF	Risk Ranking and Filtering
RVLP	Retrovirus-Like Particles
SDS-PAGE	Sodium Dodecyl Sulfate - Polyacrylamide Gel Electrophoresis
SE-HPLC	Size-Exclusion High-Performance Liquid Chromatography;
SOP	Standard Operating Procedure
SSF	South San Francisco
STB	Seed Train Bioreactor
SV40	Simian Virus type 40
TI	Tolerance Interval
TMAC	tetramethylammonium chloride
TMP	transmembrane pressure
TOST	two one-sided testing
Tris	tris(hydroxymethyl)aminomethane
TSE	transmissible spongiform encephalopathy
UFDF	ultrafiltration and diafiltration

USP	United States Pharmacopoeia
V	Variable Domain
VHS	Valine Histidine Serine
VV	Vacaville
VV CCP1	Vacaville Cell Culture Plant 1.
WCB	Working Cell Bank
WFI	Water For Injection
WHO	World Health Organization
X-MuLV	Xenotropic Murine Leukemia Virus

Non clinical

ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
ADA	anti-drug antibody (also known as ATA)
ATA	anti-therapeutic antibody (also known as ADA)
AUC	area under the curve
CDC	complement-dependent cytotoxicity
CL or CL/F	clearance; CL is calculated with IV bolus input and CL/F is calculated with extravascular input
Cmax	maximum serum concentration
DB	day post-birth
DPC	Day Post coitum
DPP	Day Post partum
ECG	electrocardiogram
Fcγ	Fc gamma
GD	gestation day
GLP	Good Laboratory Practice
huCD20	human CD20
ICH	International Conference on Harmonization
Ig	immunoglobulin
IHC.	immunohistochemistry
i.v.	intravenous
LoD	loading dose
LD	Lactation Day
mAb	monoclonal antibody
MFD	maximum feasible dose
MS	multiple sclerosis
NK	natural killer
NOAEL	no-observable-adverse-effect level
PD	pharmacodynamic
PK	pharmacokinetic
Q2W	once every 2 weeks
Q3W	once every 3 weeks
RMS	relapsing multiple sclerosis
s.c.	subcutaneous
SD	study dose
t1/2	half-life
TK	toxicokinetic
Vss or or Vss/F	volume of distribution at steady state; Vss is calculated with i.v. bolus input and Vss/F is calculated with extravascular input

Clinical

9-HPT	nine-hole peg test
ALT	alanine aminotransferase

AST	aspartate aminotransferase
AUC	area under the curve
ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
ANCOVA	analysis of covariance
ARR	annualized relapse rate
ATA	anti-therapeutic antibody
AUC	area under the concentration-time curve
AUC_{last}	area under the concentration-time curve from time 0 to the last measurable concentration
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AUC_{T}	area under the concentration-time curve within a dosing interval
BCC	basal cell carcinoma
BLA	Biologics License Application
BLQ	below the limit of quantification
BMI	body mass index
BSA	body surface area
CCOD	clinical cut-off date
CDC	complement-dependent cytotoxicity
CDI	confirmed disability improvement
CDP	confirmed disability progression
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CLL	chronic lymphocytic leukemia
Cmax	maximum serum concentration
CL	clearance
CRCL	creatinine clearance
CNS	central nervous system
CSF	cerebrospinal fluid
CSR	clinical study report
CV	coefficient of variation
CYP	cytochrome P 450
DMARD	disease-modifying antirheumatic drug
DMT	disease modifying treatment
DRESS	drug rash with eosinophilia and systemic symptoms
DSS	Disability Status Scale
ECG	electrocardiogram
ECLA	electrochemiluminescence assay
eCRF	electronic case report form
EDSS	Expanded Disability Status Scale
ELISA	enzyme-linked immunosorbent assay
EPAR	European Public Assessment Report
EULAR	European League Against Rheumatism
FACS	fluorescence-activated cell sorting
FDA	Food and Drug Administration
FS	functional system
FSS	Functional System Score
GCP	good clinical practice
GD	gadolinium
GPA	granulomatosis with polyangiitis
HAHA	human anti-human antibody
HBV	hepatitis B virus
HR	hazard ratio
ICH	International Conference on Harmonisation
iDMC	independent Data Monitoring Committee
IFN	interferon beta-1a
Ig	immunoglobulin

IM	intramuscular
iPSP	initial Pediatric Study Plan
IV	intravenous
IRR	infusion-related reaction
ISS	Integrated Summary of Safety
ITT	intent-to-treat
KM	Kaplan-Meier
LLN	lower limit of normal
LN	lupus nephritis
LOCF	last observation carried forward
MAA	Marketing Authorization Application
mAb	monoclonal antibody
MQC	minimum quantifiable concentration
MMRM	mixed-effects model repeated measures
MPA	microscopic polyangiitis
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
NAb	neutralizing antibody
NCA	non-compartmental analysis
NCI	National Cancer Institute
NEDA	no evidence of disease activity
NHL	non-Hodgkin's lymphoma
NK	natural killer
OCR	OCR
OLE	open-label extension
PASAT	Paced Auditory Serial Addition Test
PBRER	periodic benefit-risk evaluation report
PCS	physical component summary
PD	pharmacodynamics
PDR	protocol-defined relapse
PIP	Paediatric Investigation Plan
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
popPK	population PK
PPMS	primary progressive MS
PRMS	progressive-relapsing MS
PT	preferred term
PY	patient years
Q	intercompartmental clearance
QoL	quality of life
RA	rheumatoid arthritis
RMS	relapsing forms of MS
RRMS	relapsing-remitting MS
ROW	rest-of-world
SAE	serious adverse event
SAP	statistical analysis plan
SBS	Summary of Biopharmaceutics and Bioanalytical Methods
SC	subcutaneous
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SEER	surveillance epidemiology and end result
SF-36	SF-36 Health Survey
SFU	safety follow-up
SIRS	systemic inflammatory response syndrome
SLE	systemic lupus erythematosus
SmPC	Summary of Product Characteristics

SMQ	standard MedDRA query
SOC	system organ class
SPMS	secondary progressive MS
T25-FW	timed 25-foot walk
TNF	tumor necrosis factor
t.u.	titer units
US	United States of America
USPI	US Product Information
V	volume of distribution

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Roche Registration Limited submitted on 25 April 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Ocrevus, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 June 2014.

The applicant applied for the following indication:

Ocrevus is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS).

Ocrevus is indicated for the treatment of adult patients with primary progressive multiple sclerosis (PPMS).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that ocrelizumab was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0143/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0143/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request(s) for consideration

New active Substance status

The applicant requested the active substance ocrelizumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 21 June 2007, 19 February 2009, 23

September 2010 and 20 March 2014. The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Hanne Lomholt Larsen Co-Rapporteur: Daniela Melchiorri

- The application was received by the EMA on 25 April 2016.
- The procedure started on 19 May 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 5 August 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 2 August 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 22 August 2016.
- During the meeting on 15 September 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 January 2017.
- The following GCP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
  - A GCP inspection at 4 sites (Sponsor, two CRO and one clinical investigator site) in Switzerland and UK between April and June 2017. The outcome of the inspection carried out was issued on 7 August 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 February 2017.
- During the PRAC meeting on 9 March 2017 the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 23 March 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- During a meeting of SAG on 8 June 2017, experts were convened to address questions raised by the CHMP. The CHMP considered the views of the SAG as presented in the minutes of this meeting.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 15 August 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 31 August 2017.
- During the CHMP meeting on 13 September 2017, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the CHMP meeting on 14 September 2017, the CHMP agreed on a 2nd list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the 2nd CHMP List of Outstanding Issues on 20 September 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 2nd

List of Outstanding Issues to all CHMP members on 29 September 2017.

- During the CHMP meeting on 10 October 2017, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the CHMP meeting on 12 October 2017, the CHMP agreed on a 3rd list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the 3rd CHMP List of Outstanding Issues on 17 October 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 3rd List of Outstanding Issues to all CHMP members on 26 October 2017.
- During the meeting on 6-9 November 2017 the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ocrevus on 9 November 2017.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system (CNS) resulting in neurological impairment and severe disability. With the present application the applicant intended to seek approval of ocrelizumab for the following indications:

"Ocrevus is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS).

Ocrevus is indicated for the treatment of adult patients with primary progressive multiple sclerosis (PPMS)."

2.1.2. Epidemiology

MS is the most common cause of serious neurological disability in young adults. It is estimated that more than 2.3 million people have MS worldwide. While MS is a global disease, its prevalence increases with distance from the equator. The prevalence of MS is highest in North America and Europe (140 and 108 per 100,000 respectively) and lowest in sub-Saharan Africa and East Asia at 2.1 and 2.2 per 100,000, respectively.

MS typically begins between the ages of 20 to 40 years. Overall, women are affected approximately twice as often as men, except in individuals with the primary-progressive form of the disease, where there is no gender prevalence difference. For the past two decades, MS has been clinically subcategorized into four phenotypic disease patterns distinguished by the occurrence and timing of episodes of transient neurological compromise (relapses) relative to disease onset and disability progression: relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and progressive-relapsing MS (PRMS). A recently proposed revision to this classification discusses the potential to abandon the term PRMS as it is considered vague and overlapping with other disease course subtypes. In that line of argument PRMS and PPMS should therefore no longer be considered distinct entities but rather be characterized both as PPMS, with or without activity. More

recently, it has been proposed that PPMS is not a separate entity but rather a part of the spectrum of progressive disease and as such RMS and PPMS can be considered closely related diseases.

The vast majority of patients (approximately 85%) first present with the RRMS form (Lublin et al., 2014), which usually later evolves into secondary-progressive MS (SPMS), whereas PPMS affects about 15% of the patients.

2.1.3. Aetiology and pathogenesis

While the exact cause of MS is unknown, an autoimmune process has been implicated involving both a genetic predisposition and environmental triggers.

The neuropathology of the disease is marked by an aberrant activation of specific T and B cells that recognize auto-antigens (i.e., myelin) expressed in the CNS. MS relapses are considered the clinical expression of acute inflammatory focal lesions associated with an influx of inflammatory T cells into the CNS, leading to breakdown of the blood-brain barrier, followed by entry of B cells and macrophages. This leads to oligodendrocyte loss, demyelination, axonal damage, and neuronal loss.

In recent years there has been increasing evidence supporting the hypothesis that B cells may play a key role in the treatment of MS. Four possible mechanisms of B-cell associated pathophysiology in MS have been described: Presenting auto-antigens and co-stimulatory signals to activate T cells, secreting pro-inflammatory cytokines at greater relative proportions than protective cytokines, producing auto-antibodies which may cause tissue damage and activate macrophages and NK cells and creating meningeal lymphoid follicle-like structures, linked to microglia activation, local inflammation and neuronal loss in the nearby cortex.

2.1.4. Clinical presentation and diagnosis

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 (Polman et al. 2011). Prognosis is highly variable and if left untreated, half of patients with MS require assistance to walk within 15 years of disease onset (Expanded Disability Status Scale [EDSS] 6).

In approximately 85% of patients, MS begins as a relapsing, episodic disorder with gradual complete or incomplete recovery (RRMS). If left untreated, the majority of these patients will transition to a progressive form characterized by worsening neurologic disability either with or without occasional super-imposed relapses (relapsing or non-relapsing secondary progressive MS). 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.

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. 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 at which 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. The mean age of onset for PPMS is approximately 40 years and men are affected nearly as often as women. In PPMS, diagnostic criteria require 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 (Disability Status Scale [DSS] landmark 6) was 8 years and the median time to wheelchair use (DSS landmark 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.

2.1.5. Management

Currently there is no cure for MS, but the aberrant activation of self-specific T and B cells observed in MS has been shown to be affected by immunomodulatory treatments, which can favourably alter the course of the disease. These therapeutic interventions are referred to as disease modifying drugs (DMDs) or disease modifying therapies (DMTs). The goal of treatment of RMS with DMDs is to reduce the rate and severity of relapses and to delay disease progression by preventing accumulation of disability.

MS therapies also include treatment of relapses and symptomatic treatment applied to improve symptoms and complications caused by the disease, e.g. fatigue, spasticity, ataxia, walking disability, weakness, bladder and bowel disturbances, and cognition disturbances etc. As per the current treatment consensus acute relapses can be treated with corticosteroids and the standard of care is IV methylprednisolone.

Currently in the EU there are number of approved DMDs for MS, each presenting with a different efficacy and safety profile. Long-standing injectable therapies in RMS include the interferon beta class (interferon beta-1a intramuscular [IM], interferon beta-1a subcutaneous [SC], interferon beta-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. In the real world setting, suboptimal adherence due to side effects, injection anxiety and lack of perceived efficacy is also a recognized issue for many of these treatments.

Other recently approved medicines like dimethylfumarate and teriflunomide are indicated for patients with RRMS and are considered to have modest efficacy (reduction of ARR approximately by 50% for

dimethylfumarate and by 30% for teriflunomide). Despite convenient way of administration (per os [p.o.] once or twice daily), these medications have a more complex safety profile. Teriflunomide reduces white blood cell count approximately by 15 % from baseline values, requires frequent monitoring of liver function and has very slow plasma elimination, which could take up to 2 years. Dimethylfumarate lowers lymphocyte counts by approximately 30% from baseline values and cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients with moderate or severe prolonged lymphopenia. Daclizumab has been approved for patients with RMS and has shown a more significant efficacy (approximately 46% relative reduction of ARR). It also induces reduction of total lymphocyte, T and B cell counts on average ≤10% from baseline during the first year of treatment, and recently severe hepatotoxicity reactions have been reported.

Alemtuzumab is indicated for 'RRMS patients with active disease defined by clinical or imaging features', while natalizumab and fingolimod have been approved for 'highly active RRMS'. Disease activity was defined based on clinical and MRI parameters with or without prior DMD. Alemtuzumab is administered as intravenous (IV) infusions during two treatment courses lasting 3-5 days each and separated by 12 months with safety follow up for 48 months after the last infusion (relative reduction of ARR by approximately 50%). Infusion related reactions, infections as well as autoimmune disorders including immune thrombocytopenia, nephropathies and thyroid disorders (up to 36% of treated patients) were reported in clinical trials with alemtuzumab. Alemtuzumab depletes T and B lymphocytes and total lymphocyte counts return to lower limit of normal by 6 months after the last infusion in 40% of patients. Natalizumab is administered as IV infusion every 4 weeks. It is very effective in highly active RRMS (relative reduction of ARR by approximately 70%). In contrast to other treatment alternatives in MS it is not inducing lymphopenia, but is associated with seriously increased risk of PML (varies from 0.1 to 10 per 1000 treated patient). Fingolimod is another alternative for patients with highly active RRMS (relative reduction of ARR by approximately 50-55%). However, it induces reduction of the peripheral lymphocyte count by approximately 70-80% from baseline value. Fingolimod is also associated with the occurrence of PML cases, basal cell cancer and serious cardiac adverse reactions including bradycardia, as well as cases of QT prolongation and atrioventricular block.

Although there are several approved therapies for RMS, some lack sufficient efficacy to effectively reduce disability progression, while more effective therapies are often reserved for later use because they are associated with serious risks. Therefore, it can be summarized that there is still an unmet medical need in RMS for treatment options which are easy and convenient for the patient, e.g. short treatment courses, and which have high efficacy with a benign safety profile.

No treatment has been demonstrated to significantly slow the progression of disability in patients with PPMS, including therapies approved for the treatment of RMS. A large Phase III, randomized, controlled trial with glatiramer acetate and smaller randomized, controlled clinical trials evaluating mitoxantrone, interferon beta-1a IM, and interferon beta-1b did not demonstrate significant impact on clinical progression in the PPMS population. In a Phase II/III randomized, placebo controlled clinical trial evaluating rituximab; a statistically significant treatment effect was not shown for the primary endpoint. Moreover, most recently, a Phase III placebo controlled trial of fingolimod in patients with PPMS failed to meet its primary endpoint.

In the absence of any approved treatment for PPMS, a variety of unapproved agents including mycophenolate mofetil, cyclophosphamide, mitoxantrone or rituximab, in addition to other therapies approved for the treatment of RMS (e.g. interferon beta-1a or glatiramer acetate), are used in clinical practice despite the lack of Level 1 evidence. This exposes patients to risk without expected benefits. Currently, PPMS remains a severely disabling condition with no approved DMTs and where a high unmet medical need is recognized.

About the product

Ocrelizumab is a recombinant, humanized immunoglobulin (Ig) G1 monoclonal antibody (mAb) that selectively targets CD20-expressing B cells. CD20 is a cell surface antigen found on pre-B cells and mature memory B cells, but it is not expressed on lymphoid stem cells and plasma cells. While ocrelizumab selectively depletes CD20-expressing B cells, the capacity of B-cell reconstitution and pre-existing humoral immunity are preserved. In addition, innate immunity and total T-cell numbers are not affected.

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. In vitro, binding of ocrelizumab to CD20 on target cells induces immune effector mechanisms such as antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and apoptosis. In vivo, ocrelizumab selectively and effectively depletes CD20 B cells presumably through one or more of the mechanisms cited above.

Type of Application and aspects on development

This application was submitted in accordance with Article 8.3 of Directive 2001/83/EC.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a concentrate for solution for infusion containing 300 mg (30 mg/mL) of ocrelizumab as active substance. Other ingredients are: sodium acetate trihydrate, glacial acetic acid, trehalose dihydrate, polysorbate 20 and water for injections.

The container closure system consists of a 15 mL colorless Type I glass vial with a 20 mm rubber stopper crimped with a 20 mm aluminum seal fitted with a plastic flip-off cap.

The Ocrevus active substance and finished product manufacturing processes have been developed by extensive use of the tools offered by ICHQ8, i.e. Quality by Design (QbD) principles. However, no Design Space is claimed at present.

2.2.2. Active Substance

General Information

Ocrelizumab is a humanized monoclonal antibody based on the human immunoglobulin G1 (IgG1) framework that contains heavy chain VHIII and light chain $V_{\kappa}I$ subgroup sequences. The recombinant antibody is produced in Chinese hamster ovary (CHO) cells and consists of two identical 213 residue light chains and two identical 451 or 452 residue heavy chains.

The molecular formula of intact ocrelizumab is $C_{6482}H_{9952}N_{1712}O2_{014}S_{46}$. The calculated molecular mass of intact deglycosylated ocrelizumab is approximately 145,564 Da (peptide chains only, without heavy chain C-terminal lysine residues).

The light and heavy chain sequences of ocrelizumab have been presented in the dossier.

The C_H2 domain of each heavy chain has a single conserved glycosylation site at Asn302. The N-linked oligosaccharides of ocrelizumab are typical of those observed on other CHO-produced monoclonal antibodies.

The C-terminal lysine residues of the heavy chains (Lys452) are removed by the action of basic carboxypeptidases during the cell culture process.

Fourier transform infrared spectroscopy (FTIR) confirmed that ocrelizumab primarily has a β-sheet structure, consistent with the structure of an IgG1 antibody.

Intact IgG1 antibodies have five cysteine residues per light chain involved in disulfide linkages, including two intrachain disulfide linkages per light chain (Cys23-Cys87 and Cys133-Cys193) and one interchain disulfide linkage (Cys213 of the light chain-Cys225 of the heavy chain). Intact IgG1 antibodies have eleven cysteine residues per heavy chain involved in disulfide linkages. These linkages include four intrachain bonds per heavy chain (Cys22-Cys96, Cys149-Cys205, Cys266-Cys326 and Cys372-Cys430), two disulfide bonds between the two heavy chains (Cys231-Cys231 and Cys234-Cys234), and one disulfide bond between the heavy chain and the light chain of each of the heterodimers (Cys213 of the light chain-Cys225 of the heavy chain).

Manufacture, characterisation and process controls

Ocrelizumab active substance is manufactured by Genentech, a member of the Roche Group, at New Horizons Way, Vacaville (VV), CA, USA. Storage of the active substance occurs in Basel, Switzerland.

Description of the manufacturing process and process controls

The manufacture of ocrelizumab active substance is following the Applicant's standard production techniques, including a stable, transfected CHO cell line, with thaw, seed, and inoculum stages leading up to production culture using a fed-batch process. The culture fluid is harvested using a centrifuge/filtration system.

The purification of ocrelizumab is also following the Applicant's standard purification techniques for monoclonal antibodies, including immobilized Protein A affinity, low pH hold for viral inactivation, cation exchange chromatography, anion exchange chromatography, small-virus retentive filtration, and ultrafiltration and diafiltration steps.

Control of materials

The origin of the cell substrate, relevant information on the vector map, as well as the complete nucleotide sequence of the expression vector has been presented. The cell banking system is conventional using standard culture conditions for mammalian cells. Specifications for the cell banks have been presented and were found adequate.

The protocol for establishing a new Working Cell Bank (WCB) is provided.

The Master Cell Bank (MCB) MCB and WCBs have been tested for identity, microbial purity and freedom of adventitious agents, in accordance with relevant monographs and guidelines.

Genetic consistency testing has been performed in accordance with ICH Q5B.

The information on the raw materials used in the manufacturing process has been presented in detail. Specifications for the non-compendial (in-house) raw materials used in the manufacture of ocrelizumab active substance have been provided.

The raw materials of biological origin are regarded as safe with respect to virus and transmissible spongiform encephalopathy safety.

Controls of critical steps and intermediates

The microbial control strategy for the active substance manufacture consists of action limits and acceptance criteria.

Small-scale models were used in the process characterisation studies to guide the designation of process parameters as critical or not. The small-scale models used for the fermentation- and purification process of ocrelizumab active substance manufacturing process have been evaluated to assure that they are representative of the full scale process. Characterisation of the ocrelizumab active substance manufacturing process is extensive and has been carefully outlined in the dossier. Risk Ranking and Filtering (RRF) of process parameters in the seed train-, in the inocolumn train-, in the production fermenter-, in the harvest and in the centrifugation step have been detailed in the dossier. Based on the identified process parameters, process characterisation studies have been designed to evaluate the possible impact of the process parameters on the identified ocrelizumab Critical Quality Attributes (CQAs). Uni- and Multivariate studies have been conducted to study the possible correlation between single Critical Process Parameters (CPPs) and CQAs as well as the combination of several CPPs on the CQAs. Multivariate studies were statistically designed experiments (DoE). Initial DoE studies aimed at understanding main effect on key performance indicators (KPIs) and CQAs. Based on the outcome of the initial DoE in some cases a follow-up study was performed to improve process understanding or to apply process knowledge to other steps. The results of all production culture process characterisation/process validation (PC/PV) studies support the proposed acceptable ranges for the production process parameters.

The small-scale characterisation- and validation studies designed and conducted for the purification process have also been carefully outlined in the dossier. PC/PV studies for each purification step included multivariate studies with additional univariate studies conducted for each of the chromatography steps. Multivariate studies were either statistically designed experiments or studies with multiple parameters set to worst-case conditions. Initial Design of Experiments (DoE) studies aimed at understanding main effect on KPIs and CQAs. Based on the outcome of the initial DoE in some cases a follow-up study was performed to improve process understanding or to apply process knowledge to other steps.

In the initial submission a design space was claimed for the active substance manufacturing process. The design space claim was, however, withdrawn later in the evaluation process.

Process validation and/or evaluation

The proposed commercial process was demonstrated to be reproducible and produce active substance of consistent quality. Data generated from the validation batches all meet the predefined validation study acceptance criteria as well as the proposed commercial acceptance criteria.

The active substance manufacturing processes have been evaluated for consistency of CQAs, other quality attributes, and KPIs.

Data presented also support that material produced with the proposed commercial process is overall consistent with the clinical material (produced using previous versions of the manufacturing process).

Removal of product- and process related substances and impurities, as well as, raw materials and leachables to a consistent and acceptable level has been demonstrated.

In-process pool hold times have been appropriately evaluated. Reuse of the resins as well as the reuse of the ultra-diafiltration (UFDF) membrane has been evaluated in small-scale and full scale studies. Data support the proposed reuse.

The shipping qualification studies have demonstrated that the transport processes are capable of maintaining frozen drug substance inside the vessel at the appropriate storage condition.

Manufacturing process development

Ocrelizumab has a long clinical and manufacturing development history. In addition to the intended commercial process, four development versions of the process have been used over time. Data from

the various comparability studies conducted shows a difference in glycosylation with consequential differences in potency between early clinical, pivotal clinical and commercial process materials.

Studies concluded that the manganese level in the production cell culture medium contributed to the glycosylation differences observed. The ocrelizumab glycoform distribution is sensitive to manganese (Mn) levels in the production culture medium. Manganese levels in the production medium can vary based on contributions from multiple sources.

The Applicant explored a process change to bring the commercial process material more in line with the pivotal clinical trial material.

A Major Objection was however raised in relation to the proposed process change and the Applicant was requested to provide further data.

The Applicant responded that the strategy chosen by the Applicant was to not change the process but rather control the Mn level in the cell culture medium. This proposal was found acceptable as comparability at the quality level between the material used for pivotal clinical studies and the material produced with the proposed commercial process is acceptably ensured. In addition, the Applicant has committed to provide further data to support the proposed approach once further experience has been gained.

To ensure process consistency, two measures of potency testing (CDC and ADCC), as well as the correlated glycan attributes (G0 and G0-F), are included on the control system.

Characterisation

The predicted masses and primary structure was confirmed by orthogonal methods: Electrospray Ionisation-Mass Spectrometry analysis (ESI-MS), Liquid Chromatography-MS and LC-UV peptide mapping. Endoproteinase Lys-C Peptide map in conjunction with high performance liquid chromatography (HPLC) MS-MS was also used for the verification of the primary structure and the assignment of the disulfide bonds.

Overall, glycan structures consistent with those found in CHO-derived monoclonal antibodies and all ocrelizumab glycans are found on other human immunoglobulins.

The oxidation pattern and, where applicable, the corresponding functional sites has been studied through analysis of forced oxidized samples. The oxidation pattern was found to be consistent between the batches from different manufacturing process versions for ocrelizmab.

Reduced tryptic peptide maps were analysed by LC-MS. The level of deamidation and isomerization was generally low and consistent between batches.

The distribution of the size related variants of ocrelizumab was found to be consistent between batches.

The charge variants were characterised by orthogonal methods.

The biological characterisation covered the combined effector functions of ocrelizumab, which are the different Fc mediated functions upon the binding to CD20 on the B-cells.

The influence of different stress parameters on the biological activity of ocrelizumab has been studied.

The biological activity of enriched fractions of variants for size, glycosylation, glycation, deaminidation, charge related variants and unpaired cysteine forms was analysed in detail.

Specification

The active substance specification (methods and acceptance criteria) is overall acceptable. The specification contains tests for pharmacopoeial methods as well as specific methods to ensure sufficient safety and quality with respect to identity, purity, quantity and potency.

The CQAs that are important for ensuring a consistent active substance quality were identified using the QbD approach. Not all identified CQAs are subject to active substance release testing as they are controlled by other means (in-process controls or control of process parameters).

For setting of individual CQA Acceptance Criteria (AC) the cumulative impact of all CQAs with regard to bioactivity and PK has been considered. For CQAs with safety and immunogenicity impact, the AC have been justified by considering clinical experience with ocrelizumab and other relevant molecules developed using the platform process. The approach has its main focus on the safety and efficacy impact of the CQAs.

Analytical methods

The analytical methods used have been appropriately described. All methods have been validated in accordance with ICH Q2.

Batch analysis

Batch analysis data of the active substance were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

Reference standards from clinical processes have been established. The current Primary reference standard and Secondary reference standard are from the proposed commercial process.

Acceptable information has been provided on the generation and testing of the reference standards.

Stability

A shelf-life of 36 months has been proposed and agreed for the active substance. The shelf-life is supported by real-time, real-condition stability data. Primary stability data consist of six active substance batches, including three validation batches and three representative clinical batches.

Selected analytical methods used in the stability study have been justified based on their stability indicating properties. No significant changes have been introduced to the methods over time.

The data presented do support the proposed shelf-life. All results met the acceptance criteria for all parameters tested..

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The commercial ocrelizumab finished product contains a nominal fill volume of 10.0 mL at 30 mg/mL ocrelizumab in 20 mM sodium acetate, 106 mM trehalose dihydrate, 0.02% (w/v) polysorbate 20, at pH 5.3. The container closure system consists of a 15 mL colourless Type I glass vial with a 20 mm rubber stopper crimped with a 20 mm aluminum seal fitted with a plastic flip-off cap.

Ocrevus is presented as a sterile, single-use concentrate for solution for intravenous (IV) infusion. The formulation does not contain preservative. A minimum fill volume of 10.5 mL will assure the delivery of the nominal quantity declared on the label.

The excipients used are common for biopharmaceutical products.

No excipients of human or animal origin or novel excipients are used in the manufacture of ocrelizumab finished product. The excipients all comply with the specification of relevant monographs (Ph.Eur).

Formulation development

Formulation studies have been carefully outlined in the dossier. The robustness of the formulation has been established via a multivariate formulation study.

For clinical studies carried out in the multiple sclerosis indication, the finished product formulation 1 as well as formulation 2 was used. However, non-clinical studies were performed using formulation 1.

Formulation 1 and 2 mainly differ in relation to the concentration of ocrelizumab and excipients used. Both formulations use well known excipients for injectable biopharmaceuticals.

Finished product process development

Clinical material was manufactured at Genentech's Clinical Parenteral Manufacturing Facility (CPMF) in South San Francisco (SSF), California; Genentech Parenteral Manufacturing Facility (GPMF) in SSF; and Roche Diagnostics GmbH (RDG), Mannheim, Germany. The proposed commercial manufacturing site is RDG Mannheim.

The comparability study conducted for material from SSF and RDG included three validation batches from the commercial site (RDG), which were compared to the historical manufacturing ranges. All data were within the release criteria and thereby supported comparability of the finished product from the two sites. Comparability was further supported by comparisons of degradation rates and profiles from forced stability studies.

Manufacturing process characterisation

A detailed description of the development of the finished product manufacturing process has been provided. No Design Space has been claimed for the finished product manufacturing process, however, QbD tools have been used for the process development and characterisation. A number of small-scale studies have been conducted, which are further supported by the full-scale validation studies.

Based on results from process characterisation/development and validation studies, no CPPs were identified for the buffer preparation and pooling/dilution/mixing processes. No significant impact on any of the relevant QAs was observed during studies of the mixing processes. These studies support the process parameter ranges proposed.

No quantifiable impact on any of the relevant QAs was measured during process characterisation and validation studies of the bioburden reduction or sterile filtration process. Based on results from process characterisation and validation studies, no parameters were considered to be CPPs for the filling process. No significant impact on any of the relevant quality attributes was measured during studies of the filling process.

Linkage-study

The results from the two manufacturing scale linkage studies, which subjected the bulk active substance and finished product to several cumulative worst case stress conditions and extended hold times, demonstrated that the finished product unit operation is robust.

Container closure system

The container closure system consists of a 15 mL Type I glass vial (Ph.Eur), a fluoro-resin-laminated liquid rubber stopper and an aluminium seal fitted with flip-off plastic cap. The results of extractables

and leachables studies demonstrate that this vial/stopper configuration is suitable for use with the finished product.

The primary packaging components are made of commonly used materials for the packing of biopharmaceutical medicinal products. The components of the packing materials comply with relevant monographs (Ph.Eur.). Secondary packaging is a paperboard box and label.

Microbiological attributes

The microbiological quality and sterility of is the finished product is controlled by a combination of measures: measurement of pre-filtration bioburden level, two serial steam-sterilized 0.22 µm pore size filters, use of depyrogenated and sterilised vials and stoppers, use of a validated capping and crimping process, test for sterility and endotoxin and closure integrity testing.

Manufacture of the product and process controls

RDG Mannheim is the manufacturer responsible for manufacture of the finished product, quality control testing, batch release and storage of finished product (unlabelled vials). F. Hoffmann-La Roche Ltd., Kaiseraugst, Switzerland is responsible for labelling, secondary packaging and storage of finished product.

The finished product manufacturing process starts with thawing of the active substance, followed by optional pooling, mixing, filtration and aseptic filling. Finished product filtration is performed by in-line sterile filtration during the vial filling process step.

Finished product process validation was performed on batches manufactured with the commercial process at the commercial site RDG Mannheim.

All analytical release data met the specifications. Stability studies of the validation batches were initiated and are currently ongoing. The validation study covered thawing of active substance, buffer preparation and pooling/dilution/mixing, bioburden reduction filtration and in-line sterile filtration, hold times and process times for finished product in stainless steel vessels, aseptic filling, capping and crimping, final inspection of vials and filter validation.

The process validation data demonstrate that the ocrelizumab finished product manufacturing process is robust and consistently yields finished product that meets the predetermined acceptance criteria of all quality attributes, and that the in-process tests are suitable to monitor the manufacturing process.

Environmental monitoring, equipment validation and media fills have been addressed.

Product specification

The finished product specifications are generally found acceptable. The specifications contain tests for pharmacopoeial methods as well as specific methods, covering appearance and description, general tests, identity, purity, endotoxins, quantity, potency, sterility and container closure integrity.

Analytical methods

The compendial methods have been verified for their intended use.

The finished product has essentially the same specifications as the active substance. The attributes that are specific for the finished product are all pharmacopoeia requirements and thereby considered mandatory to test.

Potency testing at finished product level is done by CDC bioassay.

Batch analysis

Batch analysis data for the finished product were provided. The results are within specifications and confirm consistency of the manufacturing process.

Reference materials

The reference standard used for the finished product release and stability is the same as that used for the active substance.

Stability of the product

The commercial shelf life of the finished product is determined based on the long-term stability data of all primary batches and is supported by the accelerated, stress, and additional stability studies performed. The data provided support a shelf life of 18 months at the storage condition of 5°C (unopened vial).

An accelerated stability study (25°C) and a study under stressed conditions (40°C) have been conducted to support comparability between the materials from different processes (active substance) and formulations (finished product).

The photostability study demonstrated that the finished product in unprotected vials should not be exposed to intense light for prolonged periods and that the vials should be stored in the carton.

A compatibility study was conducted to confirm the physicochemical stability of diluted solutions of ocrelizumab stored in 0.9% sodium chloride solution under recommended in-use conditions. The study supported the proposed in-use stability of 24 hours at 2-8°C and subsequently for 8 hours at room temperature for the diluted solution. The study also demonstrated that diluted solutions can be administered interchangeably with the various components tested: IV bags with product-contacting surfaces of polyvinyl chloride (PVC), polyolefin (PO), polyethylene (PE), or polypropylene (PP); in-line filter membranes composed of polyethersulfone (PES) or polysulfone (PSU); and infusion sets and other infusion aids composed of PVC, PE, polybutadiene (PBD), or polyetherurethane (PEU). The diluted solutions should be administered by IV infusion with an in-line filter.

Overall, the proposed shelf-life is considered supported by the data provided.

Adventitious agents

The materials of biological origin are obtained from a controlled safe source or treated appropriately to ensure absence of viral and non-viral adventitious agents.

The in-process testing system documents the absence of contamination throughout the active substance manufacturing process.

The viral clearance capacity of the purification process has been validated for the low-pH step, AEX chromatography and small-virus retentive filtration. The cumulative effect of the three process steps reduces the viral risk to a negligible level.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

One major objection on quality was raised during the procedure, relating to comparability between material used in the pivotal clinical trials (v0.4) and the commercial material (v1.0) and the related control of Manganese levels in the production bioreactor media.

To assure that the commercial material is comparable to the clinical trial material the Applicant has included controls for Mn concentration in the cell culture media and also introduced ADCC potency as an active substance release test.

The Applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing processes. A design space was initially claimed for the active substance. However, the Applicant has withdrawn their claim for a design space during the review. No design space was claimed for the finished product.

Two recommendations have been agreed relating to the control of glycosylation.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends two points for investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical development program consisted of a battery of primary and safety pharmacology studies as well as pharmacokinetics (PK) and toxicology studies. These studies, except for the pilot toxicology study in cynomolgus monkeys (see below), were conducted using IV administration and were consistent with International Conference of Harmonisation (ICH) guidelines. The cynomolgus monkey was considered the most appropriate model for assessing PK, pharmacodynamics (PD) and nonclinical safety *in vivo* since ocrelizumab is only known to bind to human and nonhuman primate CD20. No dedicated secondary and drug interaction pharmacology studies were performed.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Several in vitro studies were conducted to characterize the binding of ocrelizumab to human CD20, complement C1q, and Fc gamma (Fcγ) receptors, and the antibody's ability to mediate antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and apoptosis. According to the Applicant, ocrelizumab is only known to bind to human and non-human primate CD20 but not rodent CD20, therefore, in vitro pharmacology studies were performed using human reagents or cell lines, and utilized a known chimeric anti CD20 molecule, rituximab, as a reference because ocrelizumab and rituximab may share similar mechanisms of action, as well as may differ in activities.

Nonclinical in vivo pharmacology investigations of B cell depletion were conducted in cynomolgus monkeys in which the effectiveness of ocrelizumab in depleting B cells in peripheral blood was

assessed using three measures: B cell counts immediately before administration of the second dose, nadir B cell counts, and duration of total B cell depletion. In some studies, the degree of tissue B cell depletion from spleen, lymph nodes, and bone marrow was also measured.

Binding potencies of Ocrelizumab for the high affinity Fcγ receptor, FcγRIa, and for the low affinity Fcγ receptors, FcγRIIa and FcγRIIb, were very similar to those of rituximab. Binding of Ocrelizumab to the low affinity Fcγ receptor, FcγRIIIa, was stronger than that of rituximab for both allotypes of this receptor. Binding of Ocrelizumab to human complement C1q was very similar to that of rituximab with EC50 values of 0.72 ± 0.015 µg/mL (n = 3) and 0.62 ± 0.14 µg/mL (n = 3), respectively.

Ocrelizumab showed strong activity in NK cell mediated antibody-dependent cellular cytotoxicity (ADCC). The potency of ocrelizumab was approximately four times that of rituximab based upon EC50 values. Ocrelizumab also effectively promoted ADCC mediated by PBMCs.

Both ocrelizumab and rituximab induced apoptosis of Ramos cells when cross linked with anti-human Fc. The apoptotic activity of ocrelizumab was slightly lower than that of rituximab.

Finally, the ability of ocrelizumab to mediate CDC activity was demonstrated using human complement and WIL2 S cells as targets where ocrelizumab was approximately 3 to 4 fold less potent than rituximab in promoting this activity.

Antibody-dependent cellular phagocytosis (ADCP) was assessed by both microscopic imaging and two-color fluorescence flow cytometry. In each experiment, maximal ADCP with ocrelizumab was at least 20%, whereas ADCP without antibody or with trastuzumab was always less than 10%. According to the study report, the extent of phagocytosis of ocrelizumab-opsonized target cells by macrophages appeared to correlate with the concentrations of ocrelizumab in a dose-responsive manner. Thus, the results of the study suggest that ocrelizumab induces ADCP of CD20-expressing target cells by monocyte-derived macrophages. A two-week (non-GLP) in vivo study was performed in cynomolgus monkeys (n=4/group) to assess the pharmacodynamics properties of ocrelizumab (study 02-182-352). Two animals per group were kept for an 8-week recovery period before euthanization. Animals were administered two intravenous (IV) bolus doses (0.05 or 10 mg/kg) of ocrelizumab 1 week apart (Day 1 and Day 8). No signs of test-article related toxicity was seen. Partial depletion of B-cells at the low dose (0.05 mg/kg x 2) and full depletion at the high dose (10 mg/kg x 2) of ocrelizumab was demonstrated. There were no observed differences between vehicle control and ocrelizumab cohorts in absolute T cell counts. The duration of full depletion for total B cells in the high dose groups was at least 9 days and less than 35 days. Total B cells returned to near baseline levels in recovery animals at the time of terminal necropsy.

An additional PD study was performed in cynomolgus monkeys to further assess the B-cell depleting properties of ocrelizumab (Study 03-0235-0349). Animals were given two IV bolus doses of ocrelizumab at 0.2, 0.5, or 2.0 mg/kg on Days 1 and 8 and thereafter all entered a 12-week recovery period. B cell numbers (measured by flow cytometry analysis) were depleted in animals one hour after receiving ocrelizumab on Day 1 at all three dose levels. B cell numbers partially recovered by Day 8 in the low dose group, and to a lesser extent in the medium dose group. The high dose resulted in a nearly complete depletion of peripheral blood B cells from which the animals did not recoup as quickly. After the second dose of ocrelizumab, B cells decreased with increasing dose and were suppressed to a nadir value. A decrease in mean lymphocyte counts was observed after the Day 1 dose administration in all dose levels. This decrease in mean lymphocyte counts was less pronounced after the second dose administration (Day 8) and recovered to near baseline for the two lowest dose groups; however, lymphocyte counts in the high dose group remained low for at least 2 weeks after the second dose administration. T cell numbers were slightly increased following the administration of ocrelizumab, but cell numbers returned toward baseline values during the course of the study.

The Applicant has also presented data regarding B-cell depletion and –repletion from toxicity studies in cynomolgus monkeys (Studies 02-182-0352, 03-0113-0349, 03-0114-0349, and 04-0192-0134).

The long-term multiple-dose study (Study 04-0192-0134) and retreatment study (Study 03-0114-0349) provided the most extensive follow-up data on duration of B-cell depletion and repletion because blood samples were collected from animals for a prolonged period (approximately 10.5 months from

first dose to recovery necropsy). The duration of peripheral depletion was approximately 3 months at the 50 and 100 mg/kg (x 2) dose levels (Study 03-0114-0349).

After retreatment at 100 mg/kg x 2, the duration of peripheral depletion was again approximately 3 months even though mean B-cell counts were only approximately 35% of baseline values at the time of retreatment. B-cell depletion in lymphatic organs was high but not complete. Depletion in the spleen and lymph nodes was dose dependent; no dose correlation was observed in bone marrow. Depletion was also lower in bone marrow (B-cell counts reduced by approximately 2-fold in treated vs. control) when compared with depletion in the spleen and the lymph nodes (B-cell counts reduced by as much as 5- and 30-fold, respectively).

A GLP safety, PK, and PD study in cynomolgus monkeys was conducted in which the PD profile of the v0.2 material was evaluated and compared with that of the v0.1 material. The v0.1 and v0.2 materials both depleted blood B cells effectively and showed similar PD profiles in cynomolgus monkeys (Study 07-0171).

The non-clinical studies presented by the Applicant to demonstrate the pharmacodynamic properties of ocrelizumab support its mode of action as a reversible B-cell depleting molecule. In vitro and in vivo comparability studies indicate similar activity and potency for the two batches of early clinical process material (Study 06-1069). In the Quality section of the dossier, further comparability data are presented that show a difference in potency between early clinical, pivotal clinical and commercial materials. The material used within the nonclinical studies was, if anything, more potent than the material used in pivotal studies. Although the material used in nonclinical studies may not adequately provide toxicology coverage of the commercial material, any concern can be mitigated since the material represents a worst-case with respect to safety outcomes.

To provide further reassurance that the intent-for-market batches and previous ocrelizumab batches used for non-clinical and clinical studies are indeed comparable, and that quality differences do not give rise to e.g. differences in efficacy and safety end points in the clinical setting, the Applicant commits to provide pharmacokinetic (PK) and pharmacodynamic (PD) (blood B-cell depletion) clinical data from the commercial material as a post-marketing commitment.

No secondary pharmacodynamic or pharmacodynamics drug interaction studies have been conducted. No stand-alone safety pharmacology studies were performed. Safety pharmacology endpoints were included in repeat dose studies in monkey. This approach is endorsed. Respiratory and cardiovascular measurements were performed in two studies where the animals were non-sedated and two studies where the animals were lightly sedated with ketamine. CNS observational battery was included in one study, males only. No treatment related observations in either respiratory, cardiovascular or CNS observations were noted following doses of up to 100 mg/kg ocrelizumab.

Safety pharmacology programme

No stand-alone safety pharmacology studies were performed. Safety pharmacology endpoints were included in repeat dose studies in monkey. This approach is endorsed. Respiratory and cardiovascular measurements were performed in two studies where the animals were non-sedated and two studies where the animals were lightly sedated with ketamine. CNS observational battery was included in one study, males only. No treatment related observations in either respiratory, cardiovascular or CNS observations were noted following doses of up to 100 mg/kg ocrelizumab.

2.3.3. Pharmacokinetics

The pharmacokinetics of ocrelizumab were investigated in mice (including wild type and huCD20 transgenic mice), rats, and cynomolgus monkeys. The pharmacokinetics of ocrelizumab were evaluated in several single- and multiple dose studies at various dose levels. Several assays to detect antibodies to ocrelizumab were used in the non-clinical PK studies and the Applicant presents a table for overview of which studies the methods were used. This is considered appropriate.

Study Report 4.2H7.2.AVR_1 was validated to quantify both mouse and rat ocrelizumab serum levels.

PK parameters in wild-type mice and wild-type rats given a single IV bolus dose of ocrelizumab across a 100-fold range of doses (0.5, 5, and 50 mg/kg) lacked dose dependence, as expected for a non-binding species (Studies 03-0155-0349 and 03-0157-0349). Further studies were performed in cynomolgus monkeys as this species was considered the most appropriate.

In cynomolgus monkeys, ocrelizumab CL and T½ were dose dependent and non-linear. As the dose increased, CL decreased and T½ increased. Ocrelizumab had a long terminal T½ following a rapid initial distribution phase and, which could indicate that binding to circulating and tissue-resident B cells reduces levels of free ocrelizumab, CL was partly dependent on CD20 antigen-bearing B cells (Studies 02-0182-0352, 03-0235-0349, 03-0113-0349, 03-0684-0134, 04-0192-0134). No gender differences were observed in PK parameters.

At lower dose levels (0.2-10 mg/kg) given intravenously, ocrelizumab exhibited nonlinear CL in cynomolgus monkeys. In general, as the dose or dosing frequency or both were increased in cynomolgus monkeys, CL decreased (from 154 mL/day/kg at 0.2 mg/kg to 10.3 mL/day/kg at 10 mg/kg). Accordingly, T½ increased from 1 to 7 days when the dose was increased from 0.2 to 10 mg/kg (Studies 02-0182-0352 and 03-0235-0349).

At higher doses (above 10 mg/kg) in the cynomolgus monkey, ocrelizumab exhibited mostly linear CL (Studies 03-0113-0349, 03-0114-0349, and 03-0684-0134). Typically, a fast distribution phase followed by a prolonged elimination phase was observed. However, increased dosing frequency also resulted in decreased CL and increased T½.

Toxicokinetics were also assessed in reproductive toxicology studies (Study 04-1272-1342). Similar to non-pregnant cynomolgus monkeys, maximum serum concentration (Cmax) and area under the curve (AUC) for ocrelizumab increased in an approximately dose-proportional manner. Ocrelizumab serum concentrations were generally higher in maternal serum compared with fetal serum at the time of cesarean section; the fetal-to-maternal serum concentration ratio of ocrelizumab was variable and ranged from 0.495 to 4.47 (90%, or 17/19, of the fetus-dam pairs had maternal concentrations higher than those of the fetus). Low amniotic fluid concentrations were detected in 11 of 12 animals.

In a perinatal and postnatal developmental toxicity study, ocrelizumab was administered weekly to pregnant cynomolgus monkeys from the beginning of organogenesis through approximately 1 month after natural delivery. Exposure (Cmax and AUC) to ocrelizumab increased generally dose proportionally. Neonate to maternal concentration ratios ranged from 0.0205 to 0.848 at the 20 mg/kg dose level and from 0.0283 to 0.411 at the 100 mg/kg dose level. Measurable levels of ocrelizumab were detected in milk during the lactation period in most of the animals (Study 06-1260).

Anti-drug antibodies (ADAs) to ocrelizumab were detected in most studies in cynomolgus monkeys and were discussed by the Applicant. The presence of ADAs to ocrelizumab did impact exposure in some low-dose animals but there was only minimal impact in ocrelizumab exposure in animals given doses above 10 mg/kg. It is acknowledged that the induction of antibody formation in animals is not predictive of a potential for antibody formation in humans, in compliance with ICH S6 (R1) guideline.

PK parameters for the two different clones were found to be similar in a cynomolgus monkey study testing two doses of i.v. ocrelizumab 50 mg/kg (given 2 weeks apart). No additional studies comparing subsequent versions (production batches) could be identified and as such, the data from PK studies presented in the non-clinical dossier can only be considered supportive for assessment of the PK profile of ocrelizumab subsequent versions.

Tissue distribution studies in mice engineered to express huCD20 (huCD20 transgenic mice) demonstrated that, while ocrelizumab does not recognize CD20 in wild-type mice, there was clear binding of ocrelizumab with B cells in huCD20 transgenic mice. Moreover, huCD20 transgenic mice cleared ocrelizumab significantly faster and in a dose-dependent manner than wild-type mice.

Tissue distribution studies by positron emission tomography imaging in cynomolgus monkeys indicated the presence of the labelled antibody within blood pool and distribution to organs having high levels of

B cells (e.g., spleen and lymphoid tissues). These data support the assertion that CD20 expression on B cells is involved in the in vivo distribution and clearance of ocrelizumab (Study 15-0538).

A dosimetry study was also performed in nonhuman primates to determine radiation absorbed dose estimates to critical organs. Using whole-body imaging in cynomolgus monkeys, radiation exposure of [111In]ocrelizumab to human subjects was estimated. The uptake and bio-distribution was consistent with other radiolabeled anti-CD20 therapies. As a measure of radiation exposure to the entire body, the effective dose of [111In]ocrelizumab was 0.16 mSv/MBq (Study 14-3756).

The expected products of the metabolism derived proteins and peptides, including IgG1 monoclonal antibodies such as ocrelizumab, are small peptides and individual amino acids. Free circulating ocrelizumab enters the metabolic pathway of endogenous soluble IgG, whereas ocrelizumab bound to CD20+ lymphocytes can be phagocytosed together with destroyed B cells by infiltrating macrophages and granulocytes. Therefore, in accordance with ICH S6, no formal metabolism studies were performed and this is acceptable.

2.3.4. Toxicology

In the toxicology program a variety of dosing regimens were evaluated in cynomolgus monkeys, including weekly x 2, Q2W x 2, Q2W x 2 for two cycles [cycle x Q2W x 2], weekly x 4, and Q3W x 8. No single dose toxicity studies were performed. This is acceptable. In each repeat-dose study, all available animals were evaluated for clinical signs and changes in food consumption, body weight, physiological indices (heart rate, blood pressure, respiration rate, body temperature), ECG's, physical and ophthalmic examinations, clinical pathology, hematology, urinalysis, organ weight, and gross and histologic pathology. Additionally, peripheral blood and lymphoid tissue B cells were evaluated by flow cytometry and lymphoid tissue B cells were evaluated by IHC in the GLP studies.

In the repeat dose toxicity studies, labelled anti CD20 reagents could not be used to identify CD20+ B cells in these studies as the target is masked by drug, therefore anti CD40 was used to identify B cells in cynomolgus monkeys (Vugmeyster et al. 2003).

In all studies, ocrelizumab was well tolerated. A dose dependent CD40+ B-cell depletion was observed. Overall, ocrelizumab was well tolerated with no adverse findings identified. Drug related findings were restricted to pharmacologically mediated reductions in B cells and secondary findings related to B cell depletion, including reduction in size and/or numbers of lymphoid germinal centres in spleen and lymph nodes. Following recovery periods B-cell repletion was observed to some degree, more so in groups treated with 50 mg/kg or less, but following 100 mg/kg ocrelizumab, B-cell repletion was also observed following recovery phase of sufficient degree.

In study report Study 04 0192 0134, slight to mild reductions in circulating red blood cell mass was observed in both treated groups. This was considered related to ocrelizumab treatment in this study. However in most other repeat dose studies performed, some degree of fluctuations were observed in red blood cell parameters, and considered not related to treatment, but rather related to the frequent blood sampling procedures. Indeed one female in the present study, which showed low red blood cell count (2.65 and 2.69 106 µL on Days 147 and 149 respectively, compared to the pre-dose count of 5.15 106 µL for the same animal) also presented with bruising on the femoral area (but so did a number of other animals with higher blood cell counts as well). The observed reductions in red blood cell parameters in this study is considered related to the procedure of blood sampling in this study as well as in the remaining studies. The observed reductions are not higher or more severe in this study than in the remaining toxicology studies.

In the study 03-0114-0349, following Cycle 1 (Q2W), peripheral blood B cells ($CD3^{+}CD40^{+}$) were rapidly reduced to undetectable levels for all treated groups, with repopulation beginning at Week 6 (10 mg/kg) and Week 14 (50 and 100 mg/kg). Following the second cycle administered 14 weeks after the first cycle (50 and 100 mg/kg cohorts, only) there was near complete B cell repletion by Week 43. The rate of B cell repletion was similar for cohorts receiving either one or two cycles (evaluated at 100 mg/kg only). Diffuse lymphocytic and plasmacytic cell infiltrates were observed in the choroid and ciliary body of the eyes in two mid dose females and one male and one female at high dose level. No

related finding were observed in other toxicity studies, but in the tissue cross reactivity study, diffuse staining of lens protein was observed in one of the cynomolgus tissue slides, and in two of the human tissue slides. However, the choroid and ciliary body and lens are distinct anatomical structures that do not share any communication within the eye. As such, there is no linkage between the observation of inflammation in the choroid and ciliary body of four cynomolgus monkeys in Study 03-0114-0349 and the lens protein reactivity noted in one cynomolgus and two human eye frozen tissue sections in the Tissue Cross-Reactivity (TCR) study (Study 03-0216-0349).

In study 07-0171, two batches of ocrelizumab, produced by two different processes was compared. None of the two clones used for producing ocrelizumab compared in this study, are the intent to marked formulation. To support the process change from v0.1 to v0.2 a nonclinical in vivo study was performed, however, the proposed commercial supply is from v1.0, and no nonclinical studies have been described in the nonclinical parts of the dossier to support the transition from the experimental drug substance processes to the final drug substance to be marketed.

The lack of genotoxicity and carcinogenicity studies is in line with the relevant guidance document (ICH S6).

Reproductive toxicity studies

In all the reproductive studies, loading doses were utilized at the start of dosing. The dose level of 20 mg/kg has not been used in the remaining repeat dose studies, where 10, and 50 were most often used, in addition to the high dose level of 100 mg/kg which is also the high dose level in the reproductive studies. In these studies, as well as in the repeat dose studies performed, the general findings of B-cell depletion, both in peripheral blood circulation as well as in lymphoid follicles of the spleen and lymph nodes is expected findings linked to the pharmacology.

For the reproductive study (04-1272-1342) the Applicant describes safety margins of 14.6 and 72.9 based on accumulated dose administered to the animals, for low and high dose respectively.

In the two fertility studies, ocrelizumab treatment at 15/20 or 75/100 mg/kg did not cause any observable changes to fertility parameters or the reproductive organs in males or females. In both studies, depletion of CD40+ B-cells was observed, as well as microscopically observable hypocellularity of lymphoid follicles in spleen and lymph nodes of the treated animals.

In the study of female fertility, one animal in the 15/20 mg/kg/dose presented with clinical signs from Day 164, which upon necropsy was correlated to the finding of a nasal carcinoma. The same animal had shown body weight loss during the treatment cycles and lack of menstrual bleeding at the end of treatment cycle 3. According to the Applicant, the present finding should be regarded as incidental, due to the absence of abnormal proliferative findings in any other animals. The present statement leads therefore to the suggestion that such an effect could be observed also in control (or naïve) animals. However, as seen in the literature, only three cases of spontaneous tumours of the nasal cavity have been found in monkeys [for references see Experimental tumours in monkeys, by Dzhemal Sh. Beniashvili, 1994]. Moreover, more recent data [J. Kaspareit, et al. “Spontaneous neoplasms observed in cynomolgus monkeys (Macaca fascicularis) during a 15-year period”, Experimental and Toxicologic Pathology Volume 59, Issues 3–4, 26 November 2007, Pages 163–169] described only one nasal cavity adenoma.

The occurrence of nasal cavity carcinoma is hence of concern, in light also of clinical data, reporting a higher incidence rate of malignancies in ocrelizumab-treated patients when compared to IFN or placebo groups (Module 2.7.4, Summary of Clinical Safety). A review of historical data from an estimate of more than 20,000 animals over a 24 year period form the CRO, showed only 50 benign and 14 malignant tumours had been found. The only nasal adenocarcinoma identified was from the present study. Overall, it is difficult to draw any firm conclusion on both the incidence and nature of all neoplasms occurring in cynomolgus monkeys over the period 1992-2016. Nevertheless, the neoplasm occurring in just one ocrelizumab-treated animal, leads to the suggestion that a relationship to drug administration is unlikely, given also that this was the only identified nasal neoplasm.

In the embryofetal toxicity study, only expected pharmacology findings consistent with what has been seen in the other repeat-dose toxicity studies, including fertility studies was observed. No adverse toxicity was observed in the pregnant dams nor any signs of teratogenicity or embryotoxicity.

In the maternal animals, persistent B-cell depletion in peripheral blood was observed. Three animals were euthanized moribund, one in each group, including the control group. The cause of moribundity was not established, and relation to treatment with ocrelizumab was not ascertained. The female treated with 15/20 mg/kg/dose ocrelizumab showed renal cortical necrosis. Prior to the third weekly dose, this animal showed a marked ADA response, and the cause of this animal's moribundity may be due to an adverse immune response to ocrelizumab treatment. The adverse immune response in the monkey is not necessarily an indication of risk of human immune response following treatment with ocrelizumab.

Two neonates in the high dose group (75/100 mg/kg/dose) were found dead or euthanized moribund on DB 6 and 138 respectively. The cause of death or moribundity of these two neonates was in part attributed to an opportunistic infection in one animal; weakness due to premature delivery, and immaturity may have been a predisposing factor. The second animal became moribund while nursing from a dam diagnosed with concurrent staphylococcal mastitis. Both the maternal mastitis and the neonatal infections could have potentially been impacted by B cell depletion related to systemic exposure to ocrelizumab.

In the peri- and post-natal study, testicular weights (absolute and relative to brain weight) of the neonates were significantly decreased in the high dose group as compared to study control neonates. Although a relationship to ocrelizumab administration cannot be excluded, given the lack of differences in weights of the accessory reproductive organs (epididymis, prostate/ seminal vesicle weights), the small sample size and the age of neonates in this study, toxicological significance of the testicular weight decrease on testis maturity remains unclear.

Other ocrelizumab-related microscopic changes observed in the neonates included glomerulopathy, lymphoplasmacytic inflammation in the kidney, and lymphoid follicle formation in the sternal bone marrow. Minimal to mild glomerulopathy was noted in 4 of 11 neonates in the 75/100 mg/kg group and 3 of 13 animals in the 15/20 mg/kg group. This comprised a spectrum of glomerular changes ranging from small immature (fetal) glomeruli with concentric fibrosis of the Bowman's capsule (crescent formation) to severely contracted sclerotic glomeruli. Mild lymphoplasmacytic inflammation of the kidneys was observed in 2 of 11 animals in the 75/100 mg/kg group. The extent of lymphoplasmacytic infiltrates was greater than concurrent control animals, and the infiltrating cells were present in nodular aggregates in the interstitium resembling lymphoid follicles. Lymphoid follicle formation was noted in the sternal bone marrow in 5 of 11 animals in the 75/100 mg/kg group, 4 of 13 animals in the 15/20 mg/kg group, and 0 of 13 control animals.

A juvenile toxicity study in cynomolgus monkeys is planned. In the PIP agreed upon with EMA no nonclinical studies are mentioned. However the study is a requirement from authorities in different regions, and when the study is completed it should be submitted to the EMA as well.

However, if the study has been started, and/or the performance of the study is sufficiently justified, the study report should be submitted for assessment upon completion.

Local tolerance

Ocrelizumab local tolerance following IV administration was assessed in a study where a SC formulation was tested, as well as in the repeat dose studies. The IV administration of ocrelizumab did not give rise to any test article related changes, unlike the SC administrations. The local tolerance changes observed following SC administration, led to the discontinuation of the SC formulation, hence the study is not discussed in further detail here.

No dedicated studies on antigenicity, immunotoxicity, dependence, metabolites or impurities were performed. Immunotoxicity was assessed as part of the repeat dose studies as well as the reproductive toxicity studies.

Ocrelizumab at concentrations of 1.0, 5.0, or 10 mg/mL did not cause hemolysis when mixed with an equal volume of human or cynomolgus monkey whole blood, or precipitation or coagulation in human or monkey serum or plasma at equal volume.

2.3.5. Ecotoxicity / environmental risk assessment

The Applicant has provided a justification for not performing a formal ERA. As the drug substance is a monoclonal antibody, this is in line with the current relevant guideline (EMEA/CHMP/SWP/4447/00) and Q&A document (EMA/CHMP/SWP/44609/2010 Rev. 1). In spite of this, the Applicant has performed two acute toxicity studies in aquatic compartment (Manometric Respirometry Test and Acute Ecotoxicity Limit Tests), which showed that the maximal tested concentration was tolerated by the test systems. Furthermore, ocrelizumab was biodegradable.

Ocrelizumab is a monoclonal antibody, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, ocrelizumab is not expected to pose a risk to the environment and no further studies are considered necessary.

2.3.6. Discussion on non-clinical aspects

The non-clinical testing strategy is consistent with ICH S6(R2) guideline. A number of in vitro and in vivo studies were presented in this non-clinical dossier that do indeed support the mode of action for ocrelizumab as a reversible B-cell depleting antibody. The cynomolgus monkey was found to be the most relevant species for in vivo studies, and although anti-drug-antibodies (ADAs) were detected primarily in studies using low doses, this finding is common in studies using monoclonal antibodies and the clinical relevance is considered uncertain. Toxicity findings could be ascribed mostly to the pharmacology of the drug, i.e. B-cell depletion in peripheral blood and lymphoid organs etc, although one concern regarding the finding of an adenoma in the nasal cavity of one female monkey should be further addressed by the Applicant to rule out clinical relevance.

The non-clinical studies presented by the Applicant to demonstrate the pharmacodynamic properties of ocrelizumab support its mode of action as a reversible B-cell depleting molecule. In vitro and in vivo comparability studies indicate similar activity and potency for the two batches of early clinical process materials, (Study 06-1069). In the Quality section of the dossier, further comparability data are presented that show a difference in potency between early clinical, pivotal clinical and commercial process materials. The material used within the nonclinical studies was, if anything, more potent than the material used in pivotal studies. Although the material used in nonclinical studies may not adequately provide toxicology coverage of the commercial material, any concern can be mitigated since the material represents a worst-case with respect to safety outcomes.

To provide further reassurance that the intent-for-market batches and previous ocrelizumab batches used for non-clinical and clinical studies are indeed comparable, and that quality differences do not give rise to e.g. differences in efficacy and safety end points in the clinical setting, the Applicant commits to provide pharmacokinetic (PK) and pharmacodynamic (PD) (blood B-cell depletion) clinical data from the commercial process material as a post-marketing commitment.

2.3.7. Conclusion on the non-clinical aspects

In vitro pharmacology studies provided adequate evidence that upon binding to CD20 expressed on mature B cells, ocrelizumab could mediate B-cell lysis through one or more of the following mechanisms: ADCP, ADCC, CDC, and apoptosis. *In vivo* studies demonstrated a dose-dependent initial rapid depletion of circulating B cells followed by full repletion.

From a pharmacokinetic point of view, the cynomolgus monkey was the most relevant species for non-clinical efficacy and safety studies.

The toxicology program revealed that B-cell depletion was the most prominent effect exerted by ocrelizumab. It moreover provides evidence of safety, to support treatment of the proposed clinical population with ocrelizumab. Adequate information has been included in the SmPC.

Based on the non-clinical data presented by the Applicant regarding pharmacodynamics, pharmacokinetic and toxicology, the application could be approvable.

From a non-clinical perspective the CHMP considered the following measures necessary:

- In order to provide further reassurance on the comparability of the intent-for-market batches and previous ocrelizumab batches used for non-clinical and clinical studies, the Applicant should provide pharmacokinetic (PK) and pharmacodynamic (PD) (blood B-cell depletion) clinical data from the commercial process material as a post-marketing commitment.
- It is recommended that the study report from the planned juvenile toxicity study in cynomolgus monkeys be submitted to EMA upon completion.

2.4. Clinical aspects

2.4.1. Introduction

The clinical pharmacology data supporting this application is based on the three pivotal Phase III trials in MS (WA21092 and WA21093 in RMS, and WA25046 in PPMS). In addition, supportive data from the Phase II study in RRMS patients as well as data from studies conducted in other indications (see

Table 1) have been submitted in order to underpin this application from a clinical pharmacology perspective.

Good Clinical Practice (GCP)

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1: Tabular overview of clinical studies

Study identifier or no.	Phase	Duration of treatment	Indication	Dosage regimen, route of administration	Included in safety analysis	Included in efficacy analysis
Main studies: MS population						
Protocol WA21493	II	96 weeks OLE ongoing	RRMS	**Dose I** Placebo OCR 600 mg IV 2000 mg IV IFN beta-1a IM **Doses 2-4** 600 mg IV 1000/600 mg IV every 24 weeks **OLE** 600 mg IV every 24 weeks	Yes	Yes

Study identifier or no.	Phase	Duration of treatment	Indication	Dosage regimen, route of administration	Included in safety analysis	Included in efficacy analysis
Protocol WA21092	III	96 weeks OLE ongoing	Relapsing MS	IFN beta-1a SC three times/week; OCR 600 mg IV every 24 weeks **OLE** 600 mg IV every 24 weeks	Yes	Yes
Protocol WA21093	III	96 weeks OLE ongoing	Relapsing MS	IFN beta-1a SC three times/week; OCR 600 mg IV every 24 weeks **OLE** 600 mg IV every 24 weeks	Yes	Yes
Protocol WA25046	III	At least 120 weeks. The shortest time on study for a patient contributing to the primary analysis was 132 weeks. The longest was 217 weeks OLE ongoing	PPMS	Placebo IV OCR 600 mg IV every 24 weeks	Yes	Yes
Supportive studies: rheumatoid arthritis (RA) population						
ACT2847g	I/II	One dose	Moderate to severe RA	Placebo IV OCR 20 mg IV 100 mg IV 400 mg IV 1000 mg IV 2000 mg IV All received MTX	Yes	No
ACT4562g	II	20 weeks	Active RA	infliximab IV OCR 400 mg all received MTX	Yes	No
WA18230	I/II	**Part I** Single infusion **Part II** Single infusion	Moderate to severe RA	**Part I** Placebo IV OCR 400 mg IV 1000 mg IV	Yes	No

Study identifier or no.	Phase	Duration of treatment	Indication	Dosage regimen, route of administration	Included in safety analysis	Included in efficacy analysis
		every 24 weeks		1500 mg IV 2000 mg IV **Part II** OCR 400 mg IV 100 mg IV 1500 mg IV All received MTX		
WA20494	III	48 weeks	Active RA	Placebo IV OCR 400 mg IV 1000 mg IV every 24 weeks All received MTX	Yes	No
WA20495	III	48 weeks	Active RA	Placebo IV OCR 400 mg IV 1000 mg IV or MTX every 24 weeks All received leflunomide	Yes	No
WA20496	III	48 weeks	Active RA	Placebo IV OCR 200x2mg IV 400 mg IV Week 24: OCR 200x2mg IV 400 mg IV every 24 weeks All received MTX	Yes	No
WA20497	III	104 weeks	Active RA	Placebo IV OCR 400 mg IV 1000 mg IV every 24 weeks	Yes	No
JA21963	II	24 weeks	RA (≥ 6 months)	Placebo IV OCR 100 mg IV 400 mg IV 1000 mg IV	Yes	No
JA22003	II	24 weeks	RA (≥ 6 months)	OCR 400 mg IV every 24 weeks	Yes	No
Other supportive studies: systemic lupus erythematosus (SLE) and lupus nephritis (LN) population						
WA20499/ ACT4071g	III	One dose	Moderate to severe SLE	Placebo IV OCR	Yes	No

Study identifier or no.	Phase	Duration of treatment	Indication	Dosage regimen, route of administration	Included in safety analysis	Included in efficacy analysis
				400 mg IV 1000 mg IV every 24 weeks		
WA20500/ ACT4072g	III	48 weeks	LN (Class III or IV nephritis due to SLE)	Placebo IV OCR 400 mg IV 1000 mg IV every 16 weeks	Yes	No

OCR=ocrelizumab; IFN=interferon; IV=intravenous; IM=intramuscular; SC=subcutaneous; OLE=open label extension

2.4.2. Pharmacokinetics

The clinical studies contributing with pharmacokinetic (PK) data in the MS population are presented above. One-thousand-four-hundred-twenty-three (1,423) MS patients treated with ocrelizumab and with PK data were included in the studies. Population PK (pop-PK) analyses and exposure-response analyses were submitted in support of the PK and pharmacodynamic (PD) dossier.

In addition, supportive data from seven studies (Studies ACT2847g, JA21963, WA18230, WA20494, WA20495, WA20946, WA20947) in patients with rheumatoid arthritis (RA) was also submitted.

Analytical methods and pharmacokinetic data analysis

A validated enzyme-linked immunosorbent assay (ELISA) was used to quantify ocrelizumab concentrations in serum samples from patients.

Anti-drug antibodies (ADAs) to ocrelizumab in human serum were detected using two validated bridging assay methods. Using affinity-purified polyclonal antibodies directed against ocrelizumab, the relative sensitivity was determined to be ≤7 ng/mL for MS serum (in the absence of ocrelizumab) and in the presence of 20 µg/mL of ocrelizumab, the assay was able to detect 500 ng/mL of the affinity purified antibodies. The two ADA methods showed comparable desired relative sensitivities.

Overall, the analytical methods are adequately validated and are suitable for the purpose.

The final PK model was a 2-compartment model with time-variant clearance. The PK population included all patients in the ocrelizumab group who had at least one measurable concentration value. Ocrelizumab serum concentration-time data were described using non-linear mixed effect analysis to obtain the following pop-PK parameters:

- Clearances with associated inter-individual variability.
- Volumes of distributions with associated inter-individual variability.
- Influence of covariates on above pop-PK parameters.
- Derived exposure measures: cumulative AUC, Cmax and Cmin.

Bioequivalence

During the clinical development program, 4 development versions of ocrelizumab were used. A single development process version has been use in the pivotal MS studies WA21092, WA21093, WA25046, whereas in study WA21493, multiple development process versions were used. A fifth process versionis intended for commercial use but has not been used in any of the pivotal studies. It is currently used in the open-label extension studies, but no clinical data from this study have been submitted.

Bioequivalence studies between any of the product versions have not been performed but analytical comparability has been performed between the development process versions and the commercial process version. The comparability approach is evaluated in the Quality assessment report.

Between the development process used for the manufacture of the pivotal trial material and the commercial process proposed for the manufacture of commercial material, process changes were made and an extensive comparability assessment in accordance with ICH Q5E was applied. The main difference between the versions relates to the glycosylation. In vitro studies have demonstrated that upon binding to CD20 expressed on mature B cells, ocrelizumab selectively depletes B cells through several potential mechanisms, including antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cellular cytotoxicity (ADCC), CDC, and induction of apoptosis. These mechanisms are influenced by the glycosylation profile of the molecule.

The observed differences (between pivotal clinical and commercial versions) are not expected to impact the PK of ocrelizumab but it potentially affects the PD.The activity/potency is lower in the commercial process version compared to the development process versions; this can at least theoretical impact efficacy and safety of ocrelizumab. To further elucidate this issue, a clarification meeting was held in November 2016. At this meeting, the Agencies stated that if full and robust analytical and biological comparability for the 2016 material was demonstrated, additional clinical data may not be required. The Applicant informed that the proposed marketing material would be aligned with material used in the pivotal trials. Further, the Applicant committed to provide PK and PD (blood B-cell depletion) data for the 2014 commercial process material as a post-marketing commitment if required. At the response on Day 180, the Applicant informs that at the quality level several actions have been taken to assure that the commercial process ocrelizumab material is of the same quality as used in the pivotal clinical trial. Manganese level in the production culture contributed to the differences observed in glycosylation profile, and the manganese level in the cell culture medium will now be controlled to ensure product quality consistent with pivotal clinical material.In additionthe Applicant has two measures of potency testing (CDC and ADCC), as well as the correlated glycan attributes (G0 and G0-F) onthe drug substance control system. All test limits are aligned with the clinical experience of pivotal clinical drug substance. Due to these findings of comparability between the two manufacturing processes, the Applicant does not consider that it is necessary to present clinical data. This is agreed and therefore clinical PK and PD data will not be requested.

Absorption, distribution and elimination

As ocrelizumab is administered intravenously, bioavailability is 100%.

Data regarding distribution in RMS patients derive from the pop-PK analysis of Studies WA21492, WA21093 and Study WA21493. The concentration-time course of ocrelizumab was accurately described by a two-compartment PK model and with steady-state PK parameters typical for an IgG1 mAb. For a reference patient (female, weighing 75 kg, with a baseline B-cell count of 0.225 $x10^9$/L), ocrelizumab central volume was estimated to be 2.78 L (95% CI: 2.71–2.85 L). Peripheral volume was 2.68 L (95%CI: 2.53–2.82 L) and probably mostly represents the lymphatic liquid. The inter-compartment clearance was 0.294 L/day (95%CI: 0.251–0.337 L/day). Plasma protein binding studies have not been performed. The conditional predictions of concentration and AUC for ocrelizumab 600 mg (administrated as two IV infusions of 300 mg given 14 days apart on Day 1 and Day 15, followed by single IV infusions of 600 mg every 6 months/every 24 week) is presented in Table 2.

Table 2: RMS (WA21493, WA21092, WA21093) - Conditional Predictions of PK Parameters for 600 mg Ocrelizumab

	Statistics	Dosing Period (Weeks)			
		1 (0-24)	2 (24-48)	3 (48-72)	4 (72-96)
N		941	941	941	941
C_{max} (µg/mL)	Mean (SD)	131.4 (25.3)	212.1 (41.6)	212.3 (41.6)	212.5 (41.7)
	Median (Range)	128.8 (52.7-346.8)	208.8 (71-615.1)	208.9 (71.1-616.2)	209.1 (71.2-617.2)
	Geometric Mean (CV)	129.1 (0.19)	208.3 (0.19)	208.5 (0.19)	208.7 (0.19)
C_{trough} (µg/mL)	Mean (SD)	0.6 (0.6)	0.7 (0.7)	0.9 (0.8)	1 (0.9)
	Median (Range)	0.5 (0-8)	0.6 (0-9.6)	0.7 (0-11.5)	0.8 (0-12.8)
	Geometric Mean (CV)	0.5 (0.82)	0.5 (0.86)	0.7 (0.86)	0.7 (0.86)
AUC_τ (µg/mL • day)	Mean (SD)	2904 (750)	3190 (848)	3382 (909)	3513 (955)
	Median (Range)	2826 (1261-8849)	3124 (1337-10137)	3312 (1390-10821)	3434 (1423-11321)
	Geometric Mean (CV)	2813 (0.25)	3085 (0.26)	3268 (0.26)	3391 (0.27)
Cumulative AUC (µg/mL • day)	Mean (SD)	2904 (750)	6094 (1597)	9476 (2504)	12989 (3455)
	Median (Range)	2826 (1261-8849)	5958 (2599-18986)	9286 (3988-29807)	12719 (5411-41128)
	Geometric Mean (CV)	2813 (0.25)	5898 (0.26)	9167 (0.26)	12559 (0.26)

Data from PPMS patients derive from study WA25046. Exposure metrics are comparable to the RMS data, besides the lower Cmax as 2x300 mg IV infusions were given every 24 weeks throughout the PPMS study, while RMS patients received 600 mg IV infusions (after the first dose which was given as 2 infusions of 300 mg on Days 1 and 15 in all RMS and PPMS studies).

No classic biotransformation studies were conducted *in vitro* or *in vivo*. The expected metabolic products of proteins and peptides, including IgG1 mAbs such as ocrelizumab, are small peptides and amino acids. For a reference patient (female, weighing 75 kg, with a baseline B-cell count of 0.225 $x10^9$/L), ocrelizumab constant clearance (CL_{inf}) was estimated at 0.17 L/day (95%CI: 0.166–0.174 L/day) and the terminal half-life (T½) of ocrelizumab was 26 days. There is no information available regarding excretion of ocrelizumab but as a mAb, excretion of intact ocrelizumab is not expected.

Dose proportionality and Time dependency

Dose proportionality was investigated in the early RA studies. Higher clearance was observed at the low dose levels of 20 mg and 100 mg, whereas linear PK was approached at dose levels above 400 mg (Table 3, and Figure 1).

Table 3: ACT2847g - Ocrelizumab PK Parameters

Dose	C_{max} (µg/mL)	AUC_{inf} (µg • day/mL)	$t_{1/2}$ (days)	Vz (mL)	CL (mL/day)
50 mg×2 (n=40)	18.9± 7.19 (n=40)	248 ± 141 (n=33)	11.7± 4.51 (n=33)	7360± 2090 (n=33)	478 ±166 (n=32)
200 mg×2 (n=40)	77.4± 32.2 (n=40)	1280± 470 (n=35)	15.1± 6.26 (n=35)	7080± 3000 (n=35)	350 ±146 (n=35)
500 mg x 2 (n=40)	211 ± 61.7 (n=40)	3810 ± 1380 (n=39)	16.7 ± 4.14 (n=39)	6790 ± 2180 (n=39)	294 ± 95.9 (n=39)
1000 mg×2 (n=40)	391±128 (n=40)	7990± 2960 (n=37)	17.4± 5.34 (n=37)	6940± 2930 (n=37)	291±130 (n=37)

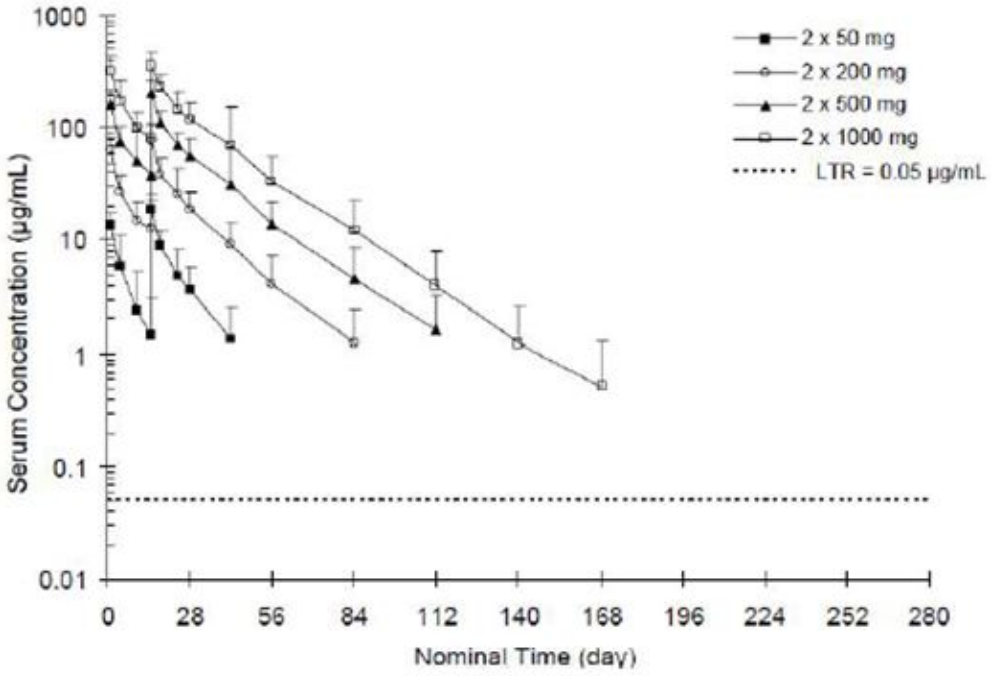


Figure 1 ACT2847g: Ocrelizumab Concentration versus Time

Dose proportionality and time dependency in MS patients was investigated in Study WA21493. Ocrelizumab generally demonstrates a biphasic disposition, with a rapid initial decline in serum concentration followed by a more prolonged terminal disposition phase (Figure 2).

The pop-PK analysis of the pooled RMS studies WA21493, WA21092 and WA21093 showed a time-dependent clearance (Figure 2) most likely attributable to target-mediated drug disposition via depletion of B-cells, the target for ocrelizumab binding (and elimination).

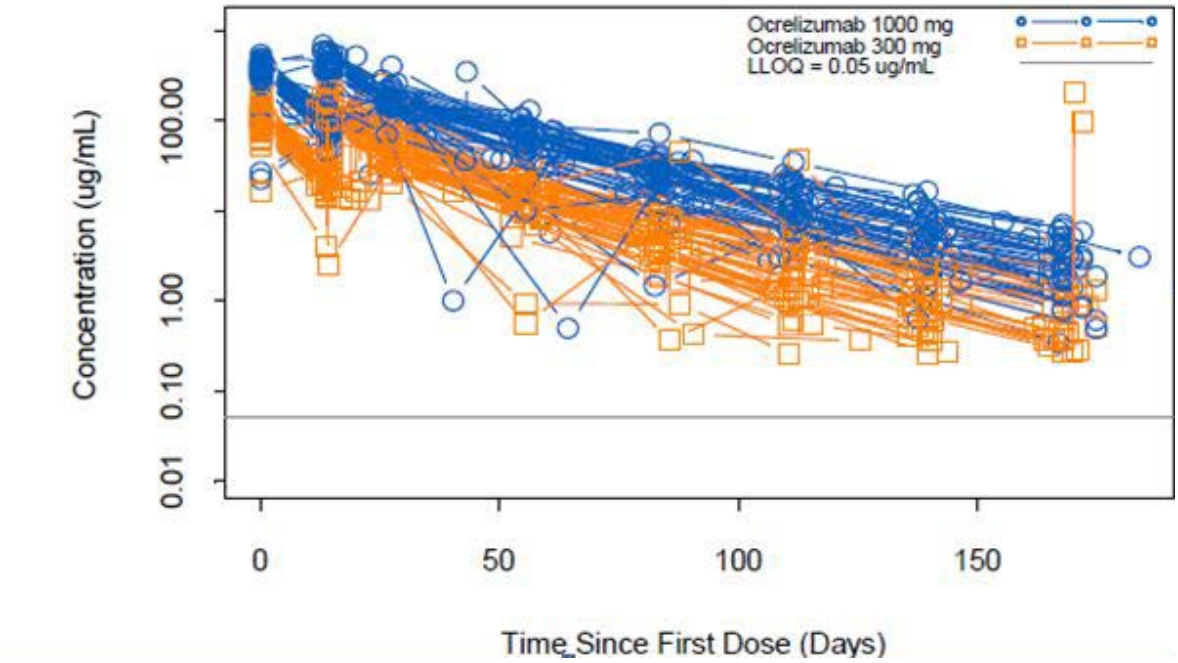


Figure 2: Ocrelizumab Concentration–Time Profiles by Dose

Inter- and intra-individual variability

Inter-individual variability was calculated in the population-PK analysis. Overall, inter-patient variability in PK parameters in MS patients was moderate up to 30% (coefficient of variation).

There is no data regarding intra-individual variability. This is adequately justified by the final PK-PD model, which showed an excellent fit though it did not include the inter-occation variability indicating that including only the residual variability was sufficient.

Interactions

As ocrelizumab is a monoclonal antibody, no drug-drug interactions are expected via the CYPs, other metabolising enzymes, or transporters. Therefore, no formal drug-drug interaction studies have been performed *in vitro* or *in vivo.*

There is no information regarding potential PD interaction with other immunomodulatory multiple sclerosis (MS) therapies; especially the safety of ocrelizumab following or concomitant with other immunosuppressive/ immunomodulating disease modifying therapies (DMTs) is unclear.

Pharmacokinetics in target population and in special populations

All pivotal PK studies have been performed in the target population (patients with MS); therefore, the results are considered representative for the target population.

In the pop-PK analyses of Studies WA21493, W21092 and WA21093, different covariate factors were investigated for the influence of the disposition of ocrelizumab.

No effect of neither creatinine clearance (CRCL) or the hepatic enzymes ALT, AST or bilirubin was observed but only one patient with CRCL (≤50 and >30 mL/min) was included and few patients with increased hepatic enzymes/bilirubin were included.

B-cell counts at baseline as well as gender were included in the final covariate model (Table 10), but the influence was small and without clinical relevance.

As typical for mAbs, ocrelizumab clearances and volumes of distribution increased with body weight but terminal and effective half-lives were unaffected by body weight (Table 4).

Table 4: Summary of Conditional Predictions for CL_{inf} , V_1, V_{ss}, $t_{½\ term}$ and $t_{½\ eff}$, Overall and by Body Weight Categories

	Statistics	All	Body weight (kg)		
			<60	60-90	>90
N		941	196	572	173
CL_{inf} (L/day)	Mean (SD)	0.173 (0.0487)	0.137 (0.0326)	0.173 (0.0423)	0.216 (0.0501)
	Median (Range)	0.165 (0.0492-0.406)	0.132 (0.0492-0.275)	0.167 (0.0609-0.378)	0.214 (0.12-0.406)
	Geometric Mean (CV)	0.167 (0.272)	0.133 (0.23)	0.168 (0.233)	0.21 (0.227)
V_1 (L)	Mean (SD)	2.9 (0.597)	2.47 (0.585)	2.92 (0.539)	3.32 (0.459)
	Median (Range)	2.84 (0.952-8.56)	2.43 (0.952-8.56)	2.86 (1.65-7.93)	3.27 (2.3-5.11)
	Geometric Mean (CV)	2.85 (0.192)	2.42 (0.186)	2.88 (0.166)	3.28 (0.137)
V_{ss} (L)	Mean (SD)	5.56 (0.989)	4.49 (0.617)	5.55 (0.686)	6.82 (0.656)
	Median (Range)	5.49 (2.97-10.9)	4.49 (2.97-10.5)	5.52 (3.87-10.9)	6.74 (5.61-9.5)
	Geometric Mean (CV)	5.48 (0.175)	4.45 (0.116)	5.51 (0.119)	6.79 (0.0932)
$t_{1/2,term}$ (day)	Mean (SD)	26.8 (5)	26.8 (4.5)	26.8 (4.7)	27 (6.4)
	Median (Range)	26.4 (11.4-85.9)	26.6 (14.2-46)	26.6 (11.4-61.1)	26 (15.3-85.9)
	Geometric Mean (CV)	26.4 (0.17)	26.4 (0.17)	26.4 (0.17)	26.5 (0.19)
$t_{1/2,eff}$ (day)	Mean (SD)	23.2 (4.3)	23.6 (4.4)	23.1 (4.3)	22.8 (4.5)
	Median (Range)	23 (9.6-49.2)	23.4 (12.1-44.3)	23 (9.6-49.2)	22.1 (12.5-36.7)
	Geometric Mean (CV)	22.8 (0.19)	23.2 (0.19)	22.7 (0.19)	22.4 (0.2)

In RMS patients with low weight (48.5 kg), CLinf and V1 were respectively 26% and 16% lower compared to patients weighing 75 kg. In patients with high weight (116 kg), CLinf and V1 were respectively 35% and 19% higher compared to patients weighing 75 kg.

Cmax values were estimated to be 19% higher for RMS patients weighing <60 kg and 13% lower for patients weighing >90 kg compared with the 60-90 kg weight group. Area under the curve (AUC) over dosing interval (AUC_T) values were estimated to be 26% higher for patients weighing <60 kg and 21% lower for patients weighing >90 kg compared with the 60-90 kg weight group.

Other PK parameters (Peripheral volume [V2], Intercompartmental clearance [Q] and Time-dependent clearance [CLT0]) also increased with body weight. Peripheral volumes (V2), inter-compartment clearance (Q) and initial time-dependent clearance (CLT0) were respectively 31%, 28%, and 35% lower in patients weighing 48.5 kg compared to the reference patient (75 kg), and were respectively 45%, 39%, and 53% higher in patients weighing 116 kg compared to the reference patient (the values of 48.5 and 116 kg represent 2.5th and 97.5th percentiles of body weight in the analysis data set).

Data for efficacy and safety stratified on both weight (</≥75 kg) and BMI (</≥25 kg/m^2) and by exposure quartiles (by Cmax) showed that body weight, though inversely correlate to exposure, did not influence on ARR. Further, the increased exposure seen in patients with low BMI was not associated with an increased frequency of adverse events, serious infections or infusion related

reactions. However, there was a tendency towards a greater risk reduction in confirmed disability progression (CDP) in the subgroup of patients with a baseline body weight <75 kg (thus patients with a higher exposure) compared to patients with a body weight ≥75 kg (lower exposure). This could support a weight-based dosing regimen however, there is no clinical data supporting a weight-based dosing regimen.

Race and age were not found to influence the PK of ocrelizumab but of note, no children (age <18 years) nor elderly (age >65 years) were included in the clinical studies. This is adequately addressed in the SmPC.

Table 5 shows the covariate effects included in the final model.

Table 5 Covariate Effects in the Final Covariate Model 133

Parameter	Covariate	Reference Value	Covariate Value[a]	Covariate Effect Value [95%CI](%)
CL_{inf}	Body Weight (kg)	75	48.5	-25.8 [-23.5;-28]
			116	34.8 [30.7;38.9]
	B-cell count at baseline (10^9/L)	0.225	0.0715	-2.7 [-2;-3.5]
			0.598	6.7 [4.9;8.5]
V_1	Body Weight (kg)	75	48.5	-15.9 [-13.4;-18.2]
			116	18.9 [15.5;22.3]
	Sex	Female	Male	11.7 [7.2;16.3]
CL_{TO}	Body Weight (kg)	75	48.5	-34.8 [-30.4;-38.9]
			116	53.4 [43.7;63.8]
V_2	Body Weight (kg)	75	48.5	-31.1 [-27.7;-34.2]
			116	45.1 [38.4;52.1]
Q	Body Weight (kg)	75	48.5	-27.9 [-27.9;-27.9]
			116	38.7 [38.7;38.7]

a. The values of the continuous covariates represent 2.5th and 97.5th percentiles of the values in the analysis data set.

Exposure relevant for safety evaluation

The most prevalent AEs associated with treatment with the proposed recommended dose of ocrelizumab (600 mg IV) were IRRs and infections.

Correlation between individual exposure and occurrence and grade of SAE, serious infections, and occurrence and grade of IRRs indicated that there was no relationship with exposure for patients receiving the ocrelizumab 600 mg IV regimen across the Phase II and Phase III studies. Rates of SAE, serious infection, and IRRs seemed higher for patients receiving the ocrelizumab 1000 mg IV (i.e., first dose 2000 mg) dosing regimen in the Phase II studies but the sample size of this group was small compared with the 600 mg regimen, and 95% confidence intervals overlapped, thus not allowing a firm conclusion. Cmax ocrelizumab concentrations were not higher in patients that experienced SAE compared with patients without SAE within the 600 mg and 2000 mg group respectively.

2.4.3. Pharmacodynamics

The phase III randomised, double-blind, parallel group, active comparator controlled / placebo controlled, multicentre trials in RMS patients (WA21092, OPERA I and WA21093, OPERA II) and PPMS patients (WA25046, ORATORIO) studies all provide clinical pharmacology data for ocrelizumab. However, additional supportive data are provided by the phase II study WA21493 in RRMS patients.

Population PK (pop-PK) analyses were conducted to quantitatively describe the PK of ocrelizumab in MS patients and to evaluate the effects of relevant covariates that may contribute to the variability in exposure in individual patients. Evaluations of the relationship between PK and PD, clinical efficacy, and safety events were conducted to quantitatively assess the exposure-response relationship of ocrelizumab. Also studies with ocrelizumab in patients with rheumatoid arthritis (RA) provided PD data.

Mechanism of action

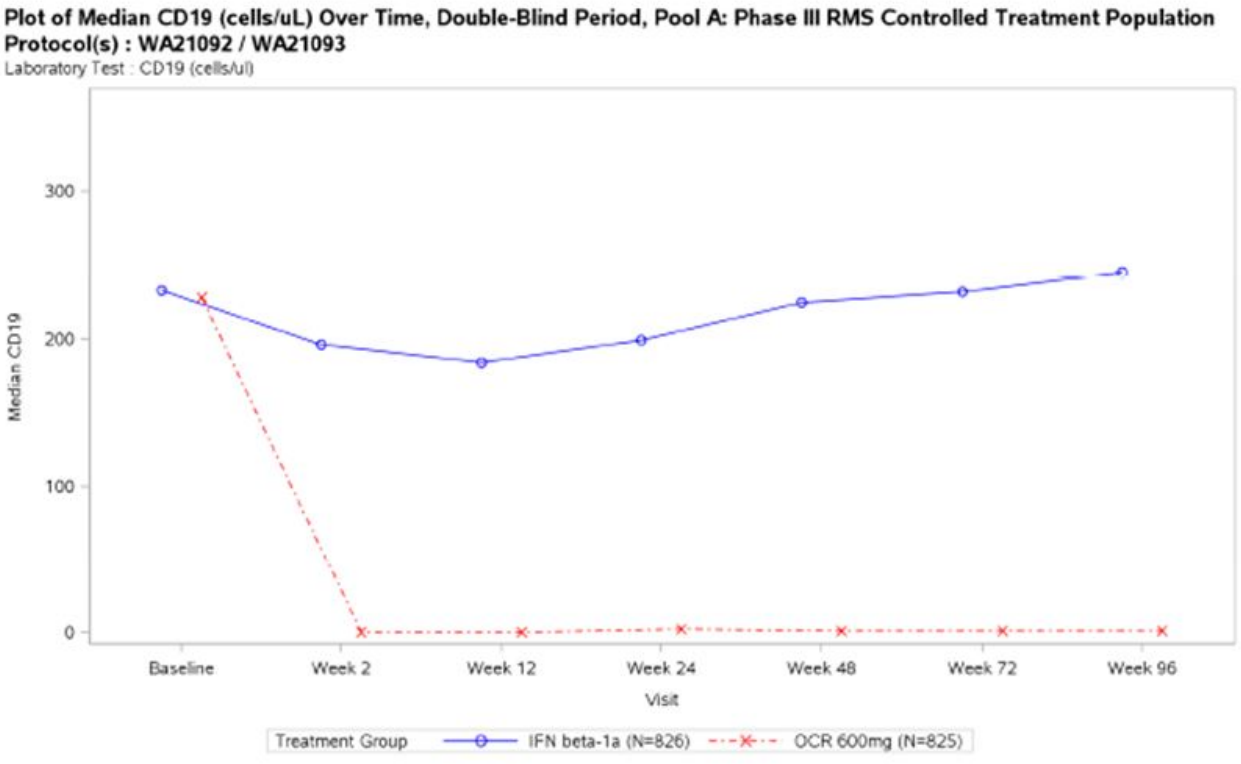
Ocrelizumab is a recombinant humanised monoclonal antibody (mAb) that selectively targets CD20-expressing B-cells. CD20 is a cell surface antigen found on pre-B cells, mature and memory B-cells but not expressed on lymphoid stem cells and plasma cells. While ocrelizumab selectively depletes CD20-expressing B cells, the capacity of B-cell reconstitution and pre-existing humoral immunity are preserved.

B-cells are thought to play an important role in the pathogenesis of multiple sclerosis (MS) by: (1) Presenting auto-antigens and co-stimulatory signals to activate T-cells, (2) secreting pro-inflammatory cytokines at greater relative proportions than protective cytokines, (3) producing auto-antibodies which may cause tissue damage and activate macrophages and natural killer cells, and (4) creating meningeal lymphoid follicle-like structures, linked to microglia activation, local inflammation and neuronal loss in the nearby cortex.

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. These changes are thought to be responsible for the consequent improvement of the disease course of MS.

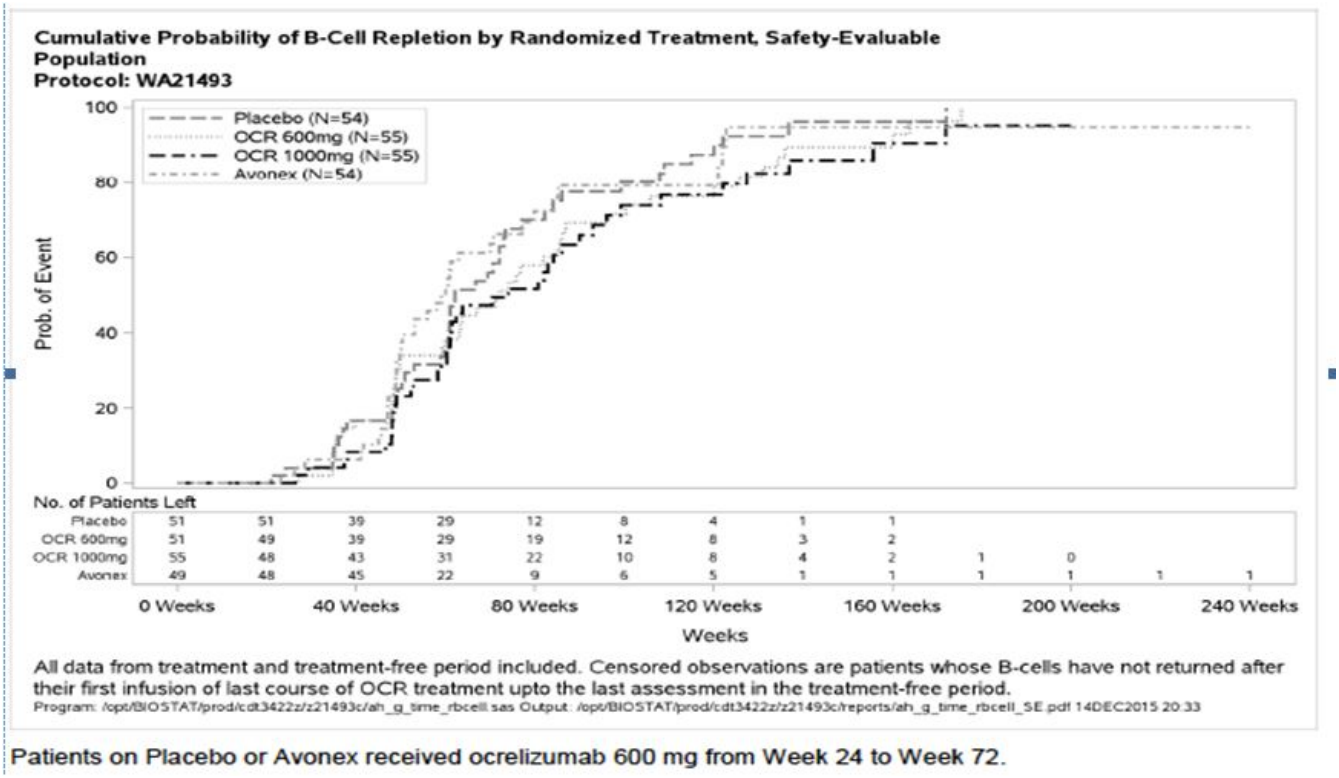
Primary pharmacology

Ocrelizumab selectively targets and depletes CD20-expressing B-cells. B-cell depletion is therefore the expected PD action of ocrelizumab; hence B-cell count in peripheral blood was used as the PD marker. B-cell counts described refer to flow cytometric counts of CD19+ cells in the peripheral blood. The rapid and sustained depletion of the CD19+ B-cell count in blood is shown in **Figure 3**



Median B-Cell Count (WA21092, WA21093)

The median time to repletion (return to baseline or LLN, whichever was lower) of B-cells was 72 weeks (range 27 to 175 weeks) after treatment with 600 mg ocrelizumab. Ninety percent (90%) of all patients had their B-cells repleted to LLN or baseline by approximately 2.5 years (120 weeks) after the last infusion. The longest individual time to repletion was 241 weeks after the last dose of ocrelizumab, in a patient treated first with interferon beta-1a IM and then with 600 mg ocrelizumab every 24 weeks.



Patients on Placebo or Avonex received ocrelizumab 600 mg from Week 24 to Week 72.

Figure 4 WA21493: Time to B-Cell Repletion

Relationship between plasma concentration and effect

There was no apparent relationship between ocrelizumab exposure and the primary endpoint of ARR in RMS. Both RMS and PPMS patients showed a trend for greater risk reduction for CDP with higher exposure of ocrelizumab and all ocrelizumab groups showed a benefit compared with control (HR <1).

Table 6 Time to Onset of Confirmed Disability Progression for at Least 12 Weeks for the Double Blind Treatment Period by Cmean Quartile (ITT population, Pooled study WA21092 and WA21093 and Study WA25046)

Quartile	RMS (Pooled Study WA21092 and WA21093)		PPMS (Study WA25046)	
	n	Hazard Ratio (95% CI)	n	Hazard Ratio (95% CI)
Ocrelizumab Mean Concentration < Q1	196	0.77 (0.49, 1.21)	120	0.87 (0.60, 1.27)
Ocrelizumab Mean Concentration ≥ Q1 and <Median	197	0.80 (0.51, 1.24)	121	0.83 (0.58, 1.19)
Ocrelizumab Mean Concentration ≥Median and <Q3	196	0.45 (0.26, 0.79)	120	0.78 (0.54, 1.13)
Ocrelizumab Mean Concentration ≥Q3	197	0.33 (0.17, 0.64)	121	0.59 (0.40, 0.86)

PPMS primary progressive multiple sclerosis; RMS relapsing multiple sclerosis. Note that patients with initial disability progression during the blinded treatment period who discontinued treatment early and did not have a subsequent EDSS measurement were censored in RMS Studies WA21092 and WA21093 and were imputed as having CDP in PPMS Study WA25046.

Due to the pronounced B-cell depletion, it was by the initial assessment questioned, if there is a potential PD interactions with ocrelizumab and (live attenuated) vaccines. In order to further elucidate this issue, the Applicant informed that a multi-centre randomised, open-label, Phase IIIb study (BN29739, VELOCE) is currently ongoing. It is endorsed that the Applicant submit both the primary study report (expected Q4 2017) and the final study report (expected Q1 2023) for assessment when available.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Pharmacokinetic (PK) data derive from three pivotal phase III studies (Study WA21092 and Study WA21093 in patients with RMS and Study WA25046 in patients with PPMS) and a supporting phase II dose-finding study (Study WA21493). In these studies, 1,423 MS patients were treated with ocrelizumab and had available PK data. Pop-PK analyses and exposure-response analyses were submitted in support of the PK and PD dossier. The statistical analyses as well as the methods for the pop-PK analyses are considered adequate and justified.

During the clinical development program, 5 versions of ocrelizumab have been used (v0.1–v0.4 and v1.0). Version 0.4 has been use in the pivotal MS studies WA21092, WA21093, WA25046, whereas in study WA21493 three batches of version 0.2, four batches of version 0.3 and five batches of version 0.4 were used. Version 1.0 is intended for commercial use but has not been used in any of the pivotal studies. It is currently used in the open-label extension studies, but no clinical data from this study have been submitted. Bioequivalence studies between any of the product versions have not been performed but analytical comparability has been performed between v0.1 and v0.2, v0.2 and v0.3, v0.3 and v0.4 and v0.4 and v1.0. The comparability approach is evaluated in the Quality assessment report.

The main difference between the versions relates to the glycosylation. This is not expected to impact the PK of ocrelizumab but it potentially affects the PD as the glycosylation has effect on the ADCC and CDC activity. The ADCC (max) and CDC activity/potency is lower in the version v1.0 compared to the initial versions (v0.1-v0.4); this can at least theoretical impact efficacy and safety of ocrelizumab.

To further overcome this issue, the Applicant informed that the proposed marketing material would be aligned with material used in the pivotal trials. Further, the Applicant committed to provide PK and PD (blood B-cell depletion) data for the 2014 v1.0 material as a post-marketing commitment if required. At the response on Day 180, the Applicant informs that at the quality level several actions have been taken to assure that the commercial v1.0 process manufacture ocrelizumab of the same quality as used in the pivotal clinical trial (v0.4). Both ADCC and CDC, which is considered part of mechanism of action of ocrelizumab, is influenced by the glycosylation profile of the molecule. Manganese has been shown to influence the glycosylation with consequential impact on potency. Manufacturing process controls are implemented to measure the manganese level in the fermentation process. In addition to the test for CDC, the Applicant has introduced a test for ADCC in the release specification of the drug substance. The two glycoforms G0 and G0-F is also controlled. All test limits are aligned with the clinical experience of v0.4 drug substance. Due to these findings of comparability between the two manufacturing processes, the Applicant does not consider that it is necessary to present clinical data. This is agreed and therefore clinical PK and PD data will not be requested

Ocrelizumab is administered as intravenous injections, and therefore the bioavailability is 100%. Ocrelizumab is distributed in a two-compartment model. The central volume of distribution was approximately 2.78 L indicating that, as many other mAbs and due to the large size (approximately 148 kDa) and the hydrophilic nature of the molecule, ocrelizumab is distributed mainly in the vascular compartment. The peripheral volume of distribution (2.68 L in the population PK model for studies WA21092, WA21093 and WA21493 and 2.42 L in Study WA25046) probably mostly representing the lymphatic liquid. Like other antibodies, ocrelizumab is assumed to be degraded into smaller proteins and amino acids. The terminal elimination half-life (T½) is 26 days, thus comparable to the T½ of endogenous IgG. At lower doses (up to 400 mg) T½ was decreased due to a higher clearance but with higher doses (>400 mg) an approximately constant clearance was observed resulting in a dose proportional increase in Cmax and AUCinf. The decrease in clearance observed with higher doses of ocrelizumab is most likely predominantly explained by saturation of the target-mediated pathway. Ocrelizumab AUC and Cmax are approximately dose-proportional between 600 mg and 2000 mg. After multiple dosing, the time-dependent clearance was approximately linear with only a small decrease in clearance which can be explained by a depletion of B-cells and thereby a saturation in the non-specific clearance (salvage pathway). With the recommended dosing regimen, steady state is reached after the second dosing.

Inter-individual variability has not been specifically addressed, but data show that the inter-individual variability in PK parameters was moderate (up to 30%). There is no data regarding intra-individual variability, however, this has adequately been justified by the Applicant. Ocrelizumab was dosed with a fixed dosage for all patients.

Weight was found to be the strongest covariate with influence on both clearance, volume of distribution, Cmax and AUCτ. Over the dosing interval (AUCτ) values were estimated to be 26% higher for patients weighing <60 kg and 21% lower for patients weighing >90 kg compared with the 60-90 kg weight group. Thus, body weight was inversely correlate to exposure (i.e. patients with a higher weight had a lower exposure to ocrelizumab). To further elucidate the possible clinical impact of these findings, the Applicant presented data for efficacy and safety stratified on both weight (</≥75 kg) and BMI (</≥25 kg/m^2) and by exposure quartiles (by Cmax). These data showed that body weight, though inversely correlated to exposure, did not influence on ARR. Further, the increased exposure seen in patients with low BMI was not associated with an increased frequency of adverse events, serious infections or infusion related reactions. However, there was a tendency towards a greater risk reduction in confirmed disability progression (CDP) in the subgroup of patients with a baseline body weight <75 kg (thus patients with a higher exposure) compared to patients with a body weight ≥75 kg (lower exposure). This supports a weight-based dosing regimen however, there is no clinical data supporting a weight-based dosing regimen and it is concluded that the issue needs not to be pursued. Gender as well as B-cell count at baseline were found to be statistically significant covariates on volume of distribution and for the constant clearance respectively, but the differences were small and

not expected to be clinically relevance. No dose-adjustment is considered necessary in any of the subgroups of special populations based on PK.

All pivotal PK studies have been performed in the target population, namely patients with MS. No dedicated studies in any special population have been performed but the influence of various covariate parameters was evaluated in pop-PK analyses. Impaired hepatic or renal function was not observed to influence the PK of ocrelizumab but only one patient with severe impaired renal function was included in the analyses. In order to further substantiate the experience with ocrelizumab in patients with hepatic impairment, the Applicant upon request, presented exposure data for RMS and PPMS patients stratified according to the NCI-ODWG classification. As expected, based on the known pharmacokinetic profile for antibodies, mild hepatic impairment did not affect the exposure of ocrelizumab. Only few patients with moderate and severe hepatic impairment were included and no conclusions could be drawn for these special populations. The SmPC is updated with the information. Overall, no dose-adjustment is considered necessary in patients with impaired renal/hepatic function.

There seem to be no clear relationship between exposure (Cmean and AUC) and adverse events however, the sample size of the population treated with the highest dose is small limiting firm conclusions. As only three patients developed anti-drug antibodies (ADAs) this has not been investigated as a covariate influencing the PK of ocrelizumab. Ocrelizumab has not been investigated in elderly (age >65 years) or in children (age <18 years). This is adequately addressed in the SmPC.

Pharmacodynamics

Ocrelizumab is a recombinant humanised mAb that exerts immunomodulatory effects by relatively selectively targeting and depleting CD20-expressing B cells. However, the mechanism through which ocrelizumab causes beneficial effects in MS is not fully understood.

Since ocrelizumab binds to CD20, and its presence in blood interferes with a B-cell count based on the surface antigen CD20 itself, CD19 was used as a marker for CD20 expression during B-cell development; this is accepted. The depletion of the CD19+ B-cell count in blood is rapid and sustained. The median time to repletion was 72 weeks. The proposed posology entails dosing every 6 months and the rationale for this dosing regimen is acceptable.

No formal (PK or PD) drug-drug interaction studies were performed, which is acceptable for a mAb. Due to the effective and long-lasting PD effect by depleting CD20-expressing B-cells, the efficacy of vaccinations and indeed also the safety if giving live attenuated vaccines (e.g. BCG vaccination and yellow fever vaccination) was questioned by the initial assessment. In order to further elucidate this issue, the MAH informs that a multi-centre randomised, open-label, Phase IIIb study (BN29739, VELOCE) is currently ongoing. The primary study report is planned to be available in Q4 2017 and the final study report in Q1 2023. The Applicant has clarified that the primary study report will be based on the clinical cut-off date (14. February 2017) whereas the final study report will be based on data from 'Last- patient last visit'. Further, the Applicant agrees to the post approval commitment of submitting both study reports as well as any necessary changes to labelling and/or to the RMP within one year from the last data-collection. The information provided in the SmPC is acceptable and adequately, the information also encourages the treating physician to Physicians consider the immunisation status of patients prior to treatment with ocrelizumab as vaccinations (at least with live attenuated vaccines) should be completed at least 6 weeks prior to initiation of treatment. Furthermore, the RMP has been updated with information regarding potential interactions with both live (attenuated) vaccines and potential drug-drug interactions with other immunomodulatory multiple sclerosis (MS) therapies; especially the safety of ocrelizumab following or concomitant with other immunosuppressive/ immunomodulating disease modifying therapies (DMTs) is unclear. Impaired immunisation response' is included as an important identified potential risk, and 'Risk of infections' is included as an 'important identified risk' in the RMP.

2.4.5. Conclusions on clinical pharmacology

Ocrelizumab is a recombinant humanised monoclonal antibody that exerts immunomodulatory effects by relatively selectively targeting and depleting CD20-expressing B cells.

The pharmacokinetic profile of ocrelizumab is overall well characterised.

The CHMP made the following recommendations:

- The Applicant should submit for assessment the primary study report (expected Q4 2017) and the final study report (expected Q1 2023) from a multi-centre randomised, open-label, Phase IIIb study (BN29739, VELOCE) that is currently ongoing.

2.5. Clinical efficacy

2.5.1. Dose response studies and Main clinical studies

The data from one dose-response study in RRMS (with placebo control and an open-label active comparator), two identically designed main studies in RRMS (with active control) and one main study in PPMS (with placebo control) were submitted. These studies are:

- Study WA21493, a supportive phase II proof-of-concept and dose finding study in RRMS.
- Studies WA21092 and WA21093, phase III trials with identical design in RRMS.
- Study WA25046, a phase III study in PPMS.

The below Table 7 presents a short summary of the design of the main clinical studies with ocrelizumab in RRMS and PPMS

Table 7 Summary of the design of the main clinical studies with ocrelizumab in RRMS and PPMS

Study	WA21092 and WA21093		WA25046	
Indication	**RMS**		**PPMS**	
Arm	**Interferon beta-1a 44 μg SC / 3 x weekly**	**Ocrelizumab 600 mg IV /24 weeks**	**Placebo**	**Ocrelizumab 600 mg IV / 24 weeks**
Patient population	MS according to McDonald criteria 2010 (RRMS or SPMS with relapses) EDSS at screening from 0-5.5 Prior to screening: ≥ 2 relapses in 2 years or one relapse in the year before screening		MS according to McDonald criteria 2005 (PPMS) EDSS at screening from 3.0 to 6.5 points	
Primary Endpoint	ARR		12-week CDP	
Randomization	1:1 ocrelizumab: interferon beta-1a		2:1 ocrelizumab: placebo	
No of treated patients	411 (WA21092) 418 (WA21093)	410 (WA21092) 417 (WA21093)	239	486
Dose	44 μg SC 3x week	600 mg IV every 24 weeks	Placebo IV every 24 weeks	600 mg IV every 24 weeks
Controlled Treatment Duration	96 weeks		Minimum duration 120 weeks (120 weeks and minimum number of CDP events observed) Median follow-up time: ocrelizumab 3.0 years, placebo 2.8 years	
Blinding	Double-blind, double-dummy		Double-blind	
Open Label extension	Patients who completed the double-blind treatment period were offered enrollment into an optional OLE of the study to further characterize the long-term safety and efficacy of ocrelizumab			
Safety follow up	Patients who completed or withdrew prematurely from double-blind or open-label treatment were encouraged to enter a SFU period, and a B-cell monitoring period			

ARR annualized relapse rate; CDP confirmed disability progression; EDSS Expanded Disability Status Scale; OLE open-label extension; IV intravenous; PPMS primary progressive multiple sclerosis; RMS relapsing multiple sclerosis; SC subcutaneous; SFU safety follow-up.

Study WA21493

The Study WA21493 was a supportive Phase II, multicenter, randomized, parallel-group, double-blind, placebo controlled, dose finding study, with open-label active comparator group (interferon beta-1a IM; Avonex 30 ug IM weekly). The placebo and active controlled part of the trial had a duration of 24 weeks (Cycle 1) followed by ocrelizumab (OCR) 600 mg or 1000 mg for three additional treatment cycles up to Week 94. The study was designed both as a proof of concept for ocrelizumab in RRMS, and as a dose finding study to inform the Phase III program. The objectives were to evaluate the efficacy as measured by brain MRI lesions, and safety of 2 dose regimens of ocrelizumab in patients with RRMS. The primary efficacy endpoint was the total number of gadolinium-enhancing T1 lesions observed on MRI scans of the brain at weeks 12, 16, 20, and 24. Secondary efficacy endpoints included additional MRI outcomes for the first 24 weeks and annualized relapse rate (ARR) by Week 24.

Of the 220 patients randomized, 218 received study treatment and 205 (93%) completed the 24-week placebo-controlled study period. The ITT and safety populations comprised the 218 patients who were

randomized and received at least one dose of study treatment. Most of the patients were female (59%-69% in the four dose groups), and nearly all were Caucasian (93%-98%). The mean age of patients across the four treatment groups ranged from 35.6 to 38.5 years (the absolute range was 19–56 years).

The study met its primary endpoint and key secondary endpoints. A statistically significant treatment effect on total T1 Gd-enhancing lesions on scans performed at weeks 12, 16, 20, and 24, on total new T1 Gd-enhancing lesions at weeks 4, 8, 12, 16, 20, and 24, and on ARR at week 24 was demonstrated for both ocrelizumab doses. The mean (standard deviation [SD]) number of Gd enhancing lesions at weeks 12, 16, 20, and 24 was reduced by 89%, to 0.6 (1.52) ($p<0.0001$), in Group B (600 mg ocrelizumab) and by 96%, to 0.2 (0.65) ($p<0.0001$), in Group A (2000 mg ocrelizumab), compared with 5.6 (12.53) in the placebo group. No clear separation in the primary endpoint was observed between Groups A and B ($p = 0.15$).

Table 8 Study WA21493 Overview of Efficacy (Primary Analysis at 24 Weeks) (ITT Population)

Endpoint	Placebo (Group C) N = 54	Ocrelizumab 600 mg (Group B) N = 55	Ocrelizumab 2000 mg (Group A) N = 55	Interferon beta-1a IM (Group D) N = 54
Total No. of Gd T1 lesions (Week 12 to 24) Mean (SD) p-value	5.6 (12.53)	0.6 (1.52) <0.0001	0.2 (0.65) <0.0001	6.9 (16.01) 0.3457
Adjusted ARR [a] (95% CI) p-value	0.557 (0.370,0.839)	0.127 (0.054,0.299) 0.0019	0.213 (0.110,0.414) 0.0136	0.364 (0.220,0.602) 0.1814
Proportion of relapse-free patients (95% CI) p-value	75.9% (64.5%,87.3%)	85.5% (76.1%,94.8%) 0.1978	87.3% (78.5%,96.1%) 0.1310	77.8% (66.7%,88.9%) 0.8206
Total No. of Gd T1 lesions (Week 4 to 24) Mean (SD) p-value	8.7 (17.54)	2.5 (5.10) <0.0001	1.8 (5.26) <0.0001	10.3 (22.15) 0.2725
Total No. of new Gd T1 lesions (Week 4 to 24) Mean (SD) p-value	5.1 (11.99)	0.8 (1.95) <0.0001	0.8 (2.16) <0.0001	6.2 (13.79) 0.4985
Total T2 volume (cm^3) (change from BL to Week 24) Median (95% CI) p-value	23.7 (-121.2,192.3)	-76.3 (-297.6,-34.2) 0.1391	-163.4 (-679.5,60.5) 0.1596	2.6 (-121.2,555.8) 0.4740

Gd = gadolinium, BL = baseline All p-values vs, placebo [a] adjusted for geographic region

The change in the volume of T2 lesions at week 24 was not significantly reduced in ocrelizumab patients (Groups A and B) compared with placebo and interferon beta-1a IM patients (Groups C and D). The treatment benefit of ocrelizumab on the total number of Gd-enhancing T1 lesions at weeks 12, 16, 20, and 24, and the unadjusted ARR at week 24 were consistently positive across all ocrelizumab subgroups based on a wide range of patient characteristics.

Treatment with both doses of OCR led to rapid and complete depletion of CD19+ peripheral B-cells, which was sustained through 24 weeks of the placebo-controlled. At week 24, no patients demonstrated a return of peripheral CD19+ cell counts to baseline values or to the lower limit of normal (LLN) of 80 cells/µL, which was used as protocol-defined measures of recovery.

Based on these efficacy findings, and the safety findings, indicating the higher dose of 2,000 mg of ocrelizumab was comparable to the lower dose of 600 mg, the Applicant elected to continue the phase III program (RMS and PPMS) with the posology of ocrelizumab 600 mg every 24 weeks.

Studies WA21092 and WA21093

The two studies in RMS mentioned above had an identical design and are therefore jointly described under below.

Clinical study WA21092, hereafter also referred to as Study 21092. Title of Study: A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif®) in patients with relapsing multiple sclerosis

Clinical study WA21093 , hereafter also referred to as Study 21093. Title of Study: A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif®) in patients with relapsing multiple sclerosis

Methods

These two studies were randomized, 96-week, double-blind, double-dummy, parallel-group, active-controlled phase III studies, designed to evaluate the efficacy and safety of ocrelizumab in comparison with interferon beta-1a in patients with RMS who experienced at least either two documented clinical attacks within 2 years or one clinical attack within one year prior to screening (but not within 30 days prior to screening). They consisted of the following periods:

- Screening
- Double-blind, double-dummy comparative treatment (96 weeks)
- Safety follow-up (SFU) (minimum of 48 weeks) and B-cell monitoring (every 24 weeks)
- Open label extension (OLE) screening
- OLE

Consenting patients were screened approximately 2 weeks prior to randomization. No study treatment was administered during SFU or B-cell monitoring. During OLE all patients received ocrelizumab. During the treatment period, patients attended 10 scheduled assessment visits (at baseline, Week 2, Week 12 and thereafter every 12 weeks). Neurological exams, EDSS and MSFCS were collected at baseline, Week 12 and then every 12 weeks. MRI was collected at baseline and every 24 weeks. SF-36 was collected at baseline and every 48 weeks. Patients were assessed for safety at each visit. In addition, structured telephone interviews were conducted every 4 weeks from Week 8 to identify any new or worsening neurological symptoms that warranted an unscheduled visit and to collect data on possible events of infections. Unscheduled visits were made for the assessment of potential relapses and safety, or if down titration of interferon beta-1a from 44 µg to 22 µg SC was needed.

- **Study participants**

RMS (male and female) patients aged 18-55 years with a diagnosis of MS as per revised McDonald criteria (2010) who experienced at least either two documented clinical attacks within 2 years or one clinical attack within one year prior to screening (but not within 30 days prior to screening). The inclusion criteria comprised subjects with RRMS as well as relapsing SPMS, neurological stability for ≥ 30 days prior to both screening and baseline,. EDSS from 0 to 5.5 (inclusive) at screening and documented MRI of brain with abnormalities consistent with MS prior to screening. The exclusion criteria included:

-PPMS.

-Disease duration of more than 10 years in patients with an EDSS ≤ 2.0 at screening.

-Treatment with dalfampridine (Ampyra®) unless on stable dose for ≥ 30 days prior to screening; wherever possible, patients remained on stable doses throughout the 96-week treatment period.

-Previous treatment with B-cell targeted therapies (i.e. rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab).

-Systemic corticosteroid therapy within 4 weeks prior to screening. The screening period was extended (but could not exceed 8 weeks) for patients who had used systemic corticosteroids for their MS before screening. For a patient to be eligible systemic corticosteroids should not have been administered also between screening and baseline.

-Any previous treatment with alemtuzumab (Campath), anti-CD4, cladribine, mitoxantrone, daclizumab, teriflunomide, laquinimod, total body irradiation, or bone marrow transplantation

-Treatment with cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, or natalizumab within 24 months prior to screening. Patients previously treated with natalizumab were eligible for this study only if duration of treatment with natalizumab was < 1 year.

-Treatment with fingolimod (Gilenya®) or other sphingosine-1-phosphate (S1P) receptor modulator (i.e. BAF312), or with BG12, within 24 weeks prior to screening (only patients with T lymphocyte count ≥ LLN were eligible for the study).

-Treatment with IV immunoglobulin (Ig) within 12 weeks prior to baseline.

- **Treatments**

The double-blind and double-dummy treatments are illustrated in the Table 9 and Table 10.

Table 9 Dosing Regimen in the Double Blind Period

Study Medication	Double-Blind, Double-Dummy Treatment Period				
	1st Dose Weeks 1-24		2nd Dose Weeks 24-48	3rd Dose Weeks 48-72	4th Dose Weeks 72-96
	Day 1 Infusion	Day 15 Infusion	Week 24 Infusion	Week 48 Infusion	Week 72 Infusion
Ocrelizumab/placebo	300 mg	300 mg	600 mg	600 mg	600 mg
Interferon beta-1a/placebo subcutaneous injection	3 times weekly	→	→	→	→

Table 10 Overview of the Interferon Beta-1a/Placebo Dosing Regimen

	Treatment Initiation		Treatment Continuation	Dose modification (if required)
Week	Weeks 1- 2	Weeks 3-4	Week 5 onwards	—
Study Day	Day 1-14	Day 15-28	Day ≥29	> Day 29
Interferon beta-1a/ placebo Dose	8.8 µg 2.4 MIU in 0.2mL 3 times weekly	22 µg 6.0 MIU in 0.5mL 3 times weekly	44 µg 12 MIU in 0.5mL 3 times weekly	22 µg 6.0 MIU in 0.5mL 3 times weekly

MIU = million international units

For patients who experienced a relapse during the study a standardized treatment regimen of 1 g IV methylprednisolone per day for 5 consecutive days was recommended if judged clinically appropriate by the treating investigator.

- **Objectives**

The primary objective of this study was to assess whether the efficacy of ocrelizumab 600 mg every 24 weeks (given as two infusions of 300 mg on Days 1 and 15 of the first 24-week treatment period, and as a single infusion of 600 mg subsequently) was superior to interferon beta-1a 44 µg SC as measured by the protocol-defined annualized relapse rate (ARR) by 2 years (96 weeks) in patients with RMS.

The key secondary objectives of this study were to evaluate whether the efficacy of ocrelizumab 600 mg was superior to interferon beta-1a 44 µg SC, as reflected by the following measures:

- The time to onset of confirmed disability progression (CDP) for at least 12 weeks with the initial event of neurological worsening occurring during the 96-week, double-blind, double-dummy, treatment period.

- The total number of T1 gadolinium (Gd) - enhancing lesions as detected by brain magnetic resonance imaging (MRI) at Weeks 24, 48, and 96.

- The total number of new, and/or enlarging T2 hyperintense lesions as detected by brain MRI at Weeks 24, 48, and 96.

- The proportion of patients who had confirmed disability improvement (CDI) for at least 12 weeks with the initial event of neurological improvement occurring during the 96-week, double-blind, double-dummy, treatment period.

- The time to onset of CDP for at least 24 weeks, with the initial event of neurological worsening occurring during the 96-week, double-blind, double-dummy, treatment period.

- The total number of new T1 hypointense lesions (chronic black holes) at Weeks 24, 48, and 96.

- The change in Multiple Sclerosis Functional Composite (MSFC) score from baseline to Week 96.

- The percentage change in brain volume as detected by brain MRI from Week 24 to Week 96.

- The change in Short Form 36 (SF-36) Physical Component Summary (PCS) Score from baseline to Week 96.

- The proportion of patients who had no evidence of disease activity (NEDA) by Week 96.

Safety:

- To evaluate the safety and tolerability of ocrelizumab 600 mg every 24 weeks (given as two infusions of ocrelizumab 300 mg on Days 1 and 15 of the first 24-week treatment period and as a single infusion of 600 mg subsequently) in patients with RMS (including exploratory, long-term safety and tolerability in those patients entering the OLE).

Pharmacokinetics/Pharmacodynamics:

- To explore the pharmacokinetics (PK), immunogenicity and pharmacodynamics (PD) of ocrelizumab in patients with RMS.

In addition, there were around 30 explorative objectives (not listed here) mainly related to clinical efficacy and MRI findings.

- **Outcomes/endpoints**

The primary efficacy endpoint was the protocol-defined ARR at 2 years (96 weeks). A protocol-defined relapse (PDR) was described by all of the following criteria:

- occurrence of new or worsening neurological symptoms attributable to MS

- symptoms persisting for >24 hours

- symptoms not attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reactions to medications)

- symptoms immediately preceded by a stable or improving neurological state for at least 30 days

- symptoms accompanied by objective neurological worsening consistent with an increase of at least half a step on the Expanded Disability Status Scale (EDSS), or 2 points on one of the appropriate Functional System Score (FSS), or 1 point on two or more of the appropriate FSS; the change had to affect the selected FSS (i.e., pyramidal, ambulation, cerebellar, brainstem, sensory, or visual).

Episodic spasms, sexual dysfunction, fatigue, mood change, or bladder or bowel urgency or incontinence did not suffice to establish a relapse.

The secondary efficacy endpoints, which were to be analyzed in a hierarchical order, were:

- The time to onset of CDP for at least 12 weeks, with the initial event of neurological worsening occurring during the 96-week, double-blind, double-dummy treatment period.

- The total number of T1 Gd-enhancing lesions as detected by brain MRI at Weeks 24, 48, and 96.

- The total number of new and/or enlarging T2 hyperintense lesions as detected by brain MRI at Weeks 24, 48, and 96.

- The proportion of patients who have CDI for at least 12 weeks, with the initial event of neurological improvement occurring during the 96-week, double-blind, double-dummy treatment period.

- The time to onset of CDP for at least 24 weeks, with the initial event of neurological worsening occurring during the 96-week, double-blind, double-dummy treatment period.

- The total number of new T1 hypointense lesions at Weeks 24, 48, and 96.

- The change in MSFC score from baseline to Week 96.

- The percentage change in brain volume as detected by brain MRI from Week 24 to Week 96.

- The change in SF-36 PCS Score from baseline to Week 96.

- The proportion of patients who have NEDA by Week 96.

The listing above of the secondary efficacy endpoints does not reflect the hierarchical order for the statistical testing (instead please refer to the section “Statistical methods”). For the statistical testing

CDP 12 weeks, CDI 12 weeks and CDP 24 weeks, data from Studies 21092 and 21093 were planned to be pooled.

The MRI assessments were standardised and read by a centralized MRI reading center for efficacy endpoints. Brain volume at 24 weeks had been chosen as the reference point in this secondary outcome to account for a potential pseudoatrophy effect that might theoretically occur early after the initiation of an anti-inflammatory treatment.

Confirmed Disability Progression Definition

Disability progression was defined as an increase in the EDSS score of:

- ≥ 1.0 point from the baseline EDSS score when the baseline score was ≤ 5.5

- ≥ 0.5 point from the baseline EDSS score when the baseline score was > 5.5

and not attributable to another etiology (e.g., fever, concurrent illness, or concomitant medication).

Disability progression was considered confirmed when the increase in the EDSS was confirmed at a regularly scheduled visit at least 12 weeks or 24 weeks, after the initial documentation of neurological worsening. The initial event of neurological worsening had to occur during the 96-week, double-blind, double-dummy treatment period.

Confirmed Disability Improvement Definition

Disability improvement was assessed only for the subgroup of patients with a baseline EDSS score of ≥ 2.0. It was defined as a reduction in EDSS score of:

- ≥ 1.0 from the baseline EDSS score when the baseline score was ≥ 2 and ≤ 5.5

- ≥ 0.5 when the baseline EDSS score > 5.5.

All patients without confirmed disability improvement were counted as not improved, independently of follow-up time.

No Evidence of Disease Activity Definition

NEDA was defined only for patients with a baseline EDSS score ≥ 2.0. Patients who completed the 96-week treatment period were considered as having evidence of disease activity if at least one protocol-defined relapse, a CDP event or at least one MRI scan showing MRI activity (defined as Gd-enhancing T1 lesions, or new or enlarging T2 lesions) was reported during the 96-week treatment period, otherwise the patient was considered as having NEDA. Patients who discontinued treatment early with at least one event before early discontinuation were considered as having evidence of disease activity.

- **Sample size**

The sample size was estimated based on data from previous RRMS trials, with the use of two-sided tests with an experiment-wise alpha of 0.05. The ARR at 96 weeks in patients receiving ocrelizumab was predicted to be 0.165 (standard deviation [SD] of approximately 0.60), compared with 0.33 (SD of approximately 0.80) in patients receiving interferon beta-1a, representing a relative reduction of 50% on ocrelizumab compared with interferon beta-1a. For the ARR, a t-test was used to determine the sample size between the OCR group and the IFN group. The sample size of 400 patients per group was predicted to provide 84% power, maintaining the type I error rate of 0.05, and assuming a drop-out rate of 20% approximately (assuming a relative reduction among patient drop-out of 25%). For confirmed disability progression, a two group log-rank test, with the assumption of exponential survival and exponential dropout was used to determine the sample size. Assuming the 2-year confirmed disability progression rate is 18% for the IFN group and 12.6% for the OCR group, representing a relative reduction of 30% on ocrelizumab compared with interferon beta-1a, and assuming a dropout rate of 20 percent over 2 years approximately, the sample size of 400 per group was predicted to provide 80% power, maintaining the type I error rate of 0.05 based on the pooled analysis of two RMS trials (800 patients treated with ocrelizumab and 800 patients treated with interferon beta-1a).

- **Randomisation**

Eligible patients were randomized to 2 groups in a 1:1 ratio via an independent IxRS provider. Randomization was stratified by region (United States versus rest of the world [ROW]) and baseline EDSS (<4.0 versus ≥4.0). The block size was 4 for each stratum. The patient Randomization List was generated by IxRS using a pre-defined randomization specification. Patient randomization numbers were allocated sequentially in the order in which the patients were enrolled.

The randomization list was not available at the study center, to the monitors, project statisticians or to the Sponsor's project team. Randomized patients were assigned a unique treatment box number (medication number) and randomization number that was incorporated into the double-blind labeling. The IxRS provider held the treatment assignment codes.

- **Blinding (masking)**

This study had a double-blind, double-dummy design with the treatment duration of 96 weeks, followed by the OLE. Site personnel remained blinded to the patient treatment allocation in the double-blind treatment period until approximately 24 weeks after the Week 96 visit of the last patient randomized, to allow the confirmation of the last 24-week confirmed disability progression event. This resulted in the treatment assignment in the double-blind period remaining blinded in the OLE at least until the database lock for the 96-week period. To prevent potential unblinding during the double-blind, double-dummy treatment period, the following additional measures were implemented:

- dedicated role of the examining investigator / EDSS assessor who was not involved with any aspect of medical management of the patient and did not have access to patient data. The examining investigator performed the neurological examination, documented the Functional System Scores (FSS) and assessed the EDSS and the Karnofsky Performance Status Scale.
- blinding of selected laboratory parameters that could reveal patient's allocation to study treatment. Note that these laboratory parameters remained blinded during the double-blind, double-dummy treatment, SFU, OLE Screening, and during the first dose of ocrelizumab during the OLE (Dose 5).
- all scheduled on-study MRI scans were assessed by an independent, central MRI reader who was blinded to the treatment assignment. All scans were also reviewed locally for safety by a radiologist who was blinded to treatment assignment.

Unblinding for the ongoing safety monitoring by the iDMC, was performed according to procedures in place to ensure integrity of the data (cf. iDMC Charter). Unblinding for analysis of biological samples and pharmacokinetic data analysis was performed according to procedures in place to ensure integrity of the data.

Unblinding of treatment assignment by the site could only occur in the case of emergency situations, where the knowledge of what study medication the patient was receiving was critical for clinical management. Unblinding was performed by means of the IxRS.

As per regulatory reporting requirements, the Sponsor unblinded the identity of study medication for all unexpected serious adverse events (SAEs) that were considered by the investigator to be related to study drug per safety reference document(s), (e.g., Investigator's Brochure, Core Data Sheet, and Summary of Product Characteristics).

- **Statistical methods**

The statistical testing hierarchy for Studies WA21092 and WA21093 are summarized in the Figure 6. Data from the studies were pooled for analysis of CDP and CDI in order to have sufficient statistical power to detect treatment differences between ocrelizumab and interferon beta-1a 44 over the course of the study duration of 96 weeks.

The hierarchical analysis was to be undertaken only once the primary endpoint of ARR had been shown to be positive in both trials, and following that the secondary endpoints were to be tested in the sequence presented in the diagram, all at the α=0.05 level. Subsequent endpoints could only be tested in a confirmatory manner if all preceding endpoints had reached a significance level of 0.05

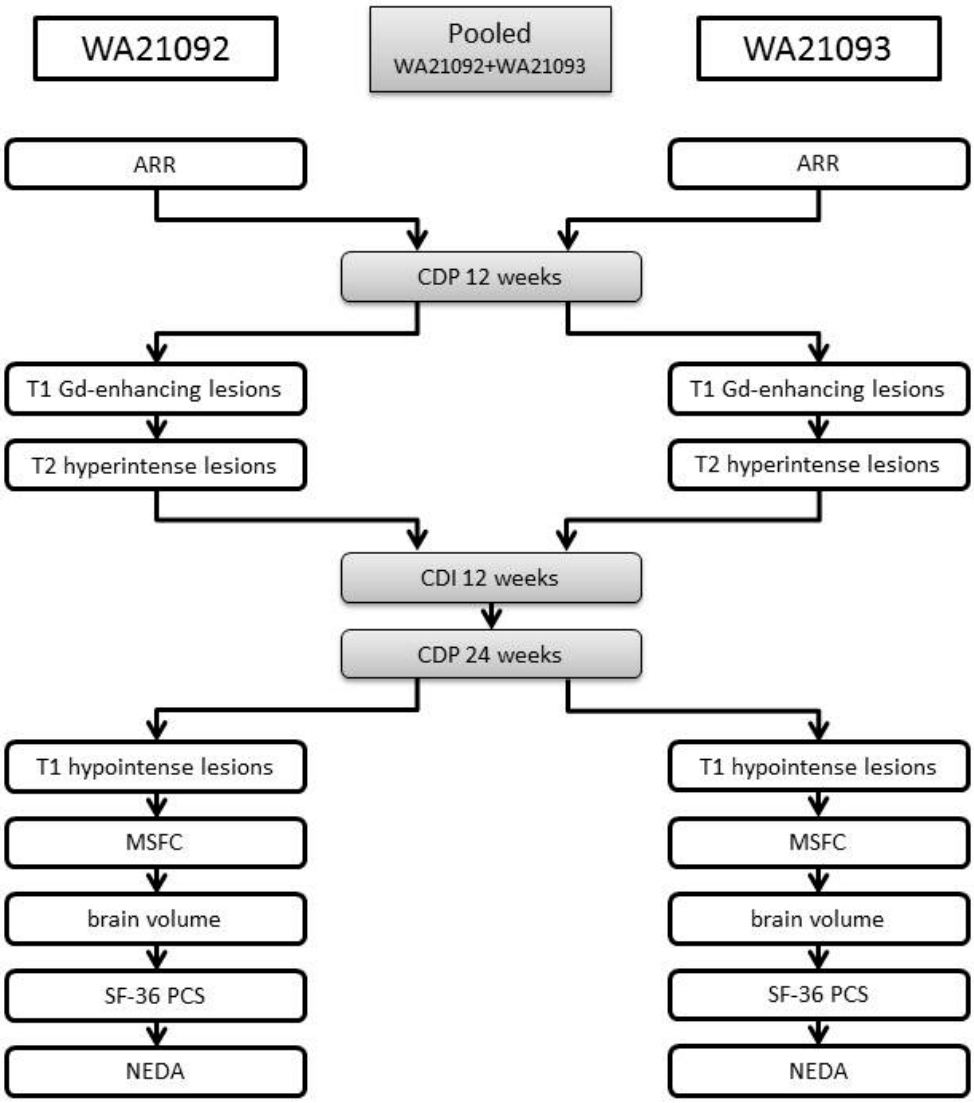


Figure 5 Statistical testing hierarchy for Studies WA21092 and WA21093

ARR = annualized relapse rate; CDI = confirmed disability improvement; CDP = confirmed disability progression; Gd = gadolinium; MSFC = Multiple Sclerosis Functional Composite; NEDA = no evidence of disease activity; SF-36 PCS = short form 36 Physical Component Summary

The hierarchical order of secondary endpoints was based primarily on clinical meaningfulness (i.e., those endpoints that were clinically more meaningful are listed higher in the hierarchy). In situations where endpoints had similar clinical relevance, those endpoints with a greater chance of achieving a statistically significant treatment difference were listed higher in the hierarchy. For example, given the lower number of 24-week CDP events than 12-week CDP events, there was a lower chance of achieving a statistically significant treatment difference, and thus 24-week CDP was listed lower in the hierarchy. In addition, established rather than novel endpoints were given higher priority within the hierarchy.

The statistical methods employed for each type of endpoint are summarized in Table 11. Patients who discontinued study treatment early during the double-blind period were censored at the date of discontinuation. However, the effects of different methods for handling missing data were tested as part of the pre-specified sensitivity analyses.

Table 11 Statistical Analysis of Primary and Secondary Efficacy Endpoints

Endpoint	Statistical Model	Stratification/adjusting factors
Primary Endpoint		
ARR	NBR (offset variable = log-transformed exposure time)	Baseline EDSS (<4.0 vs. ≥4.0), geographical region (US vs. ROW)
Secondary Endpoints		
Disability		
Time to onset of CDP for at least 12 weeks / 24 weeks	Log-rank test, Cox regression (for estimation of hazard ratio (HR))	Baseline EDSS (<4.0 vs. ≥4.0), geographical region (US vs. ROW)
Proportion of patients who have CDI for at least 12 weeks	CMH χ^2	Baseline EDSS (<4.0 vs. ≥4.0), geographical region (US vs. ROW)
Mean change from baseline in MSFC at Week 96	MMRM	Baseline MSFC, baseline EDSS (<4.0 vs. ≥4.0), geographical region (US vs. ROW)
Brain MRI		
T1 Gd-enhancing lesions per MRI scan	NBR (offset variable = log-transformed number of brain MRI scans received)	Baseline T1-Gd-enhanced lesion (present vs. absent), baseline EDSS score (<4.0 vs ≥ 4.0), geographical region (US vs. ROW)
New and/or enlarging T2 hyperintense lesions per MRI scan	NBR (offset variable = log-transformed number of brain MRI scans received)	Baseline T2 hyperintense lesion count, baseline EDSS score (<4.0 vs ≥ 4.0), geographical region (US vs. ROW)
New T1 hypointense lesions per MRI scan	NBR (offset variable = log-transformed number of brain MRI scans received)	Baseline T1-hypointense lesions count, baseline EDSS score (<4.0 vs ≥ 4.0), geographical region (US vs. ROW)
Mean % change from Week 24 in brain volume at Week 96	MMRM	Week 24 brain volume, baseline EDSS (<4.0 vs. ≥4.0), geographical region (US vs. ROW)
Disease Activity		
Proportion of patients with NEDA at Week 96	CMH χ^2	Baseline EDSS (<4.0 vs. ≥4.0), geographical region (US vs. ROW)
Quality of Life		
Mean change from baseline in SF-36 PCS at Week 96	MMRM	Baseline SF-36 PCS, baseline EDSS (<4.0 vs. ≥4.0), geographical region (US vs. ROW)

Pre-specified sensitivity analyses of the primary endpoint included inter alia:

• ARR calculated including all protocol-defined relapses occurring during the double-blind, double-dummy period or the SFU, up to 96 weeks after randomization. This analysis used all available data and estimated the treatment effect up to 96 weeks irrespective of whether patients were on study treatment or not.

• Per-protocol population

• Adjustment by additional covariates (number of relapses within 2 years prior to study entry, baseline Gd lesions [presence vs. absence], prior MS treatment, age [<40, ≥ 40 years])

• Use of two different methods for handling missing data (patients prematurely withdrawn from treatment), to explore the potential influence of informative dropouts on the results of the primary efficacy analysis (only data from the double blind double dummy treatment period was considered):

- Multiple imputation: for patients that discontinued early during the double-blind, double-dummy treatment period without any PDR in the 30 days prior to discontinuation, 50% of patients were randomly assigned an event of relapse on day of discontinuation, and 50% were censored on day of discontinuation.

- With imputation: patients that discontinued early during the double-blind, double-dummy treatment period without any PDR in the 30 days prior to discontinuation, were counted as having had a relapse on day of discontinuation.

Pre-specified sensitivity analyses of the secondary endpoints Time to CDP at 12 and 24 Weeks were:

• Per-protocol population

• Adjustment by additional covariates (number of relapses within 2 years prior to study entry, baseline Gd lesions (presence vs. absence), prior MS treatment, age [<40, ≥ 40 years])

• Use of two different methods for handling missing data (patients prematurely withdrawn from treatment), to explore the potential influence of informative dropouts on the results of the primary efficacy analysis. (only information from the double blind-double dummy treatment period was considered):

- Multiple imputation: for patients that discontinued the treatment early with an initial disability progression during the double-blind, double-dummy treatment period without a subsequent scheduled visit with EDSS measurement, 50% of patients were randomly assigned event of CDP on day of initial disability progression, and 50% were censored on day of initial disability progression.

-With imputation: patients that discontinued the treatment early with an initial disability progression during the double-blind, double-dummy treatment period without a subsequent scheduled visit with EDSS measurement counted as having had CDP on day of initial disability progression.

The primary and some of the secondary efficacy endpoints (12- and 24-week CDP) were summarized and analyzed by predefined subgroups:

· Age (≥ 40 vs. <40 years)

• Sex (male vs. female)

• Race (White vs. other)

· Body weight: ≥ 75 kg versus < 75 kg

• Geographical region (stratification factor) (United States vs. ROW)

· Baseline EDSS score (stratification factor) (<4.0 vs. ≥ 4.0)

• Previous lesions: baseline Gd-enhancing lesion (0 vs. > 0)

In addition, the following subgroups were added post-hoc:

· Body mass index (BMI) < 25 versus ≥ 25

• Geographical sub-region (EU/Switzerland/Norway, Latin America, Non-EU/Israel/Africa, USA/Canada/Australia)

Results clinical study WA21092

- **Participant flow**

A total of 1051 patients were screened for entry into the study. Of these, 230 patients failed screening; the main reasons were failure to meet the inclusion/exclusion criteria or unacceptable laboratory values (the number of screen failures is an estimate based on information collected in the IxRS). A total of 821 patients were enrolled in the study and were randomized 1:1 to interferon beta-1a (IFN group, N = 411) or ocrelizumab (OCR group, N = 410). In total, 706 patients (86%) received treatment and completed the double-blind treatment period up to Week 96. The proportion of patients who received treatment and completed the double-blind treatment period up to Week 96 was higher in the OCR group (89%) than in the IFN group (83%). The difference in withdrawal from treatment between groups was mainly due to higher incidences of withdrawals due to adverse events (6% versus 3%), withdrawal by subject (3% versus 2%) and lack of efficacy (3% versus 2%) in the IFN group versus the OCR group, respectively.

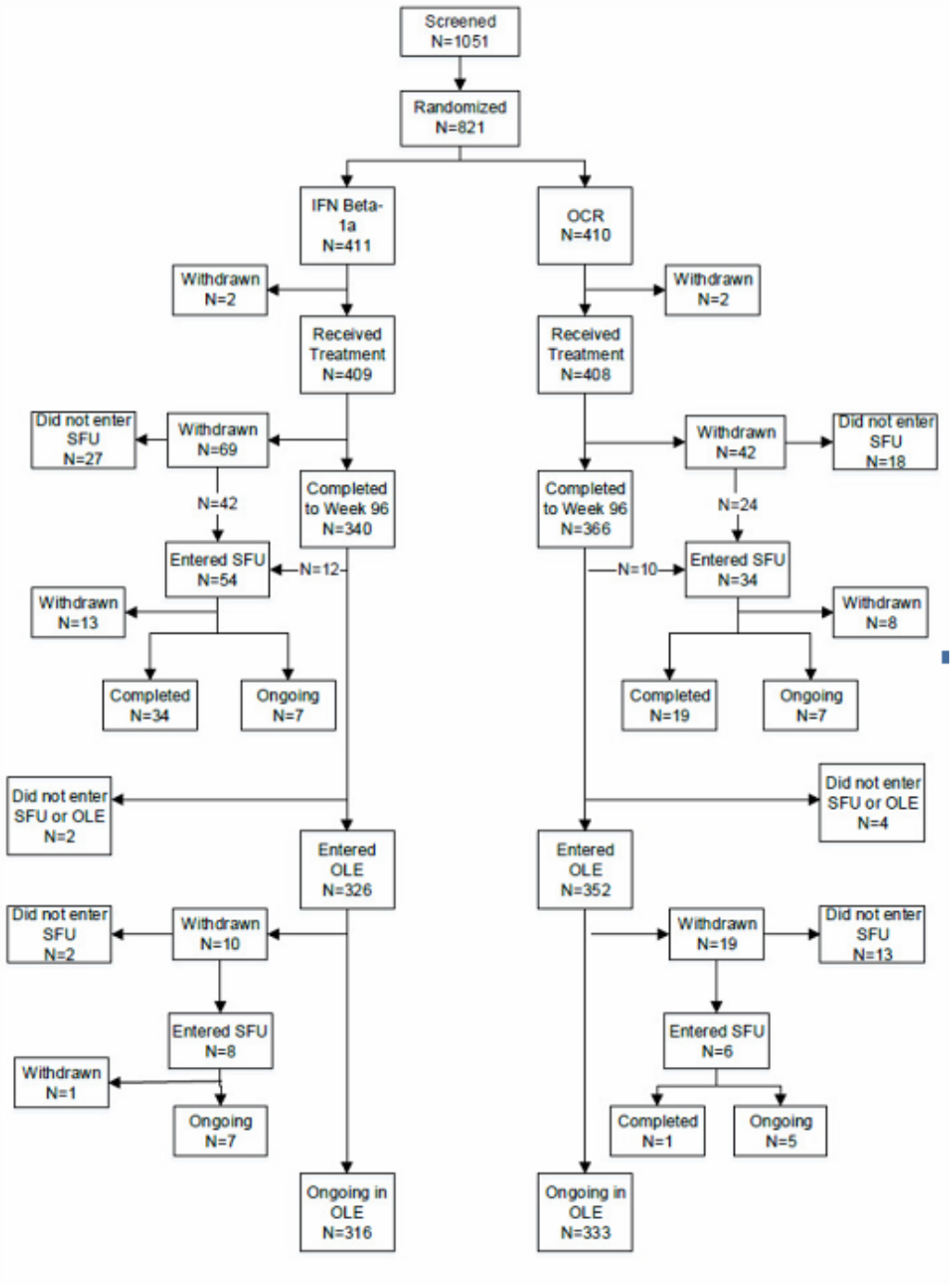


Figure 6 Overview of Patients' Disposition (Randomized Patients) – Study WA21092

- **Recruitment**

This was a multicenter study with in total 141 centers in 32 countries (USA, Europe, Latin-America, Tunisia and South Africa). The first patient randomised was in August 2011 and the clinical cut-off for the primary analysis was in April 2015.

- **Conduct of the study**

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP). Four protocol amendments were issued

- **Baseline data**

The demographic characteristics of the ITT population were well balanced across the treatment groups. The majority of patients were female (66% in both treatment groups) and were predominantly white (91% – 92% across treatment groups with median ages of 37 and 38 years in the treatment groups (range 18 – 56 years). Patients' median weight was 72 – 74 kg across groups (range 41 – 170 kg). Patients were mainly from Europe (EU, Switzerland and Norway; approximately 50% – 52% across treatment groups) or North America (USA and Canada) and Australia (approximately 26% in each treatment group). The two treatment groups had similar MS disease histories. The median duration since symptom onset was 4.62 years in the IFN group and 4.88 years in the OCR group. Approximately half (53% in each group) of patients had been diagnosed within 2 years prior to randomization. Almost all patients (98% in IFN group and 96% in OCR group) had experienced at least one relapse within 1 year prior to randomization. The baseline MRI disease characteristics of patients were well balanced between the treatment groups. Of the patients in the IFN group, 38% had one or more T1 Gdenhancing lesions at baseline; in the OCR group, 42% had one or more T1 Gd enhancing lesions at baseline. The number of T1 hypointense lesions, volume of T2 hyperintense lesions, and number of T2 hyperintense lesions were similar between the groups. Normalized brain volume was also similar between the two groups.

A total of 71% of patients in the IFN group and 74% of patients in the OCR group had not been treated with any MS medication in the 2 years prior to randomization. The number of patients who had received MS therapies in the prior two years was relatively balanced between treatment groups. The most common prior treatments for MS were glatiramer acetate and interferons. There were no imbalances in the number of patients treated with a given medication.

It was agreed that the patient characteristics were well balanced between the treatment groups.

- **Numbers analysed**

All 821 patients randomized to treatment were included in the ITT population which was appropriately defined for the primary efficacy analyses.

- **Outcomes and estimation**

Primary efficacy variable

The study met its primary endpoint: treatment with ocrelizumab significantly reduced the ARR by 46.4% at 96 weeks compared with interferon beta-1a ($p < 0.0001$). Highly consistent estimates of treatment effect were observed in all pre-specified sensitivity analyses of the primary endpoint.

Patients receiving ocrelizumab consistently showed a greater reduction of ARR compared with interferon beta-1a across all subgroups.

Patients aged < 40 years had a greater reduction of ARR on ocrelizumab versus interferon beta-1a (adjusted ARR ratio 0.423 [95% CI: 0.284, 0.631], $p<0.0001$) compared with patients aged > 40 years (adjusted ARR ratio 0.692 [95% CI: 0.447, 1.072], $p = 0.0985$).

Patients with ≥ 1 T1 Gd-enhancing lesion at baseline had a greater reduction of ARR on ocrelizumab versus interferon beta-1a (adjusted ARR ratio 0.313 [95% CI: 0.198, 0.497], $p<0.0001$) compared with patients with no T1 Gd-enhancing lesions (ARR ratio 0.787 [95% CI: 0.539, 1.148], $p = 0.2131$). However, both age groups, and both patients with or without baseline Gd-enhancing lesions, still showed a reduction of ARR on ocrelizumab compared with interferon beta-1a.

No notable differences were observed between the other subgroups. The observed effect size was regarded as clinically relevant.

Secondary efficacy variables

Results of several secondary endpoints supported the primary endpoint, demonstrating statistically significant efficacy of ocrelizumab when compared with interferon beta-1a. Treatment with

ocrelizumab resulted in significantly greater improvements in measures of disability compared with interferon beta-1a, namely:

- A 40% risk reduction in 12-week CDP in the pooled analysis of Studies WA21092 and WA21093 (hazard ratio [HR] 0.60 [95% CI: 0.45, 0.81], p=0.0006). The individual study also demonstrated a 37% risk reduction of 12-week CDP (HR 0.63 [95% CI: 0.42, 0.92], p = 0.0169)
- A 40% risk reduction in 24-week CDP in the pooled analysis of Studies WA21092 and WA21093 (HR 0.60 [95% CI: 0.43, 0.84], p=0.0025). The individual study also demonstrated a 37% risk reduction of 24-week CDP (HR 0.63 [95% CI: 0.40, 0.98], p = 0.0370)
- A 33% relative increase in the proportion of patients with 12-week CDI in the pooled analysis of Studies WA21092 and WA21093 (relative risk [RR] 1.33 [95% CI: 1.05, 1.68], p=0.0194). In this study a 14% relative increase in the proportion of patients with 12-week CDI was observed (RR 1.14 [95% CI: 0.84, 1.56], p = 0.4019)
- An improvement of 0.107 [95% CI: 0.034, 0.180] in the MSFC score change from baseline to Week 96 (p = 0.0040)

Treatment with ocrelizumab consistently resulted in significantly greater effects on the following MRI measures compared with interferon beta-1a:

- A 94.9% relative reduction in the total number of T1-Gd enhancing lesions (p<0.0001)
- An 82.9% relative reduction in the total number of new and/or enlarging T2 lesions (p<0.0001)
- A 64.3% relative reduction in the total number of new T1-hypointense lesions (p<0.0001)

Ocrelizumab also showed statistically significant outcomes in additional secondary efficacy endpoints compared with interferon beta-1a, which were not formally adjusted for multiplicity and not formally statistically significant due to the hierarchichal testing strategy:

- Greater improvement of 1.159 (95% CI: 0.051, 2.268) in SF-36 PCS mean score from baseline to Week 96 (non-confirmatory p = 0.0404)
- A 81% relative increase in the proportion of patients with NEDA (non-confirmatory p<0.0001)

Ocrelizumab showed a numerically superior but not statistically significant outcome in the remaining secondary endpoint compared to interferon beta-1a:

- A 14.9% relative reduction in mean percent brain volume loss from Week 24 to Week 96 (p=0.0900)

Table 12 Time to Onset of Confirmed Disability Progression Sustained for at Least 12 Weeks with the Initial Event of Neurological Worsening Occurring during the Double-Blind Treatment Period (Without Imputation) across RMS Studies (WA21092 and WA21093, ITT Population)

Study	WA21092		WA21093		WA21092/3 Pooled	
Treatment	IFN SC N=411	OCR 600 mg N=410	IFN SC N=418	OCR 600 mg N=417	IFN SC N=829	OCR 600 mg N=827
Patients with event (%)	50 (12.2%)	31 (7.6%)	63 (15.1%)	44 (10.6%)	113 (13.6%)	75 (9.1%)
% patients with events at 96 Week (KM estimate)	12.97	8.31	17.54	11.14	15.18	9.75
Time to event Range (Weeks)	1* to 722*	1* to 754*	1* to 714*	1* to 728	1* to 722*	1* to 754*
Stratified Analysis p-value (log rank)		0.0139		0.0169		0.0006
Hazard Ratio 95% CI		0.57 (0.37, 0.90)		0.63 (0.42, 0.92)		0.60 (0.45, 0.81)

* censored observation

Stratified by Geographical Region (US vs. ROW) and Baseline EDSS (<4.0 vs. ≥ 4.0).

Hazard ratios were estimated by stratified Cox regression.

Patients with an initial disability progression during the double-blind treatment period who discontinue the treatment early and do not have a subsequent visit with EDSS measurement are censored.

IFN SC = interferon beta-1a 44 µg subcutaneous

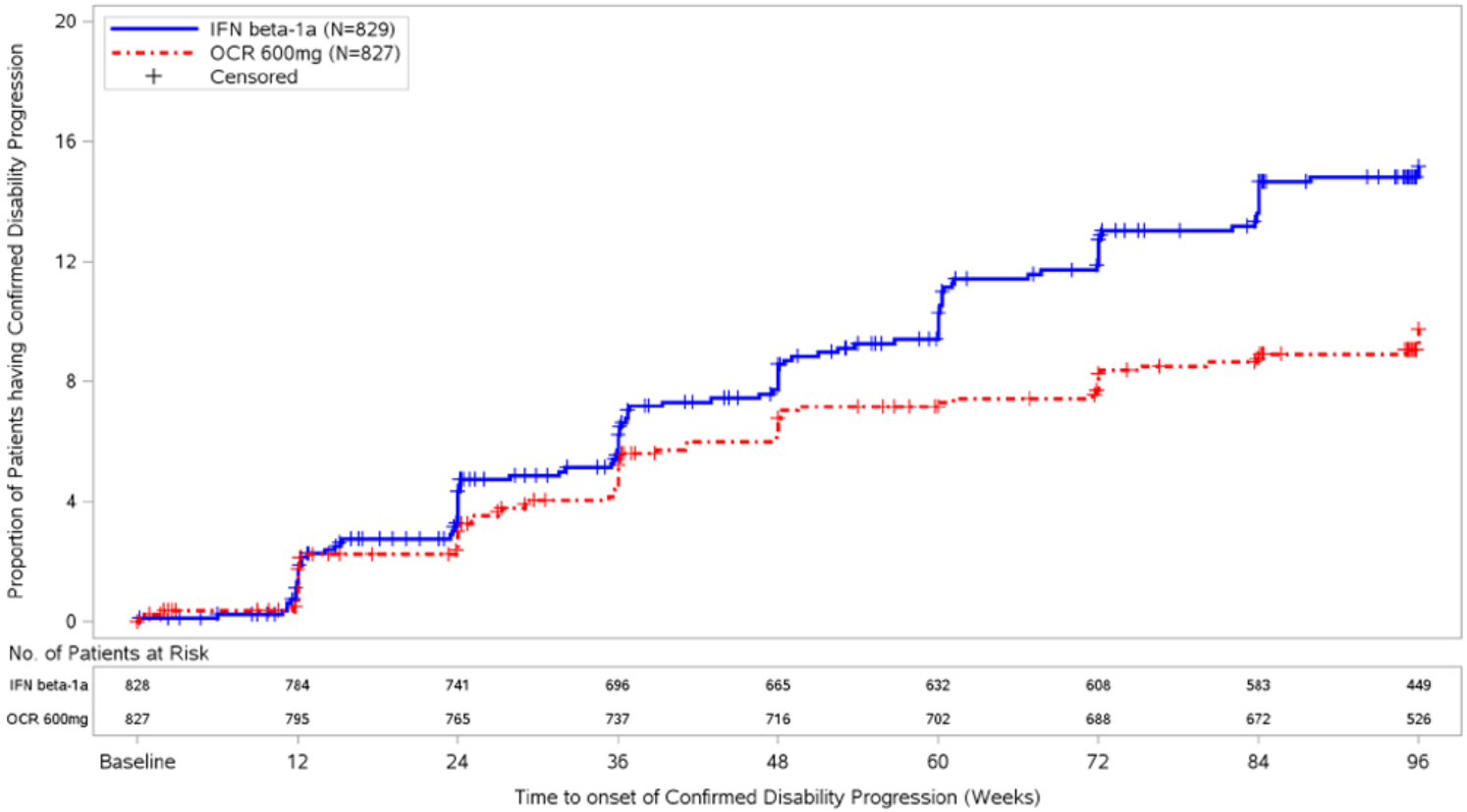


Figure 7 Kaplan-Meier Plot of Time to Onset of Confirmed Disability Progression Sustained for at Least 12 Weeks with the Initial Event of Neurological Worsening Occurring during the Double-Blind Treatment Period (Pooled WA21092 and WA21093, ITT Population)

Kaplan-Meier curves truncated at 96 weeks after randomization.

Table 13 Time to Onset of Confirmed Disability Progression Sustained for at Least 24 Weeks with the Initial Event of Neurological Worsening Occurring during the Double-Blind Treatment Period (Without Imputation) across RMS Studies (WA21092 and WA21093, ITT Population)

Study	WA21092		WA21093		WA21092/3 Pooled	
Treatment	IFN SC N=411	OCR 600 mg N=410	IFN SC N=418	OCR 600 mg N=417	IFN SC N=829	OCR 600 mg N=827
Patients with event (%)	39 (9.5%)	24 (5.9%)	48 (11.5%)	33 (7.9%)	87 (10.5%)	57 (6.9%)
% patients with events at 96 Week (KM estimate)	10.57	6.51	13.63	8.60	12.03	7.58
Time to event Range (Weeks)	1* to 722*	1* to 754*	1* to 714*	1* to 728*	1* to 722*	1* to 754*
Stratified Analysis p-value (log rank)		0.0278		0.0370		0.0025
Hazard Ratio 95% CI		0.57 (0.34, 0.95)		0.63 (0.40, 0.98)		0.60 (0.43, 0.84)

* censored observation

Stratified by Geographical Region (US vs. ROW) and Baseline EDSS (<4.0 vs. ≥ 4.0).

Hazard ratios were estimated by stratified Cox regression.

Patients with an initial disability progression during the double-blind treatment period who discontinue the treatment early and do not have a subsequent visit with EDSS measurement are censored.

IFN SC = interferon beta-1a 44 µg subcutaneous

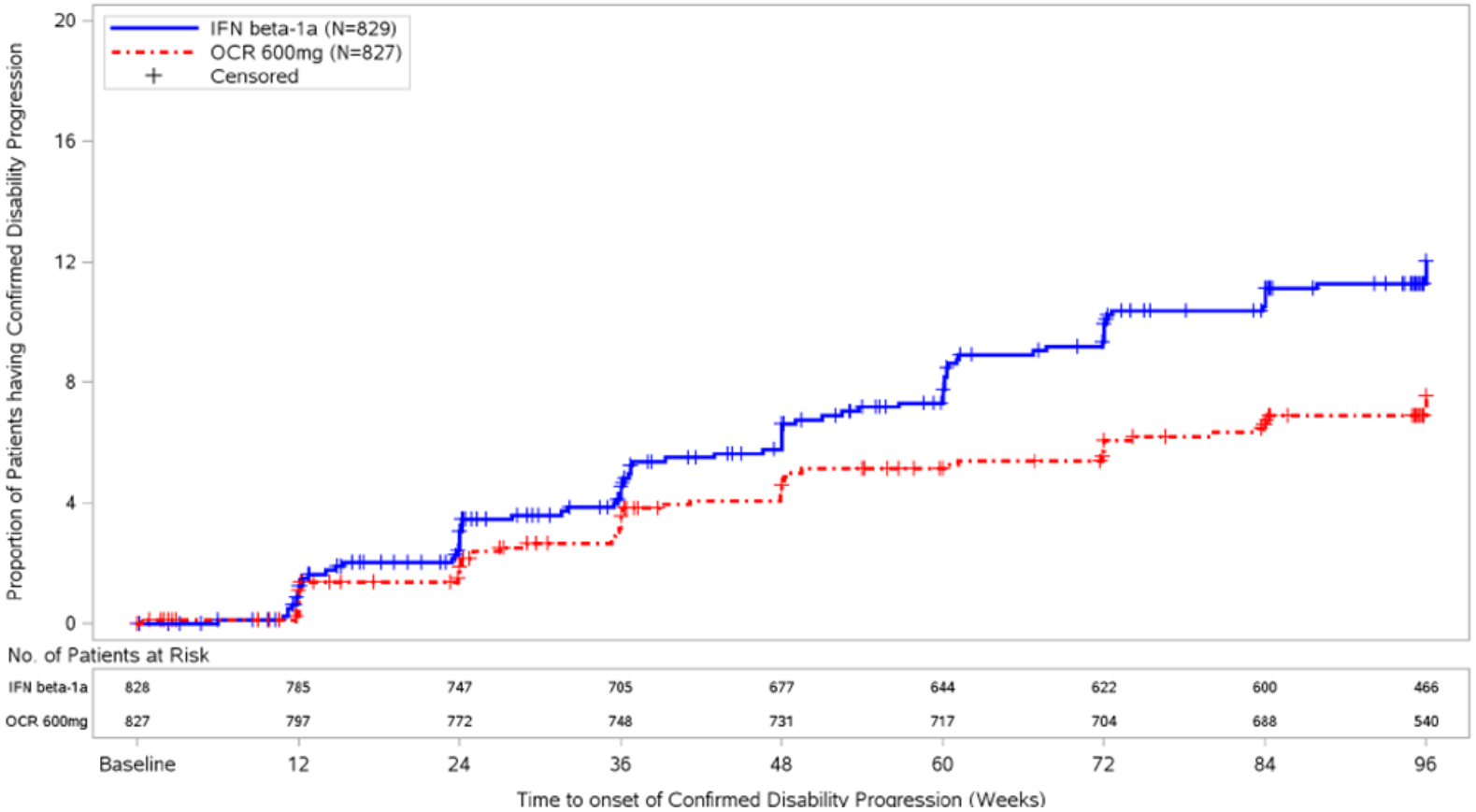


Figure 8 Kaplan-Meier Plot of Time to Onset of Confirmed Disability Progression Sustained for at Least 24 Weeks with the Initial Event of Neurological Worsening Occurring during the Double-Blind Treatment Period (Pooled WA21092 and WA21093, ITT Population)

Kaplan-Meier curves truncated at 96 weeks after randomization.

A hierarchical approach was taken for significance testing in order to control for multiplicity. CDP and CDI endpoints were analyzed in a pooled population of Studies WA21092 and WA21093 due to a lack of power and these were the results used in the hierarchy. A summary of all p-values within the hierarchical structure is provided in the table below (Table 14) and indicates those values which should be considered non-confirmatory since they follow a non-significant test result within the hierarchy structure (shaded cells). Importantly, the primary and secondary endpoints showing efficacy of ocrelizumab on both clinical and imaging measures of inflammation (ARR, T1 Gd-enhancing lesions and new and/or enlarging T2 lesions) and on clinical measures of disease progression (CDP, new T1 hypointense lesions) were all met.

Table 14 Summary of Hierarchical Significance Testing of Efficacy Endpoints (WA21092)

	Endpoints	p value
Primary	**Protocol-defined ARR by 2 years (96 weeks)**	<0.0001
Secondary	CDP for 12 weeks **(pooled data WA21092 and WA21093)**	0.0006
	T1 Gd-enhancing lesions	<0.0001
	New and/or enlarging T2 hyperintense lesions	<0.0001
	CDI for 12 weeks **(pooled data WA21092 and WA21093)**	0.0194
	CDP for 24 weeks **(pooled data WA21092 and WA21093)**	0.0025
	New T1 hypointense lesions	<0.0001
	MSFC	0.3261
	Brain volume	0.0042
	SF-36 PCS	0.2193
	NEDA	<0.0001

Grey shaded cells indicate non-confirmatory p-values that follow a non-significant test result within the hierarchy structure

Patients in the OCR group showed fewer T1 Gd-enhancing lesions when compared with those in the IFN group from as early as Week 24 (90.8% relative reduction) with greater suppression of inflammatory lesions at subsequent visits (relative reductions of 97.7% and 95.4% at Weeks 48 and 96 respectively). This reduction was seen in all numerical categories of lesions as shown in the summary of descriptive statistics and categorical analysis of T1 Gd-enhancing lesions by visit.

Patients in the OCR group showed fewer new and/or enlarging T2 lesions when compared with those in the IFN group from as early as Week 24 (41.1% relative reduction) followed by substantial reduction of new inflammation through Weeks 48 and 96 (relative reductions of 93.9% and 98.3% respectively). This reduction was seen in all numerical categories of lesions as shown in the summary of descriptive statistics and categorical analysis of new and/or enlarging T2 hyperintense lesions by visit.

A greater reduction of 12-week CDP was observed for ocrelizumab versus interferon beta-1a across all subgroups. The subgroup of patients with baseline weight < 75 kg showed a greater reduction of 12-week CDP on ocrelizumab versus interferon beta-1a (HR 0.36 [95% CI: 0.18, 0.72], p = 0.0042) compared with patients with baseline weight ≥ 75kg (HR 0.85 [95% CI: 0.46, 1.56], p = 0.6005). A similar difference was observed between the BMI subgroups. No notable differences were observed between the other subgroups.

In general a greater reduction of 24-week CDP on ocrelizumab compared with interferon beta-1a was observed across subgroups. The subgroup of patients with baseline weight < 75 kg showed a greater reduction of 24-week CDP on ocrelizumab versus interferon beta-1a (HR 0.29 [95% CI: 0.13, 0.65], p = 0.0028) whereas for patients with baseline weight ≥ 75kg there was no difference between

treatment groups (HR 1.01 [95% CI: 0.50, 2.06], p = 0.9695). A similar difference was observed between the BMI subgroups. No notable differences were observed between the other subgroups.

Most secondary endpoints were met following a hierarchical statistical significance testing, including the pooled analyses of CDP 12 Weeks, CDP 24 Weeks and CDI 12 weeks and all but one study specific MRI endpoint (Brain volume). The study in itself also had statistically significant outcomes for CDP 12 Weeks and CDP 24 Weeks, but not for CDI 12 weeks. Missingness for CDP 12 Weeks, CDP 24 Weeks and CDI 12 Weeks was handled appropriately, and with positive results, with a conservative definition of non-CDI for subjects who withdrew prematurely and appropriate imputation assumptions in the sensitivity analyses for CDP 12 Weeks and CDP 24 Weeks. The positive changes seen for CDP 12 Weeks and CDP 24 Weeks are regarded as clinically relevant in terms of effect size. Step. no. 6 in the hierarchical testing chain, change in MSFC, did not show any statistically significant difference versus the active control and the subsequent hierarchical testing was therefore broken and non-confirmatory for Brain volume and NEDA (Brain volume, p=0.0042; SF-36 PCS, p=0.2193; NEDA, p<0.0001). Still, the results for change in Brain volume (from Week 24, but also from baseline in a pre-specified explorative analysis) and NEDA are encouraging.

Results clinical study WA21093

- **Participant flow**

A total of 1045 patients were screened for entry into the study. Of these, 210 patients failed screening; the main reasons were failure to meet the inclusion/exclusion criteria or unacceptable laboratory values (the number of screen failures is an estimate based on information collected in the IxRS). A total of 835 patients were enrolled in the study and were randomized 1:1 to interferon beta-1a (IFN, N = 418) or ocrelizumab (OCR, N = 417). In total, 680 patients (81%) received treatment and completed the double-blind treatment period up to Week 96.The proportion of patients who received treatment and completed the double-blind treatment period up to Week 96 was higher in the OCR group (86%) than in the IFN group (77%). The difference in withdrawal from treatment between groups was mainly due to higher incidences of withdrawals due to adverse events (6% versus 4%), withdrawal by subject (6% versus 3%) and lack of efficacy (4% versus 1%) in the IFN group versus the OCR group, respectively.

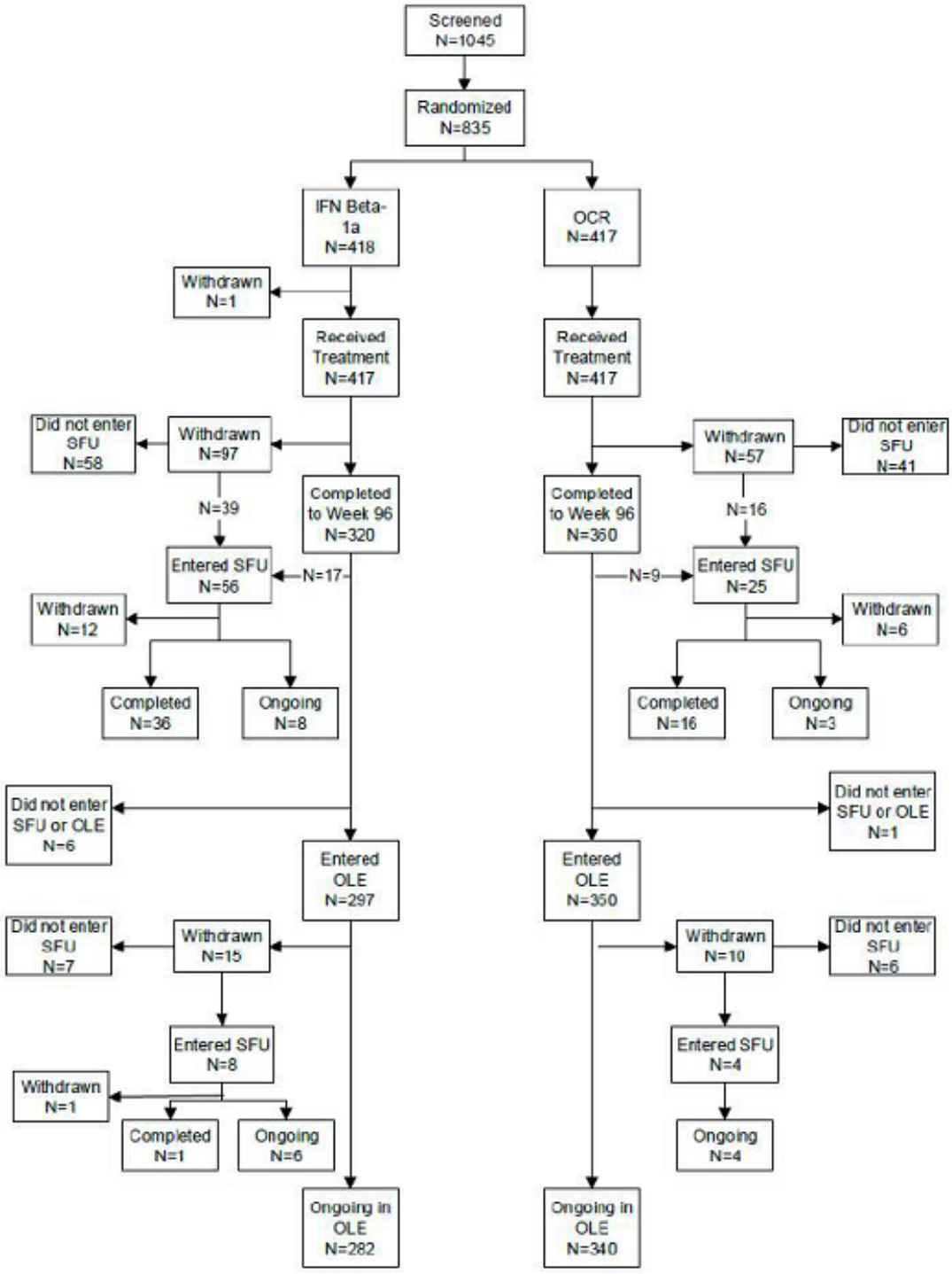


Figure 9 Overview of Patients' Disposition (Randomized Patients) – WA21093

- **Recruitment**

This was a multicentre study with in total 166 centers in 24 countries. The first patient randomised was in September 2011 and the clinical cut-off for the primary analysis was in May 2015.

- **Conduct of the study**

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP). Three protocol amendments were issued

- **Baseline data**

The demographic characteristics of the ITT population were well balanced across the treatment groups. The majority of patients were female (65% - 67% across treatment groups) and were predominantly white (88% - 91% across treatment groups) with median ages of 37 and 38 years in the treatment groups (range 18 - 55 years). Patients' median weight was approximately 73 - 74 kg across groups (range 38.0 - 163.6 kg). Patients were mainly from Europe (EU, Switzerland and Norway; approximately 44% - 45% across treatment groups) or North America (USA and Canada) and Australia (approximately 37% - 38% across treatment groups). The two treatment groups had similar MS disease histories. The median duration since symptom onset was 5.07 years in the IFN group and 5.16 years in the OCR group. Approximately half of patients (49% - 53% in each group) had been diagnosed within 2 years prior to randomization. Almost all patients (96% in both treatment groups) had experienced at least one relapse within 1 year prior to randomization. The baseline MRI disease characteristics of patients were well balanced between the treatment groups. The proportion of patients with one or more T1 Gd-enhancing lesions was 41% in the IFN group and 39% in the OCR group. The number of T1 hypointense lesions, volume of T2 hyperintense lesions, and number of T2 hyperintense lesions were similar between the groups. In both groups, 92% of patients had > 9 T2 hyperintense lesions at baseline. Median normalized brain volume was also similar between the two groups

A total of 75% of patients in the IFN group and 73% of patients in the OCR group had not been treated with any MS medication in the 2 years prior to randomization. The number of patients who had received prior MS therapies was relatively balanced between treatment groups. The most common prior treatments for MS were glatiramer acetate and interferons. There were no imbalances in the number of patients treated with a given medication.

- **Numbers analysed**

All 835 patients randomized to treatment were included in the ITT population.

- **Outcomes and estimation**

Primary efficacy variable

The study met its primary endpoint: treatment with ocrelizumab significantly reduced the ARR by 46.8% ($p<0.0001$) at 96 weeks compared with interferon beta-1a ($p<0.0001$). Highly consistent estimates of treatment effect were observed in all pre-specified sensitivity analyses of the primary endpoint.

Patients receiving ocrelizumab consistently showed a greater reduction of ARR compared with interferon beta-1a across all subgroups. Patients aged < 40 years had a greater reduction of ARR on ocrelizumab versus interferon beta-1a (adjusted ARR ratio 0.403 [95% CI: 0.271, 0.600], $p<0.0001$) compared with patients aged > 40 years (adjusted ARR ratio 0.807 [95% CI: 0.523, 1.245], $p = 0.3335$). Patients with ≥ 1 T1 Gd-enhancing lesion at baseline had a greater reduction of ARR on ocrelizumab versus interferon beta-1a (adjusted ARR ratio 0.422 [95% CI: 0.267, 0.668],$p = 0.0002$) compared with patients with no T1 Gd-enhancing lesions (ARR ratio 0.684 [95% CI: 0.465, 1.006], $p = 0.0527$). However, both age groups, and both patients with or without baseline Gd-enhancing lesions, still showed a reduction of ARR on ocrelizumab compared with interferon beta-1a. No notable differences were observed between the other subgroups.

Secondary efficacy variables

Results of several secondary endpoints supported the primary endpoint, demonstrating statistically significant efficacy of ocrelizumab when compared with interferon beta-1a. Treatment with ocrelizumab resulted in significantly greater improvements in measures of disability compared with interferon beta-1a, namely:

-A 40% risk reduction in 12-week CDP in the pooled analysis of Studies WA21092 and WA21093 (hazard ratio [HR] 0.60 [95% CI: 0.45, 0.81], p=0.0006). The individual study also demonstrated a 37% risk reduction of 12-week CDP (HR 0.63 [95% CI: 0.42, 0.92], p = 0.0169).

-A 40% risk reduction in 24-week CDP in the pooled analysis of Studies WA21092 and WA21093 (HR 0.60 [95% CI: 0.43, 0.84], p=0.0025). The individual study also demonstrated a 37% risk reduction of 24-week CDP (HR 0.63 [95% CI: 0.40, 0.98], p = 0.0370).

-A 33% relative increase in the proportion of patients with 12-week CDI in the pooled analysis of Studies WA21092 and WA21093 (relative risk [RR] 1.33 [95% CI: 1.05, 1.68], p=0.0194). In this study a 14% relative increase in the proportion of patients with 12-week CDI was observed (RR 1.14 [95% CI: 0.84, 1.56], p = 0.4019).

-An improvement of 0.107 [95% CI: 0.034, 0.180] in the MSFC score change from baseline to Week 96 (p = 0.0040).

Treatment with ocrelizumab consistently resulted in significantly greater effects on the following MRI measures compared with interferon beta-1a:

-A 94.9% relative reduction in the total number of T1-Gd enhancing lesions (p<0.0001).

-An 82.9% relative reduction in the total number of new and/or enlarging T2 lesions (p<0.0001).

-A 64.3% relative reduction in the total number of new T1-hypointense lesions (p<0.0001).

Ocrelizumab also showed statistically significant r outcomes in additional secondary efficacy endpoints compared with interferon beta-1a, which were not formally adjusted for multiplicity and not formally statistically significant due to the hierarchichal testing strategy:

-Greater improvement of 1.159 (95% CI: 0.051, 2.268) in SF-36 PCS mean score from baseline to Week 96 (non-confirmatory p = 0.0404).

-A 81% relative increase in the proportion of patients with NEDA (non-confirmatory p<0.0001).

Ocrelizumab showed a numerically superior but not statistically significant outcome in the remaining secondary endpoint compared to interferon beta-1a:

-A 14.9% relative reduction in mean percent brain volume loss from Week 24 to Week 96 (p=0.0900)

Table 15 Summary of Primary and Secondary Efficacy Endpoints at Week 96 (WA21093, ITT Population)

Endpoints	IFN beta-1a 44 μg (N=418)	OCR 600 mg (N=417)
Primary endpoint		
1. ARR at 96-weeks Rate Rate ratio (95% CI) p-value	N=418 0.290	N=417 0.155 0.532 (0.397, 0.714) <0.0001
Disability		
12-week CDP* Proportion of patients with events at 96 weeks (Kaplan Meier estimate) Hazard ratio (95% CI) p-value (Log-rank)	N=418 17.54	N=417 11.14 0.63 (0.42, 0.92) 0.0169

2. 12-week CDP (pooled WA21092 and WA21093)[a] Proportion of patients with events at 96 weeks (Kaplan Meier estimate) Hazard ratio (95% CI) p-value (Log-rank)	N=829 15.18	N=827 9.75 0.60 (0.45, 0.81) 0.0006
24-week CDP* Proportion of patients with events at 96 weeks (Kaplan Meier estimate) Hazard ratio (95% CI) p-value (Log-rank)	N=418 13.63	N=417 8.60 0.63 (0.40, 0.98) 0.0370
6. 24-week CDP (pooled WA21092 and WA21093)[a] Proportion of patients with events at 96 weeks (Kaplan Meier estimate) Hazard ratio (95% CI) p-value (Log-rank)	N=829 12.03	N=827 7.58 0.60 (0.43, 0.84) 0.0025
12-week CDI*,[a] Proportion of patients with improvement Relative risk (95% CI) p-value	N=308 18.83	N=318 21.38 1.14 (0.84, 1.56) 0.4019
5. 12-week CDI (pooled WA21092 and WA21093)[a,b] Proportion of patients with improvement Relative risk (95% CI) p-value	N=614 15.64	N=628 20.70 1.33 (1.05, 1.68) 0.0194
8. MSFC Mean z-score change from baseline to Week 96 Mean difference (95% CI) p-value	N=269[c] 0.169	N=308[c] 0.276 0.107 (0.034 0.180) 0.0040

Endpoints	IFN beta-1a 44 µg (N=411)	OCR 600 mg (N=410)
Brain MRI		
3. T1 Gd-enhancing lesions Mean number of lesions per MRI scan Rate ratio (95% CI) p-value	N=375[c] 0.416	N=389[c] 0.021 0.051 (0.029, 0.089) <0.0001
4. New and/or enlarging T2 hyperintense lesions Mean number of lesions per MRI scan Rate ratio (95% CI) p-value	N=376[c] 1.904	N=390[c] 0.325 0.171 (0.130, 0.225) <0.0001
7. New T1 hypointense lesions Mean number of lesions per MRI scan Rate ratio (95% CI) p-value	N=375[c] 1.255	N=389[c] 0.449 0.357 (0.272, 0.470) <0.0001
9. Brain volume Mean %change from Week 24 to Week 96 Mean difference (95% CI) p-value % Relative reduction (95% CI)	N=259[d] -0.750	N=287[d] -0.638 0.112 (-0.018, 0.241) 0.0900 14.933 (-2.011, 30.174)
Disease Activity		
11. NEDA[a] Proportion of patients with NEDA Relative risk (95% CI) p-value	N=270 24.1	N=289 43.9 1.81 (1.41, 2.32) <0.0001[e]
Health Related Quality of Life		
10. SF-36 PCS Mean change from baseline to Week 96 Mean difference (95% CI) p-value	N=276[b] -0.833	N=315[b] 0.326 1.159 (0.051, 2.268) 0.0404[e]

ARR annualized relapse rate, CDI confirmed disability improvement, CDP confirmed disability progression, Gd gadolinium, MSFC Multiple Sclerosis Functional Composite, NEDA No evidence of disease activity, SF-36 PCS Short Form 36 Physical Component Summary.

* Endpoint not powered for individual study.

[a] in patients with baseline EDSS score at least 2.0.

[b] number of patients with measurements at baseline and Week 96

[c] number of patients with MRI scans at Week 96

[d] number of patients with MRI scans at Weeks 24 and 96

[e] non-confirmatory p-value

The hierarchical test flow is denoted by figures in red colour.

For Time to onset of CDP 12 Weeks and CDP 24 Weeks please refer to the tables and Kaplan-Meier plots in the previous section (Table 12, Figure 7,

Table 13, Figure 8).

A hierarchical approach was taken for significance testing in order to control for multiplicity. CDP and CDI endpoints were analyzed in a pooled population of Studies WA21092 and WA21093 due to a lack of power and these were the results used in the hierarchy. A summary of all p-values within the hierarchical structure is provided in the Table 21 below and indicates those values which should be considered non-confirmatory since they follow a non-significant test result within the hierarchy structure (shaded cells). Importantly, the primary and secondary endpoints showing efficacy of ocrelizumab on both clinical and imaging measures of inflammation (ARR, T1 Gd-enhancing lesions and new and/or enlarging T2 lesions) and on clinical measures of disease progression (CDP, new T1 hypointense lesions) were all met.

Table 16 Summary of Hierarchical Significance Testing of Efficacy Endpoints (WA21093)

	Endpoints	p value
Primary	**Protocol-defined ARR by 2 years (96 weeks)**	<0.0001
Secondary	CDP for 12 weeks **(pooled data WA21092 and WA21093)**	0.0006
	T1 Gd-enhancing lesions	<0.0001
	New and/or enlargingT2 hyperintense lesions	<0.0001
	CDI for 12 weeks **(pooled data WA21092 and WA21093)**	0.0194
	CDP for 24 weeks **(pooled data WA21092 and WA21093)**	0.0025
	New T1 hypointense lesions	<0.0001
	MSFC	0.0040
	Brain volume	0.0900
	SF-36 PCS	0.0404
	NEDA	<0.0001

Grey shaded cells indicate non-confirmatory p-values that follow a non-significant test result within the hierarchy structure

Patients in the OCR group showed fewer T1 Gd-enhancing lesions when compared with those in the IFN group from as early as Week 24 (92.3% reduction) with greater suppression of inflammatory lesions at subsequent visits (relative reductions of 95.6% and 97.2% at Weeks 48 and 96 respectively). This reduction was seen in all numerical categories of lesions as shown in the summary of descriptive statistics and categorical analysis of T1 Gd-enhancing lesions by visit.

Patients in the OCR group showed fewer new and/or enlarging T2 lesions when compared with those in the IFN group from as early as Week 24 (60.7% relative reduction) followed by substantial reduction of new inflammation through Weeks 48 and 96 (relative reductions of 95.6% and 96.9% respectively). This reduction was seen in all numerical categories of lesions as shown in the summary of descriptive statistics and categorical analysis of new and/or enlarging T2 hyperintense lesions by visit.

A greater reduction of 12-week CDP was observed for ocrelizumab versus interferon beta-1a across all subgroups (Figure 7). The subgroup of patients with baseline weight < 75 kg showed a greater reduction of 12-week CDP on ocrelizumab versus interferon beta-1a (HR 0.43 [95% CI: 0.24, 0.79], p = 0.0058) compared with patients with baseline weight ≥ 75kg (HR 0.90 [95% CI: 0.53, 1.53], p = 0.6976). No notable differences were observed between the other subgroups.

In general a greater reduction of 24-week CDP on ocrelizumab compared with interferon beta-1a was observed across subgroups (Figure 9). The subgroup of patients with baseline weight < 75 kg showed a greater reduction of 24-week CDP on ocrelizumab versus interferon beta-1a (HR 0.37 [95% CI: 0.19, 0.73], p = 0.0042) than those patients with baseline weight ≥ 75kg (versus HR 1.06 [95% CI: 0.56,

2.00], p = 0.8552). A similar difference was observed between the BMI subgroups. No notable differences were observed between the other subgroups.

Study WA25046 (main study in PPMS)

Clinical study WA25046, hereafter also referred to as Study 25046. Study title: A Phase III, multicenter, randomized, parallel-group, double blinded, placebo controlled study to evaluate the efficacy and safety of ocrelizumab in adults with primary progressive multiple sclerosis.

Methods

This study was a randomized double-blind, parallel-group, placebo-controlled phase III study, designed to evaluate the efficacy and safety of ocrelizumab in adults with primary progressive multiple sclerosis (PPMS). The study consisted of the following periods:

- Screening
- Double-blind treatment
- Safety follow-up (SFU) followed by B-cell monitoring
- Open label extension (OLE); at the time of the clinical cut-off date, the OLE had not started and hence is not included in this report.

Consenting patients were screened within 4 weeks prior to the start of the study. Eligible patients were then randomized. Treatment was administered in a double-blind fashion for a minimum of 5 treatment doses, each of 24 weeks duration. Additional treatment doses were to take place until the last enrolled patient reached 120 weeks of treatment and the planned total number of 253 confirmed disability progression events had occurred. No study treatment was administered during SFU or B-cell monitoring.

Two infusion visits occurred 14 days apart every 24 weeks until the end of the double-blind treatment period (i.e. Day 1 and Week 2, Weeks 24 and 26, Weeks 48 and 50, and so forth). Non-infusion visits occurred at Week 12 and at the midpoint of each treatment dose thereafter through the end of the double-blind treatment period (i.e. Weeks 36, 60, 84, and so forth). In addition, a structured telephone interview was performed on an every 4-week basis between study visits from Week 8 through the end of the double-blind treatment period to identify any new or worsening neurological symptoms that warranted an unscheduled visit.

Neurological exams were collected at baseline and each subsequent visit during the double-blind treatment period. EDSS and MSFC assessment were recorded at baseline, Week 12 and then every 12 weeks. MRI was collected at baseline, Week 24, Week 48, and Week 120. SF-36 was collected at baseline, Week 48 and Week 120.

- **Study participants**

The inclusion criteria included among others:

- Ability to provide written informed consent and to be able to follow the schedule of

protocol assessments.

- Diagnosis of PPMS in accordance with the revised McDonald criteria (2005).

- Ages 18-55 years, inclusive.

- EDSS at screening from 3.0 to 6.5 points.

- Score of ≥ 2.0 on the Functional Systems (FS) scale for the pyramidal system that was due to lower extremity findings.

- Disease duration from the onset of MS symptoms:

a) less than 15 years in patients with an EDSS at screening > 5.0.

b) less than 10 years in patients with an EDSS at screening ≤ 5.0.

- Documented history or presence at screening of at least one of the following laboratory findings in a CSF specimen:

a) elevated IgG index.

b) one or more IgG oligoclonal bands detected by isoelectric focusing.

Some of the exclusion criteria were:

- History of relapsing remitting multiple sclerosis, secondary progressive, or progressive relapsing multiple sclerosis at screening.

- Known presence of other neurologic disorders.

- Previous treatment with B-cell targeted therapies (e.g. rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab).

- Any previous treatment with alemtuzumab, anti-CD4, cladribine, cyclophosphamide, mitoxantrone, azathioprine, mycophenolate mofetil [MMF], cyclosporine, methotrexate, total body irradiation, or bone marrow transplantation.

- Any previous treatment with lymphocyte trafficking blockers (e.g. natalizumab, FTY720).

- Treatment with β interferons, glatiramer acetate, i.v. immunoglobulin, plasmapheresis, or other immunomodulatory therapies within 12 weeks prior to randomization.

- Systemic corticosteroid therapy within 4 weeks prior to screening.

- **Treatments**

For the blinded treatment period patients were randomly assigned to one of two treatment groups:

– ocrelizumab 600 mg every 24 weeks.

– placebo.

Each dose of ocrelizumab 600 mg/placebo was administered as two IV infusions of 300 mg ocrelizumab/placebo given 14 days apart. The first infusion was administered on study Day 1. Patients were evaluated for pre-specified re-treatment criteria prior to all subsequent infusions.

In order to lower the risk of IRRs, patients were administered 100 mg IV methylprednisolone (or an equivalent dose of alternative steroid) approximately 30 minutes prior to every infusion. It was also recommended that patients receive an analgesic/antipyretic and an antihistamine. Patients remained under observation for at least 1 hour after the completion of each infusion.

Ocrelizumab/placebo was administered on an outpatient basis, in a hospital or clinic environment under close supervision of an investigator or a medically qualified staff. A minimum interval of 20 weeks was kept between the last infusion of one treatment dose and the first infusion of the next treatment dose of ocrelizumab/placebo, e.g., Dose 1 (infusion Week 2) and the next infusion of Dose 2 (infusion Week 24).

- **Objectives**

Primary Objective

To investigate the efficacy of ocrelizumab compared with placebo in patients with primary progressive multiple sclerosis (PPMS). The primary endpoint was the time to onset of clinical disability progression (CDP) over the treatment period, defined as an increase in the expanded disability status scale (EDSS) score that was sustained for at least 12 weeks (based on regularly scheduled visits).

Secondary Objectives

To evaluate the efficacy and safety of ocrelizumab compared with placebo, as reflected by the following:

• The time to onset of CDP over the treatment period, defined as an increase in EDSS that is sustained for at least 24 weeks (based on regularly scheduled visits)

• The change in timed 25-foot walk (T25-FW) from baseline to Week 120

• The change in total volume of T2 hyperintense lesions on magnetic resonance imaging (MRI) scans of the brain from baseline to Week 120

• The percentage change in total brain volume as detected by brain MRI from Week 24 to Week 120

• The change in Short Form 36 (SF-36) Health Survey version 2 (SF 36v2) Physical Component Summary (PCS) score from baseline to Week 120

• The safety and tolerability of ocrelizumab 300 mg × 2 (administered every 24 weeks) compared with placebo in patients with PPMS

- **Outcomes/endpoints**

Primary efficacy variable

The primary efficacy endpoint was the time to onset of CDP for at least 12 weeks (12-week CDP) during the double-blind treatment period.

The time to onset of CDP was defined as the time from baseline to the first disability progression, which is confirmed at the next regularly scheduled visit ≥ 12 weeks (≥ 84 days) after the initial disability progression. Baseline for the time to onset of CDP is the date of randomization, independent of the first day of dosing. Disability progression is defined as an increase of ≥ 1.0 point from baseline EDSS score, if the baseline EDSS value is ≤ 5.5 points (inclusive), or an increase of ≥ 0.5 points, if the baseline EDSS is > 5.5 points. Assessments within 30 days after a protocol-defined relapse were not used for confirmation of disability progression. The initial disability progression had to occur when the patient was still on treatment. Non-confirmatory EDSS assessments (if any) between the initial and confirmation of disability progression had to fulfill the requirements for progression

There is evidence of higher EDSS confirmation rates in progressive versus relapsing MS with confirmation rates in progressive patients for 12-week CDP of approximately 80% [Ebers et al. 2008]. A PPMS patient who experiences initial disease progression (IDP) has an increased risk of disability progression compared to other patients without an initial event who are still ongoing in the treatment period. Patients who had an IDP and then discontinued the treatment early with no confirmatory EDSS assessments were, therefore, not censored as this would introduce substantial bias. This IDP was used as an event and these events are subsequently referred to as imputed events.

Patients who had initial disability progression with no confirmatory EDSS assessment and who were on treatment at time of CCOD were censored at the date of their last EDSS assessment. Patients who did not have initial disability progression at time of CCOD, time of early discontinuation, or loss to follow up were censored at the date of their last EDSS assessment that occurred during the treatment period.

The time to CDP for the ocrelizumab and the placebo groups was compared using a two-sided log-rank test stratifying by geographic region (US versus ROW) and age (≤ 45 versus >45). The proportion of patients with confirmed disability progression was estimated using Kaplan-Meier methodology. The overall hazard ratio was estimated using a stratified Cox regression model with the same stratification factors used in the stratified log-rank test above

Secondary efficacy variables

Each secondary efficacy endpoint was tested in the hierarchical order listed below, if the primary endpoint and each preceding endpoint had reached the significance level of 0.05.

- Time to onset of CDP for at least 24 weeks (≥ 161 days, 24-week CDP)

- Change in T25-FW from baseline to Week 120

- Change in total volume of T2 lesions from baseline to Week 120

- Percent change in total brain volume from Week 24 to Week 120

- Change in PCS (SF-36) from baseline to Week 120

- **Sample size**

The sample size was estimated on the basis of data from a rituximab Phase II/III trial in adults with PPMS (Study U2786g). The two-year progression rate among patients receiving ocrelizumab was predicted to be 30% compared with 43% among patients receiving placebo. A two group test of equal exponential survival with exponential dropout was used to determine the sample size for the time to CDP. With a 2:1 randomization ratio between the ocrelizumab and placebo groups and the assumption of a one-year accrual period with a 3.5 year maximum treatment period, the total sample size of 630 patients provides approximately 80% power, maintaining the type I error rate of 0.01 (or approximately 92% power for type I error rate of 0.05), and assuming a dropout rate of 20% over 2 years. A total of 253 disability events were required to maintain statistical power to detect the planned treatment difference.

- **Randomisation**

Eligible patients were randomized to 2 groups in a 2:1 ratio via an independent IxRS provider. Randomization was stratified by region (United States [US] versus rest of the world [RoW]) and age (≤ 45 versus >45). The patient Randomization List was generated by IxRS using a pre-defined randomization specification. Prior to unblinding, the randomization list was not available at the study center, to the monitors, project statisticians or to the Sponsor's project team. Randomized patients were assigned a unique medication number and a randomization number. The IxRS provider held the treatment assignment codes. There was no replacement of patients who withdrew from the study after randomization.

- **Blinding (masking)**

This was a double-blind study. The Sponsor remained blinded until the database lock (DBL) for the primary analysis. The study sites remained blinded until patients switched to OLE, which occurred after the primary analysis was completed. Patients continued on their original assignments in a blinded fashion until the determination of primary efficacy could be made and patients transitioned to OLE.

To prevent potential functional unblinding during the double-blind treatment period, the following additional measures were implemented:

- Dedicated role of the examining investigator / EDSS assessor who was not involved with any aspect of medical management of the patient and did not have access to patient data. The examining investigator was a neurologist or other health care practitioner and was trained and certified in administering the Functional System Scores (FSS) and EDSS prior to study start. The examining investigator was responsible for the administration of the FSS/EDSS and MSFC. Whenever possible, the same individual performed the FSS/EDSS examination for the same patient during the full study duration.

- Blinding of selected laboratory parameters that could reveal patient's allocation to study treatment. Note that these laboratory parameters remained blinded to the study sites until the start of OLE, which occurred after the primary analysis was completed.

- All scheduled on-study MRI scans were assessed by an independent, central MRI reader who was blinded to the treatment assignment. All scans were also reviewed locally for safety by a radiologist who was blinded to the treatment assignment. All scans were also reviewed locally for safety by a radiologist who was blinded to treatment assignment.

Unblinding for the ongoing safety monitoring by the iDMC, was performed according to procedures in place to ensure integrity of the data

Unblinding for analysis of biological samples and pharmacokinetic data analysis was performed according to procedures in place to ensure integrity of the data.

Unblinding of treatment assignment by the site could only occur in the case of emergency situations where the knowledge of what study medication the patient was receiving was critical for clinical management. Unblinding was performed by means of the IxRS.

As per regulatory reporting requirements, the Sponsor unblinded the identity of study medication for all unexpected serious adverse events (SAEs) that were considered by the investigator to be related to study drug per safety reference document(s), e.g. the Investigator's Brochure.

- **Statistical methods**

The statistical methods employed for each type of endpoint are summarized in Table 22. However, the effects of different methods for handling missing data were tested as part of the pre-specified sensitivity analyses of the primary endpoint.

Experience from the RMS Phase III program and blinded review of WA25046 data indicated that the use of MMRM on the absolute change in T25-FW and T2 lesion volume from baseline to Week 120 would violate assumptions of normal distribution of the residuals. Before DBL, the SAP was amended to pre-specify analysis of the relative change from baseline. The p-value comparing the percent change from baseline was based on the non-parametric ranked analysis of covariance (ranked ANCOVA) with the ranked percent change as the outcome variable and the ranked baseline value as the covariate, adjusting for geographical region (United States vs. ROW) and age ($\leqslant$ 45 vs. > 45 years). The last observation carried forward method was used to impute missing values. Estimates of treatment effects were derived using MMRM analyses on the log-transformed ratio of post-baseline / baseline values since the ranked ANCOVA does not provide these estimates

Each secondary efficacy endpoint was tested in the hierarchical order listed below, if the primary endpoint and each preceding endpoint had reached the significance level of 0.05.

Table 17 Statistical Analysis of Primary and Secondary Efficacy Endpoints (Study WA25046)

Endpoint	Statistical Model	Stratification/adjusting factors
Primary Endpoint		
Time to onset of CDP for at least 12 weeks	Log-rank test for p-value, Cox regression (for estimation of hazard ratio (HR))	Age (≤ 45 vs. > 45 years), geographical region (US vs. ROW)
Secondary Endpoints		
Disability		
Time to onset of CDP for at least 24 weeks	Log-rank test for p-value, Cox regression (for estimation of hazard ratio (HR))	Age (≤ 45 vs. > 45 years), geographical region (US vs. ROW)
Change in Timed 25-Foot Walk Relative Ratio to Baseline at Week 120	ranked ANCOVA with LOCF for p-value; MMRM for treatment estimates	Baseline T25FTW, age (≤ 45 vs. > 45 years), geographical region (US vs. ROW)
Brain MRI		
T2 Lesion Volume Relative Ratio to Baseline at Week 120	ranked ANCOVA with LOCF for p-value; MMRM for treatment estimates	Baseline T2 lesion volume, age (≤ 45 vs. > 45 years), geographical region (US vs. ROW)
Percent Change from Week 24 to Week 120 in Total Brain Volume	MMRM	Week 24 brain volume age (≤ 45 vs. > 45 years) geographical region (US vs. ROW)
Quality of Life		
Mean change from baseline in SF-36 PCS	MMRM	Baseline SF-36 PCS, age (≤ 45 vs. > 45 years), geographical region (US vs. ROW)

The analyses of the primary endpoint of time to onset of CDP for at least 12 weeks, and the secondary endpoint of time to onset of CDP for at least 24 weeks, were repeated in various pre-specified sensitivity analyses as follows:

Sensitivity Analyses of Primary Endpoint

Pre-specified sensitivity analyses of the primary endpoint time to onset of CDP for at least 12 weeks were conducted as follows:

- PP population

- ITT population with multiple imputation (patients with initial disability progression who discontinued treatment early with no confirmatory EDSS assessment were imputed as having CDP with 50% probability)

- ITT population with censoring of the imputed events (patients with initial disability progression who discontinued treatment early with no confirmatory EDSS assessment were censored as not having CDP)

- Influence of early progression events, by omission of EDSS assessments from randomization to Week 12 (≤ 83 days after randomization) (ITT Population)

- Analysis using the planned number of patients (used for study sample size calculation), i.e, using the first 630 patients randomized (ITT Population)

- Adjustment with additional strata for baseline presence of T1 Gd-enhancing lesions (present / absent) and baseline EDSS (≤ 5.5 vs. > 5.5)

- Exclusion of patients with clinical relapses (including protocol-defined relapses)

In addition, the following post-hoc sensitivity analyses of the primary endpoint were performed:

- Analysis including progression after treatment discontinuation (for patients who discontinued treatment early, inclusion of initial and confirmed disability progression events occurring after withdrawal from treatment during SFU period until CCOD, same imputation rules as for primary analysis).

- Imputation by reason for withdrawal (patients with initial disability progression who discontinued treatment early with reason for withdrawal “lack of efficacy”, or “withdrawal by subject”, and no confirmatory EDSS assessment were imputed as having CDP; other withdrawal reasons were imputed as not having CDP).

- Analysis excluding CDP events where a PDR was experienced from 30 days preceding an IDP or between IDP and CDP; this sensitivity analysis explored disability progression events that were related to an effect on relapses.

Sensitivity Analyses of Secondary Endpoint (Time to Onset of CDP for at least 24 weeks)

Pre-specified sensitivity analyses of the secondary endpoint time to onset of CDP for at least 24 weeks were conducted as follows:

- Influence of early progression events, by omission of EDSS assessments from randomization to Week 12 (≤ 83 days after randomization) (ITT Population)

- Exclusion of patients with clinical relapses (including protocol-defined relapses)

In addition, the following post-hoc sensitivity analyses listed above for the primary endpoint were repeated for the secondary endpoint time to onset of CDP for at least 24 weeks:

- PP population

- ITT population with multiple imputations

- ITT population without imputation

- Analysis including progression after treatment discontinuation (as described for the primary endpoint).

- Imputation by reason for withdrawal (as described for the primary endpoint).

- Analysis excluding CDP events where a PDR was experienced from 30 days preceding an IDP or between IDP and CDP (as described for the primary endpoint)

The primary and the following secondary efficacy endpoints (defined in the SAP: time to onset of 12- and 24-week CDP, change in T25-FW from baseline to Week 120, and changes in total volume of T2 lesions; defined post-hoc: percent change in total brain volume from Week 24 to Week 120) were summarized and analyzed by predefined subgroups:

- Age (≤ 45 vs. >45 years)

- Sex (male patients vs. female patients)

- Baseline EDSS (⩽ 5.5 vs. > 5.5)

- Region (United States vs. ROW)

- Presence or absence of gadolinium-enhancing T1 lesions at baseline MRI scan

- Prior MS disease-modifying therapies, with the exception of corticosteroids (yes vs. no)

- Duration since MS symptom onset (≤ 3 years, 3 to ≤ 5 years, 5 to ≤ 10 years, > 10 years)

- Weight (≤ 75 vs. > 75 kg at baseline)

- Body mass index (< 25 vs. ≥ 25 kg/m2, at baseline)

The following exploratory efficacy endpoints were defined in the SAP:

- MRI-derived parameters: number of gadolinium-enhancing T1 lesions and number of new or enlarging T2 hyperintense lesions

- Cognitive impairment: change from baseline to Week 120 in the Paced Auditory Serial Addition Test (PASAT)

- Percent change from baseline to Week 120 in total and cortical gray matter brain volume and the percent change from Week 24 to Week 120 in gray matter brain volume

- Proportion of patients with CDP at Week 120

- Functional impairment: change from baseline to Weeks 48, 96, and 120 in EDSS score (mean change and area under the curve), and change from baseline to Weeks 48, 96, and 120 in MSFC.

- The change in fatigue, as measured by the MFIS total score and subscale scores (physical impact, cognitive impact, and psychological impact) from baseline to Week 120.

- The change in quality of life, as measured by the SF-36v2 MCS score from baseline to Week 120

- Time to confirmed composite disability progression over the treatment period, defined as an increase in EDSS that is sustained for at least 12 weeks (0.5 or 1, same criteria as for the primary endpoint time to 12-week CDP) or a 20% increase in 25-foot timed walk that is sustained for at least 12 weeks or a 20% increase in 9-hole peg test that is sustained for at least 12 weeks.

Other exploratory efficacy endpoints not defined as pre-planned exploratory endpoints in the SAP, were as follows:

- The time to sustained 20% increase in T25-FW and 9-hole peg test.

- The proportion of patients with a 20% increase in T25-FW time.

- The proportion of patients with a 20% increase in 9-hole peg test time.

- The change from baseline in total non-enhancing T1 lesion volume.

- The percentage change in white matter volume from baseline to Week 120 and from Week 24 to Week 120.

Results

- **Participant flow**

A total of 943 patients were screened for entry into the study. Of these, 211 patients failed screening (note, 252 patients initially failed screening of which 55 patients were re-screened and 41 of these re-screened patients were eligible for entry into the study); the main reasons were failure to meet the inclusion/exclusion criteria, (e.g. unacceptable laboratory values), and withdrawal of consent.

A total of 732 patients were randomized into the study, of which 725 received at least one dose of placebo or ocrelizumab. Patients were randomized in a ratio of 2:1 (ocrelizumab:placebo), stratified by age (≤ 45 vs > 45 years) and region (US vs ROW). Of the 732 patients randomized (ITT population: placebo 244 patients vs OCR 488 patients), 725 patients received treatment (placebo 243 patients vs OCR 482 patients); 1 patient assigned to the placebo group and 6 patients assigned to the ocrelizumab group withdrew before receiving treatment (Figure 2). A total of 549 patients (placebo 162 patients,

66%, vs OCR 387 patients, 79%) were ongoing with double-blind treatment at the CCOD. Based on the ITT population, a total of 183 patients (placebo 82 patients [34%], OCR 101 patients [21%] had withdrawn at the time of the CCOD (including those withdrawn before dosing), 106 of which (placebo: 45 patients [55% of those withdrawn] vs OCR 61 patients [60% of those withdrawn]) had entered SFU (see **Figure 10** for a summary of patient disposition).

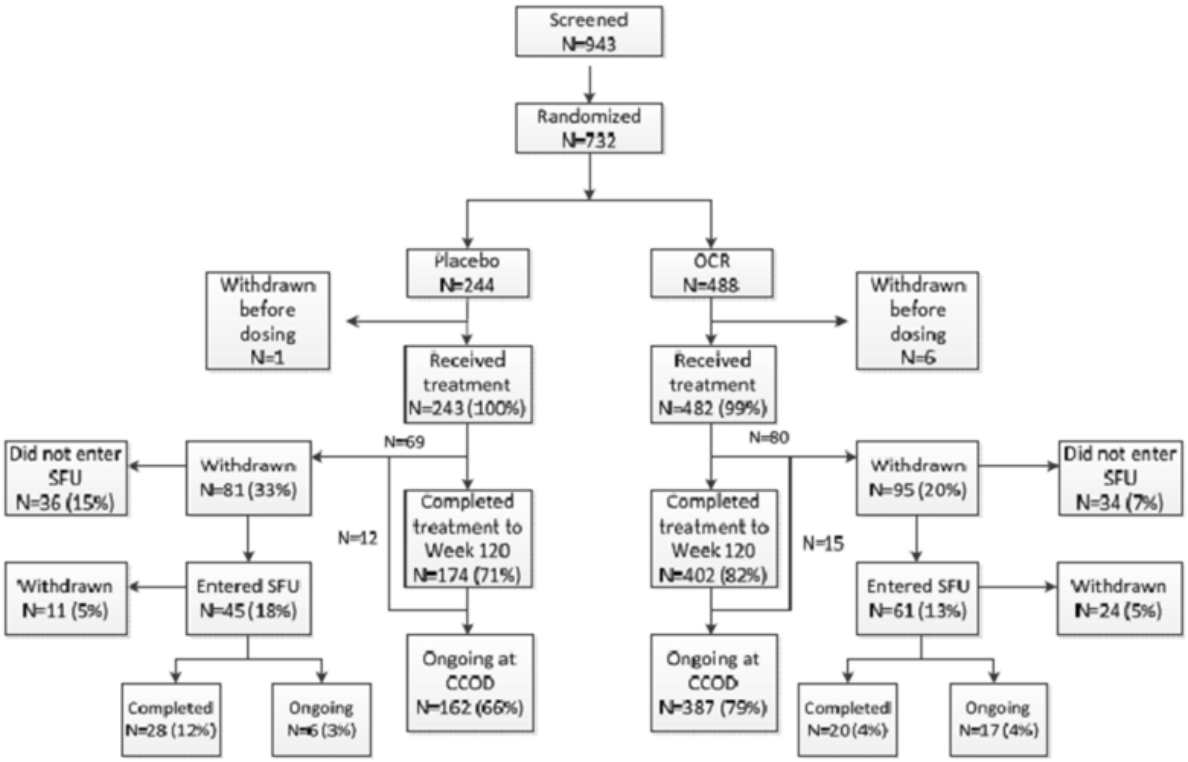


Figure 10 Overview of Patient Disposition (All Patients)

Based on the ITT population, a total of 183 patients (25%), including 7 patients who did not receive treatment, withdrew from the double-blind treatment period. The reasons for withdrawal of patients prior to dosing included patients that were randomized by error that had failed screening, abnormal ECG reading at baseline, and withdrawal of consent after randomization. A higher proportion of patients in the placebo group (34%) withdrew prematurely from treatment during the double-blind treatment period compared to the OCR group (21%). The difference was mainly due to higher incidences of withdrawals due to lack of efficacy (11% versus 4%) and withdrawal by subject (9% versus 5%) in the placebo group versus the OCR group, respectively. Withdrawal rates were approximately constant in both the placebo and ocrelizumab groups throughout the treatment period.

- **Recruitment**

This was a multicenter study with in total 182 centers in 29 countries (Europe, North America, Israel, New Zealand, Peru and Mexico). The first patient randomised was in March 2011 and the clinical cut-off for the primary analysis was in July 2015.

- **Conduct of the study**

The study was conducted in accordance with the principles of the “Declaration of Helsinki” and Good Clinical Practice (GCP). Four protocol amendments were issued, one of these included:

- Inclusion of an update to the Statistical Considerations and Analytical Plan section of the protocol in line with the Statistical Analysis Plan (SAP) for the study: These updates included:
  a) More accurate definition of the maximum duration for blinded treatment period, which was not to last more than 3 years after last patient randomized.
  b) Modifications to the secondary endpoints and their statistical definitions, including a detailed strategy for statistical testing of secondary efficacy endpoints and their hierarchical order are outlined in the SAP.
  c) Modifications to the exploratory endpoints and their statistical definitions
  d) Modifications to statistical methodology, in particular for the analysis of continuous efficacy endpoints over time, the ranked analysis of covariance (ANCOVA) method was replaced by the Mixed-Effect Model Repeated Measures (MMRM) method, a more powerful and up-to-date approach.

- **Baseline data**

Demographic characteristics of the ITT population were well balanced between groups. Consistent with the epidemiology of MS, the majority of the patients were white (>90% in both groups), with a median age of 46 years (range 18-56 years). Consistent with the sex prevalence for PPMS, approximately half of the patients were male in both groups (51% in the ocrelizumab group and 49% in the placebo group). Patients' median weight was 71 kg in the ocrelizumab group and 72 kg in the placebo group (range 40 - 136 kg across both groups). Patients were mainly from Europe (EU, Switzerland and Norway; approximately 64% across both groups) or North America (USA and Canada), Australia and New Zealand (approximately 20% in each group). Baseline disease characteristics for MS were similar across both treatment groups. The median duration of disease in terms of time from symptom onset was almost 6 years in both groups with a median time since diagnosis of 1.3 years (placebo) and 1.6 years (OCR). The majority of patients (placebo 88% vs OCR 89%) had not received any MS disease-modifying treatment prior to baseline in the previous 2 years. The mean EDSS score at baseline was 4.7 (SD 1.2) for both groups. There were no imbalances between the treatment groups in Kurtzke FS scores, nor in the MSFC total and component scores (T25-FW, 9-hole peg test and PASAT). Baseline MRI assessments showed that the majority of patients had no T1 Gd-enhancing lesions (placebo 75% vs OCR 73%). The volume and number of T2 lesions were similar between the groups. Normalized brain volume was also similar between the two groups.

A total of 88% of patients in the placebo group and 89% of patients in the OCR group had not been treated with any MS disease modifying treatments in the 2 years prior to randomization. The number of patients who had received previous MS disease modifying therapies in the prior 2 years was balanced between treatment groups (12% in the placebo group and 11% in the OCR group). The most common prior MS disease modifying treatments were interferons and glatiramer acetate.

- **Numbers analysed**

All 732 patients randomized to treatment were included in the ITT population

- **Outcomes and estimation**

Primary efficacy variable

Treatment with ocrelizumab led to a 24% reduction in the risk of 12-week CDP compared with placebo (hazard ratio 0.76 [95% CI: 0.59, 0.98], p=0.0321).

The Kaplan-Meier survival curves for time to onset of 12-week CDP show separation from 12 weeks, with a lower proportion of patients in the ocrelizumab group with CDP throughout the treatment period.

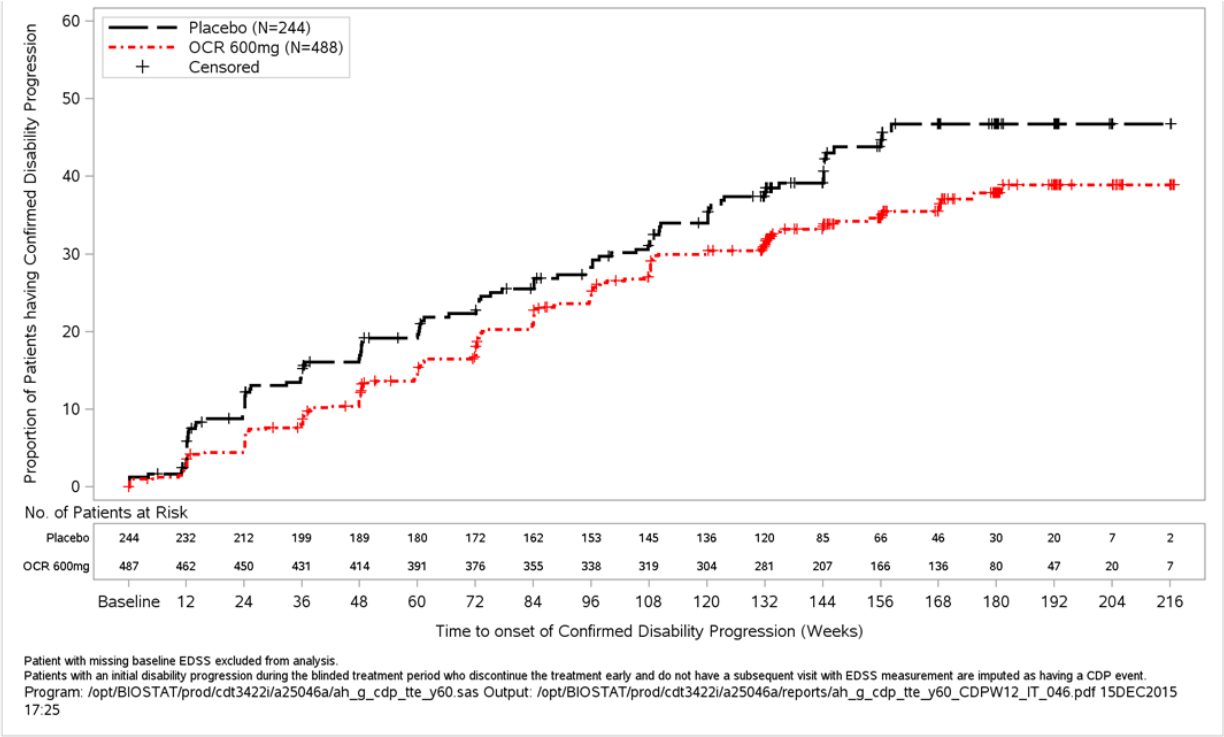


Figure 11 Kaplan-Meier Plot of Time to Onset of Confirmed Disability Progression for at Least 12 Weeks during the Double-Blind Treatment Period (with Imputation, ITT population)

The robustness of the results of the primary endpoint was analyzed by performing various sensitivity analyses the results of which were consistent with the primary analysis (treatment effect favouring ocrelizumab in each analysis). With regard to imputation of initial disability progression events for patients with early treatment discontinuation, the approach of ignoring these events resulted in a reduced treatment effect (HR 0.82 [95% CI: 0.63, 1.07], p=0.1477). However, multiple imputation (HR 0.78 [95% CI: 0.60, 1.02]) and imputation by efficacy related reason for withdrawal / withdrawal by subject (HR 0.77 [95% CI: 0.60, 1.00], p=0.0490) resulted in consistent estimates of the treatment effect.

The sensitivity analysis including progression events after treatment discontinuation resulted in a reduced treatment effect (HR 0.80 [95% CI: 0.62, 1.02], p=0.0736). Of note of the 6 additional progression events observed during the SFU of patients originally randomized to OCR, 5 events occurred more than 9 months after the last infusion (see summary and listing).

The sensitivity analysis removing progression events preceded by a PDR resulted in similar treatment effect to that seen in the primary analysis (HR 0.78 [95% CI: 0.60, 1.01], p=0.0561), suggesting the efficacy of ocrelizumab in delaying disability progression is not due to an effect on relapses.

The treatment effect of ocrelizumab on the primary endpoint of time to onset of 12-week CDP was explored in subgroups including age, sex, region, BMI, body weight, baseline EDSS, presence of T1 Gd-enhancing lesions at baseline, prior MS DMT, and duration of MS symptom onset. There was a directionally consistent treatment effect favoring ocrelizumab in all subgroups (HR <1). None of the observed differences in the size of the treatment effect between subgroups were statistically significant (interaction p>0.05) and were potentially due to the expected variation. Note, the study was not powered to demonstrate efficacy differences between these subgroups. Numerical differences in treatment effect were observed within some subgroups including sex, baseline T1 Gd-enhancing lesions, and age. Subgroup interaction p-values below 0.2 were considered a trend; between 0.2 and 0.3 were considered a weak trend. Male patients showed a greater reduction in 12-week CDP in the OCR versus placebo groups (HR 0.61 [95% CI 0.43, 0.88], p = 0.0071) compared with female patients

(HR 0.94 [95% CI 0.66, 1.36]; p = 0.7573; interaction p = 0.0962). Patients with T1 Gd-enhancing lesions at baseline had a greater reduction in 12-week CDP in the OCR versus placebo groups (HR 0.65 [95% CI 0.40, 1.06], p = 0.0826) compared to patients without T1 Gd-enhancing lesions at baseline (HR 0.84 [95% CI 0.62, 1.13];p = 0.2441; interaction p = 0.2076). In addition, patients ≤ 45 years of age showed greater reduction in 12-week CDP in the OCR versus placebo groups (HR 0.64 [95% CI 0.45, 0.92]; p = 0.0170) compared to patients > 45 years of age (HR 0.88 [95% CI 0.62, 1.26]; p = 0.4937; interaction p = 0.2278). *Post hoc* analyses suggests that younger patients with T1 Gd-enhancing lesions at baseline have a better treatment effect [≤ 45 years: HR 0.52 (0.27-1.00); ≤ 46 years (median age of the WA25046 study); HR 0.48 (0.25-0.92); <51 years: HR 0.53 (0.31-0.89)].

Secondary efficacy variables

The consistent results of the secondary endpoints for disability (24-week CDP and T25-FW) and MRI (T2 lesion volume and total brain volume) outcomes supported the primary endpoint, demonstrating statistically significant efficacy of ocrelizumab when compared with placebo. Patients in the ocrelizumab group experienced less worsening on the secondary endpoint of SF-36 PCS score compared with placebo, but this difference was not statistically significant.

Table 18 Summary of Primary and Secondary Efficacy Endpoints at Week 120 (WA25046, ITT Population)

Endpoints	Placebo (N=244)	Ocrelizumab 600 mg (N=488)
PRIMARY ENDPOINT		
12-Week CDP	N=244	N=487
Proportion of patients with events at 120 weeks (Kaplan Meier estimate)	0.340	0.302
Hazard ratio (95% CI)		0.76 (0.59, 0.98)
p-value (Log-rank)		0.0321
SECONDARY ENDPOINTS		
Disability		
24-Week CDP	N=244	N=487
Proportion of patients with events at 120 weeks (Kaplan Meier estimate)	0.327	0.283
Hazard ratio (95% CI)		0.75 (0.58, 0.98)
p-value (Log-rank)		0.0365
Change in Timed 25-Foot Walk Relative Ratio to Baseline at Week 120 (MMRM)	N=174	N=397
Adjusted Geometric Mean (% change)	55.097	38.933
% Relative reduction (95% CI)		29.337 (-1.618, 51.456)
p-value (ranked ANCOVA)		0.0404
Brain MRI		
T2 Lesion Volume Relative Ratio to Baseline at Week 120 (MMRM)	N=183	N=400
Adjusted Geometric Mean (% change)	7.426	-3.366
p-value (ranked ANCOVA)		< 0.0001
Percent Change from Week 24 to Week 120 in Total Brain Volume (MMRM)	N=150	N=325
Adjusted Mean (% change)	-1.093	-0.902
% Relative reduction (95% CI)		17.475 (3.206, 29.251)
p-value		0.0206
Quality of Life		
Change from Baseline in SF-36 PCS Score (MMRM)	N=128	N=292
Adjusted Mean	-1.108	-0.731
Difference in Adjusted Means (95% CI)		0.377 (-1.048, 1.802)
p-value		0.6034

CDP confirmed disability progression, SF-36 PCS Short Form 36 Physical Component Summary.

* P values not corrected for Type I error.

Results for CDP 24 Weeks are shown in the following figure.

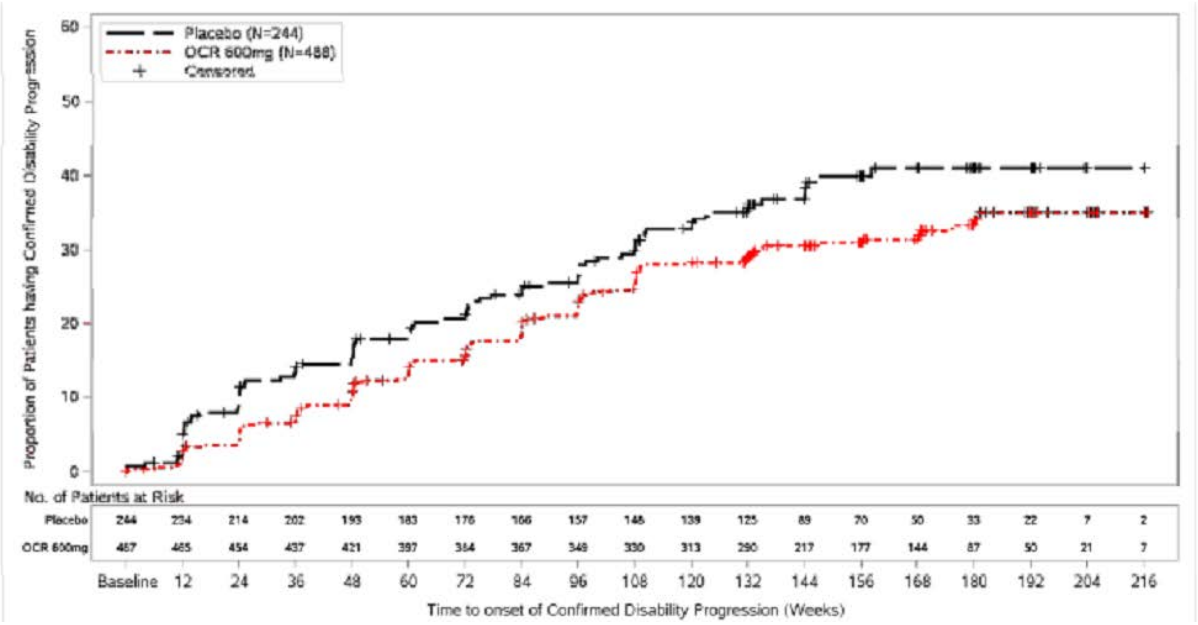


Figure 12 Kaplan-Meier Plot of Time to Onset of Confirmed Disability Progression for at Least 24 Weeks during the Double-Blind Treatment Period (With Imputation, ITT Population)

A hierarchical approach was taken for significance testing in order to control for multiplicity. A summary of all p-values within the hierarchical structure is provided in the table below. All endpoints in the hierarchy were significant with the exception of SF-36 PCS and confirm differences between ocrelizumab and placebo in favor of ocrelizumab.

Table 19 Study WA25046: Summary of Hierarchical Significance Testing of Efficacy Endpoints

	Endpoints	p value
Primary	Time to onset of CDP for 12 weeks	0.0321
Secondary	Time to onset of CDP for 24 weeks	0.0365
	Change in timed 25-foot walk from baseline to Week 120	0.0404
	Percent Change in total T2 Lesion Volume from baseline to Week 120	< 0.0001
	Percent Change in total brain volume from Week 24 to Week 120	0.0206
	Change in the SF-36 Physical Component Score from baseline to Week 120	0.6034

The robustness of the results of the secondary endpoint 24-week CDP was analyzed by performing various sensitivity analyses. The sensitivity analyses were consistent with the primary analysis (treatment effect favoring ocrelizumab in each analysis). Regarding the imputation of initial disability progression events for patients with early treatment discontinuation, the approach of ignoring these events resulted in a reduced treatment effect (HR 0.82 [95% CI: 0.62, 1.10], p=0.1884). However, multiple imputation (HR 0.78 [95% CI: 0.59, 1.04]) and imputation by efficacy related reason for withdrawal / withdrawal by subject (HR 0.76 [95% CI: 0.58, 1.00], p = 0.0493) resulted in consistent estimates of treatment effect. The sensitivity analysis including progression events after treatment

discontinuation resulted in a reduced treatment effect (HR 0.79 [95% CI: 0.60, 1.03], p=0.0745). However, all 6 additional progression events observed during the SFU of patients originally randomized to OCR occurred more than 9 months. The sensitivity analysis removing progression events preceded by a PDR resulted in a similar treatment effect to that seen in the primary analysis (HR 0.78 [95% CI: 0.59, 1.02], p=0.0705), suggesting the efficacy of ocrelizumab in delaying disability progression is not due to an effect on relapses.

The treatment effect of ocrelizumab on the secondary endpoint of time to onset of 24-week CDP was explored in the same subgroups as for the primary endpoint. Consistent with the results of the subgroup analysis for the primary endpoint, there was a directionally consistent treatment effect favoring ocrelizumab in all subgroups (HR <1). None of the observed differences in the size of the treatment effect between subgroups were statistically significant (interaction p>0.05) and were potentially due to the expected variation. Note, the study was not powered to demonstrate efficacy differences between these subgroups. Consistent with the primary endpoint, numerical differences in treatment effect were observed within some subgroups including sex and age. Subgroup interaction p-values below 0.2 were considered a trend; between 0.2 and 0.3 were considered a weak trend. Patients ≤ 45 years of age showed a greater reduction in 24-week CDP in the OCR versus placebo groups (HR 0.61 [95% CI 0.42, 0.90], p = 0.0114) compared with patients > 45 years of age (HR 0.92 [95% CI 0.63, 1.34], p = 0.6478; interaction p = 0.1558). Male patients showed a greater reduction in 24-week CDP in the OCR versus placebo groups (HR 0.64 [95% CI 0.44, 0.93], p = 0.0184) compared with female patients (HR 0.89 [95% CI 0.61, 1.31]; p = 0.5632; interaction p = 0.2091). No difference in the risk of 24-week CDP was observed between patients with or without T1 Gd-enhancing lesions

Exploratory analyses of time to disability progression as measured by a 24-week composite endpoint (CDP by EDSS or a 20% increase in T25-FW or 20% increase in 9-hole peg test, all confirmed for 24 weeks) showed a 29% relative reduction with ocrelizumab (hazard ratio [95% CI: 0.58, 0.87], p = 0.0008.

The explorative analyses for change from baseline with respect to EDSS scores, PASAT and MSFC did not demonstrate any statistically significant differences between the two treatment groups.

Extended Controlled Treatment Period

To further demonstrate that the clinical benefit of ocrelizumab relative to placebo is sustained with ongoing treatment, longer-term data taken from the WA25046 extended controlled treatment period (CCOD of 20 January 2016) was analyzed. The extended controlled treatment period results for the key disability progression endpoints are as follows:

- A 24% risk reduction for 12-week CDP (p=0.0151)
- A 30% risk reduction for 24-week CDP (p=0.0056)
- A 28% risk reduction for 12-week composite CDP (EDSS or T25-FW or 9-hole peg test) (p=0.0005)
- A 32% risk reduction for 24-week composite CDP (EDSS or T25-FW or 9-hole peg test) (p<0.0001).

At the time of the CCOD for the primary analysis (24 July 2015) of Study WA25046, patients were still on treatment as originally randomized, and remained blinded to treatment assignment. After the CCOD, and after ascertaining that the study was positive, we initiated the open label extension (OLE). In the period between the CCOD for the Primary CSR WA25046 and open label extension (OLE) initiation, the Sponsor, sites, and patients were sequentially unblinded.

The Sponsor was unblinded on 22 September 2015. Following Sponsor unblinding, the sites remained blinded to treatment assignment until 12 October 2015. After 12 October 2015, sites were able to

make patients aware of their treatment assignment at which time patients were given the opportunity to transition into the OLE. Until switch to the OLE, patients continued in their allotted treatment group. This represents approximately 3 additional months of blinded, controlled data for all patients (24 July – 12 Oct 2015), and an additional approximately 3 months of controlled follow-up (12 Oct 2015 – 20 January 2016) during which time patients were gradually unblinded and switched into the OLE. Of note, by 12 Oct 2015 all patients were able to complete their 144-week visit under fully blinded and controlled conditions.

The extended controlled treatment period includes all efficacy data from the double-blind controlled treatment period plus any additional efficacy data collected during the controlled treatment period from the time of the Primary CSR CCOD (24 July 2015) up to the CCOD of 20 January 2016 or up to the time at which the patient received their first open-label dose of ocrelizumab, whichever came first.

Efficacy results for CDP 12 and 24 weeks, plus exploratory composite results from the extended controlled treatment period are presented below.

Time to Onset of Confirmed Disability Progression Sustained for at Least 12 Weeks

From baseline, 256 events (placebo 96, ocrelizumab 160) occurred during the controlled treatment period up to the CCOD for the primary analysis (24 July 2015) and 283 events (placebo 106, ocrelizumab 177) up to the CCOD for the extended controlled treatment period (20 January 2016). These additional 27 events (placebo 10, ocrelizumab 17) events were added to the analysis at the latter cut and, while point estimates remained similar, the p-values were generally smaller due to the increase in the number of events.

Treatment with ocrelizumab led to a 26% reduction in the risk of 12-week CDP compared with placebo (HR 0.74 [95% CI: 0.58, 0.95], p=0.0151; Table 20).

Table 20 Summary of Time to Onset of 12-Week and 24-Week Confirmed Disability Progression during the Extended Controlled Treatment Period (With Imputation, ITT Population; WA25046)

Endpoints	Placebo (N=244)	Ocrelizumab 600 mg (N=488)
PRIMARY ENDPOINT		
12-Week CDP	N=244	N=487
Proportion of patients with events at 120 weeks (Kaplan Meier estimate)	0.3398	0.3023
Proportion of patients with events at 144 weeks (Kaplan Meier estimate)	0.4099	0.3418
Hazard ratio (95% CI)		0.74 (0.58, 0.95)
p-value (Log-rank)		0.0151
SECONDARY ENDPOINTS		
Disability		
24-Week CDP	N=244	N=487
Proportion of patients with events at 120 weeks (Kaplan Meier estimate)	0.3271	0.2830
Proportion of patients with events at 144 weeks (Kaplan Meier estimate)	0.3820	0.3108
Hazard ratio (95% CI)		0.70 (0.54, 0.90)
p-value (Log-rank)		0.0056

The Kaplan-Meier survival curves for time to onset of 12-week CDP are shown in Figure 13. The curves show separation from 12 weeks, with a lower proportion of patients in the ocrelizumab group with CDP throughout the treatment period. Of note, the Kaplan-Meier estimates at Week 144 and beyond confirm the increasing separation between treatment arms with confidence intervals excluding point estimates of the other arm.

Estimates of absolute risk reduction and NNT are very dependent on the selected timepoint. The hazard ratio as a weighted relative risk over the entire duration of the study provides a more comprehensive summary of the overall treatment benefit. To illustrate the fluctuation of risk estimates over time, Table 21 and Table 22 show the absolute risk reductions and corresponding NNT numbers at various timepoints for the double-blind and the extended controlled treatment period for 12-week CDP and 24-week CDP. Treatment effect estimates decrease after Week 72 and increase again after Week 120. Fluctuations in event rates occur in both arms and may be reflective of variability in clinical assessments or individual patient progression (including differences in baseline age or region that are not corrected for in Kaplan-Meier analysis). The increasing absolute treatment benefit after Week 120 is confirmed by the additional follow-up data collected during the extended controlled treatment period.

Table 21: Time to Confirmed Disability Progression for at Least 12 Weeks (With Imputation): KM Estimates and Numbers Needed to Treat (NNT)

		Double-blind treatment period			Extended controlled treatment period		
Week		Placebo	OCR	AR NNT	Placebo	OCR	AR NNT
24	Patients at risk Event rate (%) 95% CI	212 10.06 (6.24, 13.88)	450 4.65 (2.75, 6.55)	5.41 18.5	212 10.06 (6.24, 13.88)	450 4.65 (2.75, 6.55)	5.41 18.5
48	Patients at risk Event rate (%) 95% CI	189 16.96 (12.17,21.76)	414 11.05 (8.22, 13.88)	5.91 16.9	189 16.96 (12.17,21.76)	414 11.05 (8.22, 13.88)	5.91 16.9
72	Patients at risk Event rate (%) 95% CI	172 22.32 (16.96, 27.68)	376 16.95 (13.54, 20.36)	5.37 18.6	172 22.32 (16.96, 27.68)	376 16.95 (13.54, 20.36)	5.37 18.6
96	Patients at risk Event rate (%) 95% CI	153 28.28 (22.43,34.13)	338 24.75 (20.80,28.70)	3.53 28.3	153 28.28 (22.43,34.13)	338 24.75 (20.80,28.70)	3.53 28.3
120	Patients at risk Event rate (%) 95% CI	136 33.98 (27.77, 40.18)	304 30.23 (26.00, 34.45)	3.75 26.7	136 33.98 (27.77, 40.18)	304 30.23 (26.00, 34.45)	3.75 26.7
144	Patients at risk Event rate (%) 95% CI	85 39.18 (32.66, 45.69)	207 33.55 (29.12, 37.98)	5.63 17.8	114 40.99 (34.44,47.54)	283 34.18 (29.79,38.56)	6.81 14.7
168	Patients at risk Event rate (%) 95% CI	46 46.77 (39.38, 54.17)	136 35.49 (30.87,40.10)	11.29 8.9	60 48.36 (41.39, 55.34)	171 36.69 (32.20, 41.18)	11.67 8.6
192	Patients at risk Event rate (%) 95% CI				35 49.40 (42.27, 56.52)	87 41.14 (36.03, 46.22)	8.26 12.1

AR: Absolute risk reduction, NNT: Numbers needed to treat. Only visits with > 100 patients at risk shown.

Table 22: Time to Confirmed Disability Progression for at Least 24 Weeks (With Imputation): KM Estimates and Numbers Needed to Treat (NNT)

		Double-blind period			Extended controlled period		
Week		Placebo	OCR	AR NNT	Placebo	OCR	AR NNT
24	Patients at risk Event rate (%) 95% CI	214 9.23 (5.55,12.90)	454 3.81 (2.08, 5.53)	5.4 18.5	214 9.23 (5.55,12.90)	454 3.81 (2.08, 5.53)	5.4 18.5
48	Patients at risk Event rate (%) 95% CI	193 15.26 (10.67, 19.86)	421 9.56 (6.91, 12.22)	5.7 17.6	193 15.26 (10.67, 19.86)	421 9.56 (6.91, 12.22)	5.7 17.6
72	Patients at risk Event rate (%) 95% CI	176 20.61 (15.40, 25.82)	384 15.02 (11.77, 18.26)	5.6 17.9	176 20.61 (15.40, 25.82)	384 15.02 (11.77, 18.26)	5.6 17.9
96	Patients at risk Event rate (%) 95% CI	157 26.56 (20.83,32.29)	349 22.38 (18.56, 26.19)	4.2 23.9	157 26.56 (20.83,32.29)	349 22.38 (18.56, 26.19)	4.2 23.9
120	Patients at risk Event rate (%) 95% CI	139 32.71 (26.56,38.86)	313 28.30 (24.15,32.45)	4.41 22.7	139 32.71 (26.56,38.86)	313 28.30 (24.15,32.45)	4.41 22.7
144	Patients at risk Event rate (%) 95% CI	89 36.90 (30.47,43.33)	217 30.53 (26.23,34.83)	6.4 15.7	120 38.20 (31.75,44.65)	296 31.08 (26.81, 35.35)	7.12 14.0
168	Patients at risk Event rate (%) 95% CI	50 41.06 (34.07,48.06)	144 31.35 (26.95,35.74)	9.7 10.3	64 43.78 (36.93,50.63)	180 32.87 (28.50, 37.23)	10.9 9.2
192	Patients at risk Event rate (%) 95% CI				36 46.22 (38.88,35.82)	93 35.42 (30.75,40.09)	10.8 9.26

AR: Absolute risk reduction, NNT: Numbers needed to treat. Only visits with > 100 patients at risk shown.

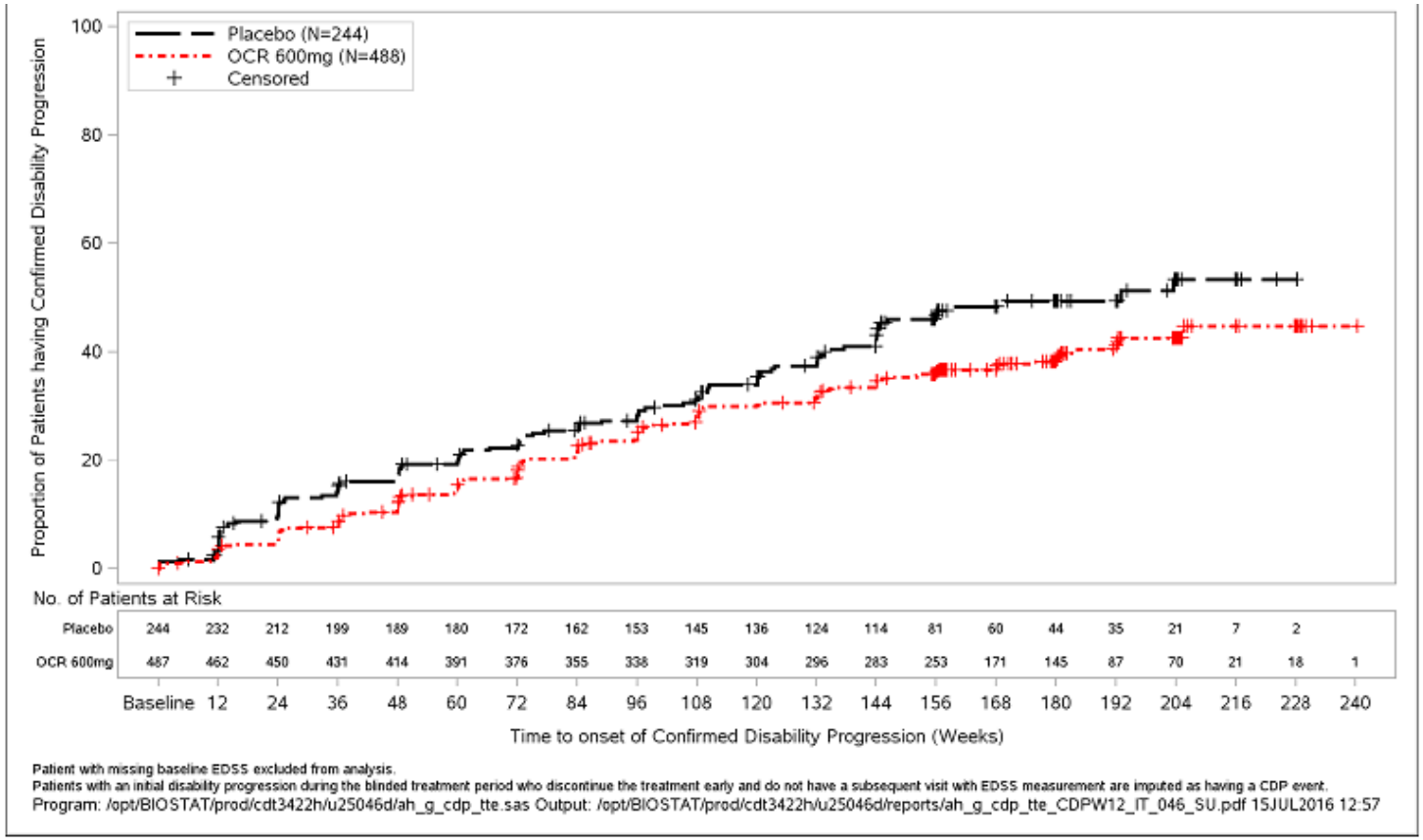


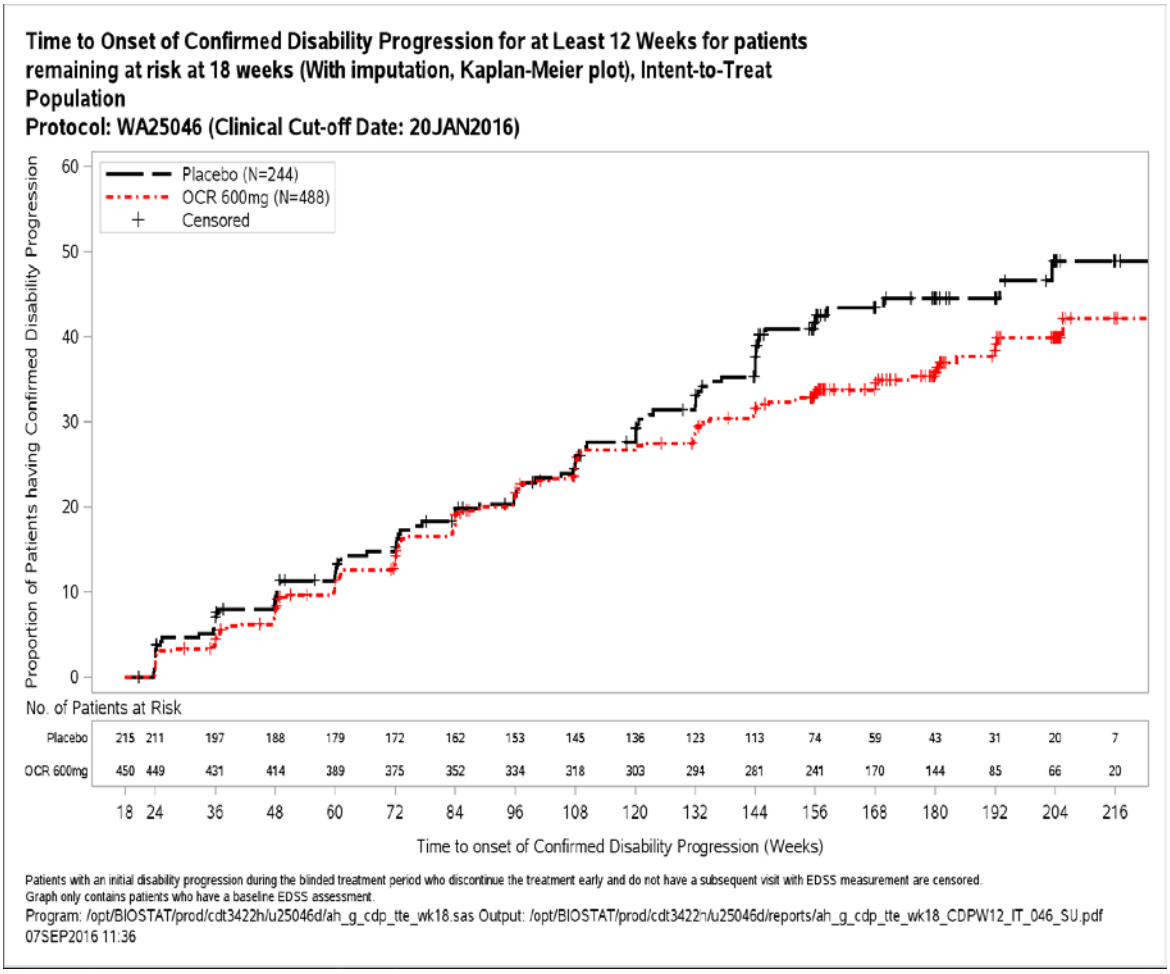
Figure 13: Kaplan-Meier Plot of Time to Onset of Confirmed Disability Progression for at Least 12 Weeks during the Extended Controlled Treatment Period (With Imputation, ITT Population; WA25046)

Longer term benefit from ocrelizumab treatment was also seen in a survival analysis which was conducted on 12-week CDP (with imputation) excluding information until after the first EDSS assessment (18 weeks) which resulted in a hazard ratio of 0.80, suggesting sustained benefit from ocrelizumab therapy beyond 18 weeks (Table 23). The respective KM curve (Figure 14) shows that after the first EDSS assessment the observed reduction in progression risk for patients treated with ocrelizumab is starting at Week 120 and sustained to the end of the extended controlled treatment period.

Table 23 Time to Onset of Confirmed Disability Progression for at Least 12 Weeks for Patients remaining at Risk at 18 Weeks during the Extended Controlled |Treatment Period (With Imputation, ITT Population)

Endpoint	Patients with Event		Hazard Ratio (95% CI)	p-value (log-rank)
	Placebo (N=244)	OCR (N=488)		
12-week CDP for patients maining at risk at 18 weeks	85 /215	156 /450	0.80 (0.61, 1.04)	p = 0.0913

Figure 14 Time to Onset of Confirmed Disability Progression for at Least 12 Weeks for Patients remaining at Risk at 18 weeks during the Extended Controlled |Treatment Period (With Imputation, ITT Population; WA25046)



Time to Onset of Confirmed Disability Progression Sustained for at Least 24 Weeks

From baseline, 231 events (placebo 87, ocrelizumab 144) occurred during the controlled treatment period up to the CCOD for the primary analysis (24 July 2015) and 252 events (placebo 98, ocrelizumab 154) up to the CCOD for the extended controlled treatment period (20 January 2016). These additional 21 events (placebo 11, ocrelizumab 10) were added to the analysis at the latter cut and, while point estimates remained similar, the p-values were generally smaller due to the increase in the number of events.

Consistent with the 12-week CDP, during the extended controlled treatment period, treatment with ocrelizumab led to a statistically significant 30% reduction in the risk of 24-week CDP compared with placebo (HR 0.70 [95% CI: 0.54, 0.90], p = 0.0056)).

The Kaplan-Meier survival curves for time to onset of 24-week CDP are shown in Figure 15. Consistent with the 12-week CDP, the curves show separation from 12 weeks, with a lower proportion of patients in the ocrelizumab group with CDP throughout the treatment period.

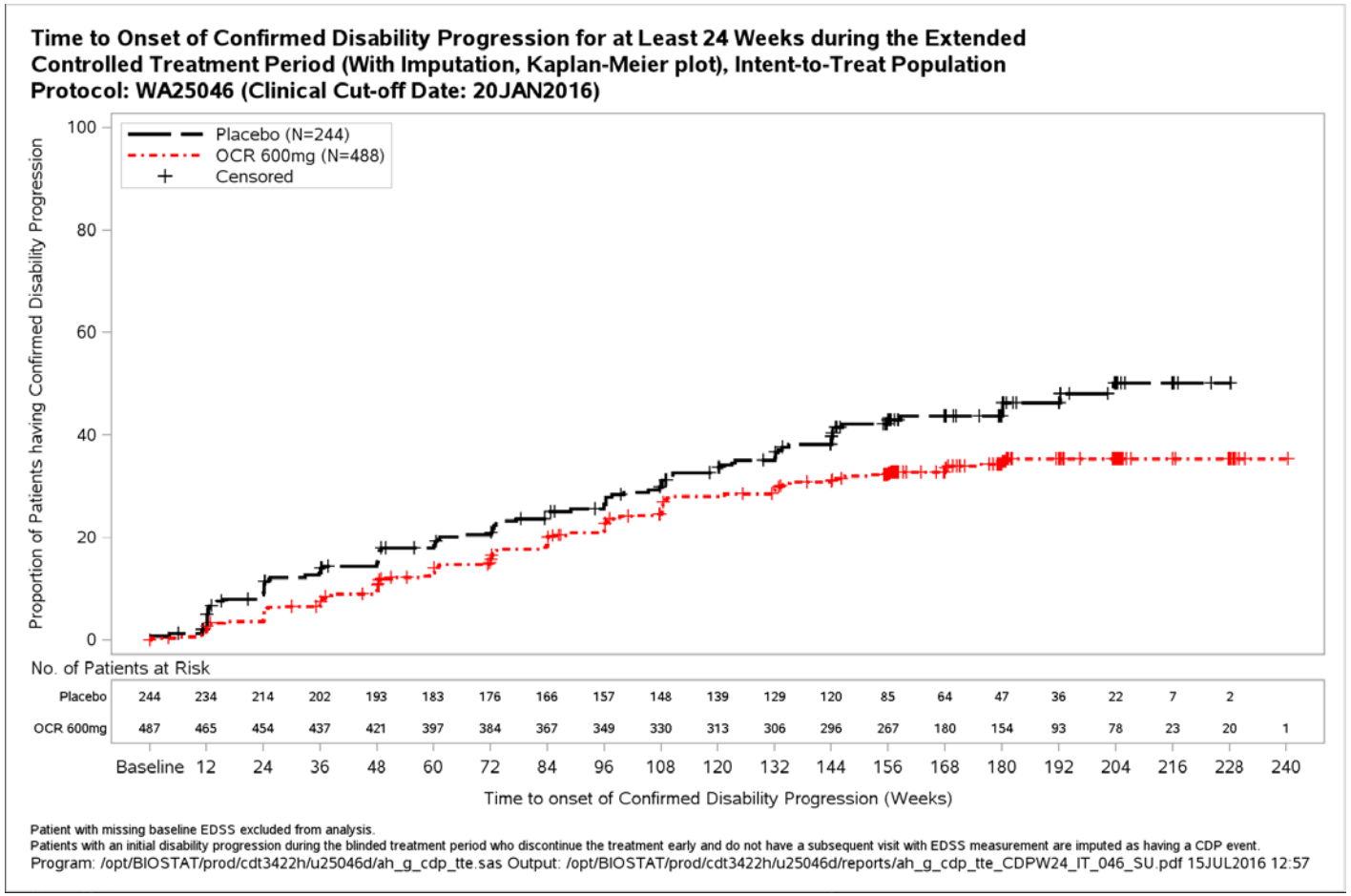


Figure 15 Kaplan-Meier Plot of Time to Onset of Confirmed Disability Progression for at Least 24 Weeks during the Extended Controlled Treatment Period (With Imputation, ITT Population; WA25046)

A survival analyses was also conducted on 24-week CDP (with imputation) excluding information until after the first EDSS assessment (18 weeks) resulting in a hazard ratio of 0.76, suggesting sustained benefit from ocrelizumab therapy beyond 18 weeks (Table 24). The respective Kaplan-Meier curve (Figure 16) shows that after the first EDSS assessment the observed reduction in progression risk for patients treated with ocrelizumab is starting at week 120 and sustained to the end of the extended controlled treatment period.

Table 24: Time to Onset of Confirmed Disability Progression for at Least 24 Weeks for Patients remaining at Risk at 18 and 30 Weeks during the Extended Controlled Treatment Period (With Imputation, ITT Population; WA25046)

Endpoint	Patients with Event		Hazard Ratio (95% CI)	p-value (log-rank)
	Placebo (N=244)	OCR (N=488)		
24-week CDP for patients remaining at risk at 18 weeks	79 /217	137 /454	0.76 (0.57, 1.00)	p = 0.0479

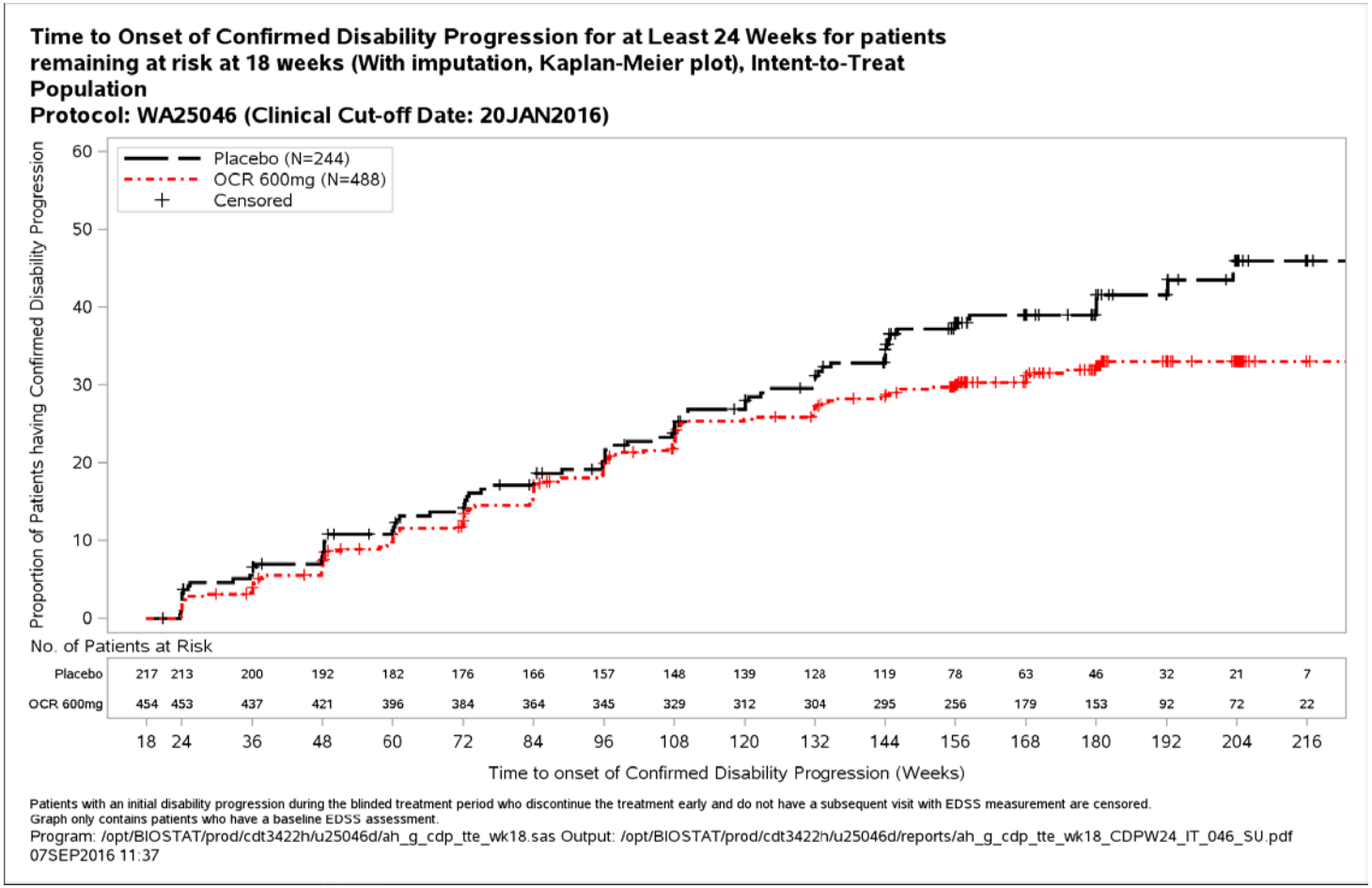


Figure 16 Time to Onset of Confirmed Disability Progression for at Least 24 Weeks for Patients remaining at Risk at 18 Weeks during the Extended Controlled Treatment Period (With Imputation, ITT Population; WA25046)

Time to Confirmed Composite Disability Progression for at Least 12 Weeks and 24 Weeks For Extended Controlled Treatment Period

In the extended controlled treatment period, new exploratory analyses of time to disability progression as measured by a 12-week composite endpoint (CDP by EDSS or a 20% increase in T25-FW or 20% increase in 9-hole peg test, all confirmed for 12 weeks) showed a 28% relative reduction with ocrelizumab (HR 0.72 [95% CI: 0.60, 0.87], p = 0.0005) (Table 25).

The relative contribution of the three components of the composite endpoint was analyzed and the significant effect seen in the composite was maintained in all components analyzed alone (Table 25).

Table 25: Analysis of Time to Confirmed Composite Disability Progression (EDSS or Timed 25-Foot Walk or 9-Hole Peg Test) for at Least 12 Weeks During the Extended Controlled Treatment Period and Contribution of Individual Component Endpoints (With Imputation, ITT Population; WA25046)

Endpoint	Patients with Event		Hazard Ratio (95% CI)	p-value (log-rank)
	Placebo (N=244)	OCR (N=488)		
12-week Composite Endpoint (EDSS or T25-FW or 9-Hole Peg Test)	180 /244	303 /488	0.72 (0.60, 0.87)	0.0005
12-week CDP (EDSS, primary endpoint)	106 /244	177 /487	0.74 (0.58, 0.95)	0.0151
20% increase in T25-FW confirmed at 12 weeks	149 /244	249 /488	0.75 (0.61, 0.92)	0.0046
20% increase in 9-Hole Peg Test confirmed at 12 weeks	70 /244	97 /488	0.59 (0.44, 0.81)	0.0008

Source: WA25046-efficacy data memo 2016 Table 5

Exploratory analyses of time to disability progression as measured by a 24-week composite endpoint (CDP by EDSS or a 20% increase in T25-FW or 20% increase in 9-hole peg test, all confirmed for 24 weeks) showed a 32% relative reduction with ocrelizumab (HR 0.68 [95% CI: 0.56, 0.82], p = 0.0001) (see Table 26).

The relative contribution of the three endpoints to the composite endpoint was analyzed. Consistent with the results observed for the 12-week composite, the significant effect seen in the 24-week composite was found to be maintained in all components analyzed alone (Table 26).

Table 26: Analysis of Time to Confirmed Composite Disability Progression (EDSS or Timed 25-Foot Walk or 9-Hole Peg Test) for at Least 24 Weeks During the Extended Controlled Treatment Period and Contribution of Individual Component Endpoints (With Imputation, ITT Population; WA25046)

Endpoint	Patients with Event		Hazard Ratio (95% CI)	p-value (log-rank)
	Placebo (N=244)	OCR (N=488)		
24-week Composite Endpoint (EDSS or T25-FW or 9-Hole Peg Test)	166 /244	261 /488	0.68 (0.56, 0.82)	<0.0001
24-week CDP (EDSS, Secondary endpoint)	98 /244	154 /487	0.70 (0.54, 0.90)	0.0056
20% increase in T25-FW confirmed at 24 weeks	136 /244	213 /488	0.70 (0.56, 0.87)	0.0011
20% increase in 9-Hole Peg Test confirmed at 24 weeks	58 /244	81 /488	0.61 (0.44, 0.86)	0.0040

CORROBORATION WITH RMS DATA

Relapse-independent Disability progression in the RMS studies

The WA21092/WA21093 studies enrolled patients with RMS, and therefore allowed enrollment of both relapsing-remitting MS and relapsing SPMS patients.

SPMS is characterized by progressive accumulation of disability after an initial relapsing course of the disease. This neurological deterioration is independent from relapses although patients with SPMS can still experience relapses which could contribute to their disability progression. Therefore a certain level of disability is usually accumulated before the diagnosis of SPMS is made.

Physician assessment of whether the patient was in the relapsing-remitting or in the secondary progressive course of MS when enrolled in the RMS studies WA21092 and WA21093 was not collected as baseline.

Patients who had relapse-independent confirmed disability progression (CDP and composite) during the conduct of Studies WA21092 and WA21093 have been identified by establishing a new baseline for EDSS, T25-TW, and 9-hole peg test for each patient after each relapse and requiring progression in the absence of relapse. Moreover, in addition to the ITT population the treatment effect of ocrelizumab was estimated in the subgroup matching the definition of SPMS identified using the MSBase cohort (disability progression independent of relapses, baseline EDSS ≥4.0 and Pyramidal FFS ≥2) (Lorscheider et al. 2016).

Of the patients putatively identified as SPMS patients using the 2 methods described above (1.9% to 10.2% SPMS patients within the ITT), these analyses showed that ocrelizumab has a treatment benefit on relapse-independent disability progression.

- A 24% risk reduction in relapse-independent 12-week composite confirmed disability progression with ocrelizumab compared with interferon beta-1a (p = 0.0098)
- A 22% risk reduction in relapse-independent 24-week composite confirmed disability progression with ocrelizumab compared with interferon beta-1a (p = 0.0456).

Assessment of progression events independent of relapses by establishing a new baseline for all assessments of disability 30 days after the onset of each protocol-defined relapse represents a rigorous method of accounting for any residual disability due to a relapse event. Although this was a post-hoc

analysis limited to the 96 weeks double-blind treatment period, the results show that ocrelizumab consistently reduces the risk of progression across all assessed measures of disability, including relapse-independent disability.

Disability progression independent of relapses is a phenomenon common to both RMS and PPMS patients. Emerging consensus opinion is that MS is a continuous spectrum rather than consisting of discrete pheontypes, and disability progression independent of relapses occurs as a result of a pathophysiological process that is universally prevalent along this spectrum but which varies in degree depending on clinical course. Therefore, the applicant considered that the observed treatment benefit on progression independent of relapses in the RMS studies was consistent with and supportive of the treatment benefit on progressive disease in the PPMS Phase III study WA25046.

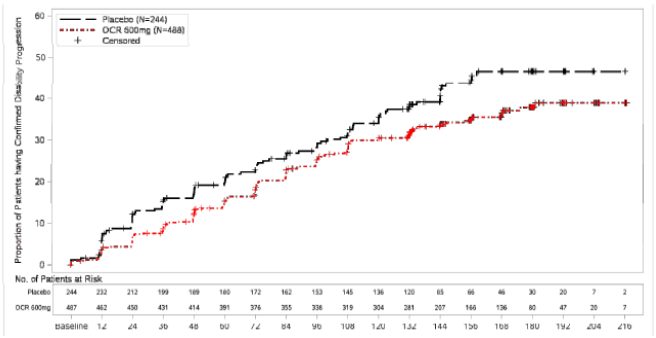
Additional Exploratory analysis and evidence from other trials

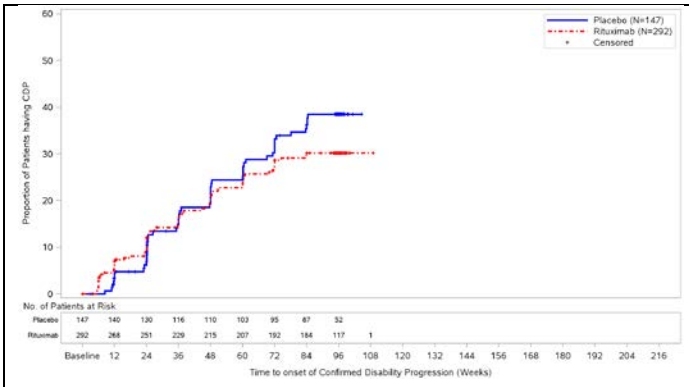
A similar Phase II/III OLYMPUS study (rituximab) (Figure 18) did not reach its primary endpoint, however Hawker et al. 2009 proposed the hypothesis that selective B-cell therapy would be more effective in patients with active inflammation as measured by T1 Gd enhanced lesions and patients younger than 51 years. Benefit-risk in PPMS has not been established with rituximab.

Below, the primary endpoint of the ORATORIO study 12-week CDP is compared with data from an age-matched population (18-55 years at baseline) from the OLYMPUS study (Figure 19).
Furthermore, since a subgroup of earlier rituximab patients (aged <51 years, with T1 Gd enhancing lesions at baseline) in OLYMPUS is the group that derived the best benefit, an equivalent population from ORATORIO was used to compare and look for similar patterns on disability progression (Figure 20; Figure 21). Similar trends showing early (Figure 20) and late (Figure 21) separation are seen with both ocrelizumab and rituximab.

There are limitations of such comparisons including being based on post-hoc analyses, underpowered, different MRI methods (acquisition, reading methods), different durations of study (the OLYMPUS study with a fixed duration and concluding at 96 weeks), etc.

Figure 17: ORATORIO (ocrelizumab) ITT Population

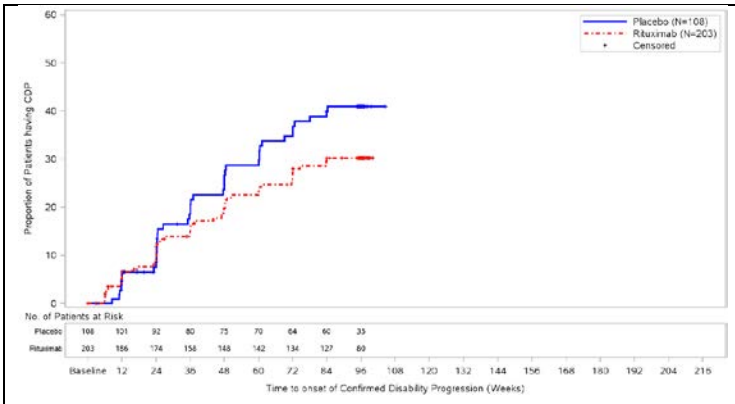
	**K-M curves of ITT populations** ORATORIO: HR=0.76 (0.59-0.98); p=0.0321 • ITT population primary analysis, 12 week confirmed disability progression ocrelizumab vs placebo, time to event analysis at ~253 events • The shortest time on study for a patient completing was 132 weeks. The longest was 217 weeks



OLYMPUS: HR=0.77 (0.55-1.09); p=0.1442

- ITT population primary analysis, 12 week confirmed disability progression rituximab vs placebo, 96 weeks fixed duration
- All patients completing the study had 96 weeks of follow-up

Figure 18 OLYMPUS (Rituximab) Patients ≤55 years Old



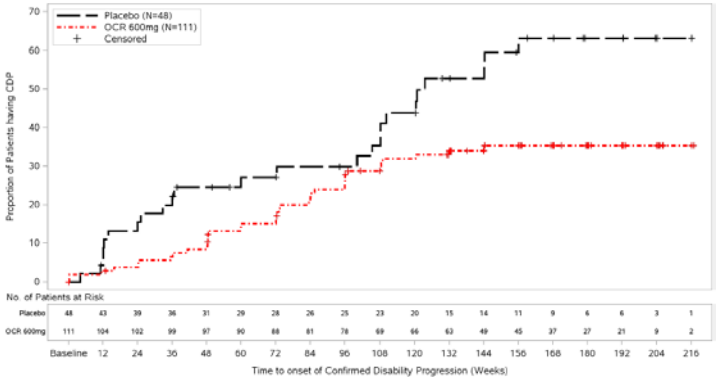
K-M curve for OLYMPUS patients up to 55 years old

OLYMPUS: HR=0.69 (0.46-1.03); p=0.0676

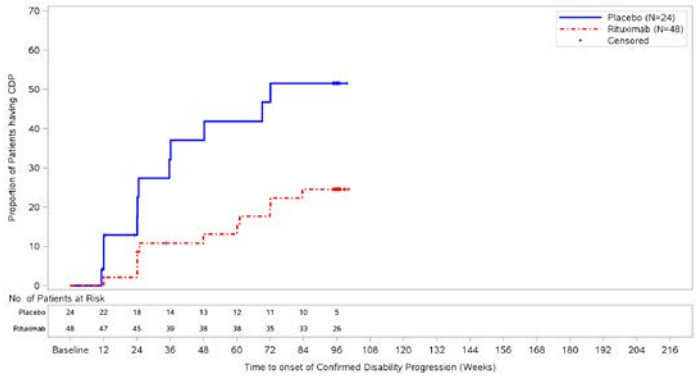
- The OLYMPUS study enrolled patients up to 65 years old. ORATORIO enrolled patients up to 55 years old. In this comparison we look at the OLYMPUS population aged ≤55 years old to compare with ORATORIO

Figure 19: Rapid Onset of Treatment Effects Demonstrated by Subgroups with Baseline T1 Gd Enhancing Lesions

ORATORIO - Patients with Age<51 with baseline active T1 Gd lesions



OLYMPUS - Patients with Age<51 with baseline active T1 Gd lesions



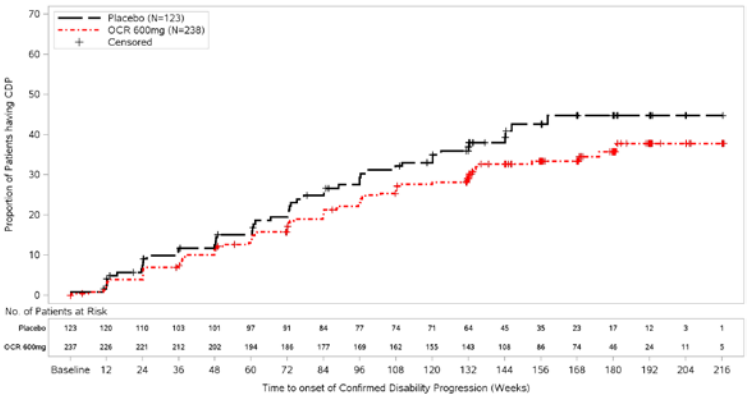
K-M curves in patients with Age<51 with baseline active T1 Gd lesions

ORATORIO: HR=0.53 (0.31-0.89); p=0.0160
OLYMPUS: HR=0.33 (0.14-0.79); p=0.0124

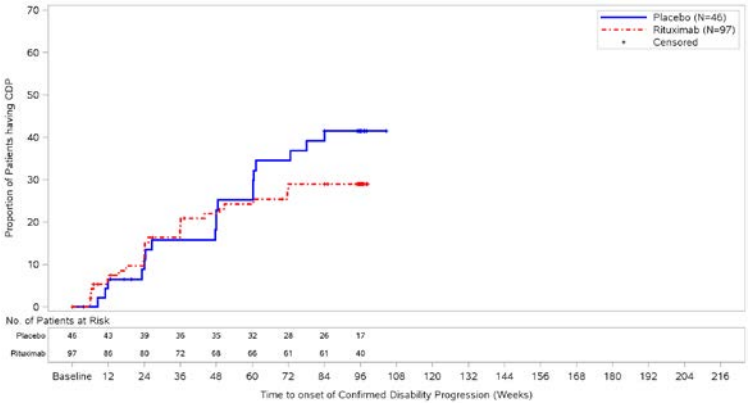
- Onset of treatment effect for both ocrelizumab and rituximab is around 12 weeks, with an immediate reduction of progression rates in the active arm compared with rapid progression in corresponding placebo patients
    - Ocrelizumab has a rapid and near complete suppressive effect on acute inflammation, as seen by a significant suppression on T1-Gd lesions by the first post-randomization MRI at week 24 (96% reduction, p<0.0001). The on treatment effects on T1-Gd lesions were not measured in OLYMPUS.
- The shape of the ocrelizumab and rituximab curve is similar. The placebo arms in both OLYMPUS and ORATORIO flaten between week 48 and week 96, although it is more pronounced in ORATORIO. This could be a chance finding (not observed in secondary endpoints)
- The later progression events observed in the placebo arm of ORATORIO are likely due to both chronic (T2 lesions) and later appearing acute (post-baseline new T1-Gd lesions) inflammation. Ocrelizumab has a suppressive effect on both T2 and new T1-Gd lesions, and this is consistent with the later separation in the treatment arms. There is no equivalent period in OLYMPUS since the study concluded at 96 weeks

Figure 20: Later Onset of Treatment Effects Demonstrated by Subgroups without Baseline T1 Gd Enhancing Lesions

ORATORIO - Patients with Age<51 without baseline active T1 Gd lesions



OLYMPUS - Patients with Age<51 without baseline active T1 Gd lesions



K-M curves in patients with Age<51 without baseline T1 Gd lesions

ORATORIO: HR=0.77 (0.53-1.11); p=0.1625
OLYMPUS: HR=0.63 (0.34-1.18); p=0.1460

- The placebo progression in both ORATORIO and OLYMPUS is slower in T1 Gd negative patients compared to T1 Gd positive patients
- In both ORATORIO and OLYMPUS treatment effect starts to emerge around week 60 and curves keep separating, consistent with constant risk reduction
- Since ocrelizumab also has a suppressive effect on chronic inflammation, as seen by a significant suppression of T2 lesion volume, more prominent on the later MRI timepoints (Figure 3, secondary endpoint). During this second period, T2 volume increases with a steeper slope in the placebo arm, coupled with near complete suppression in the ocrelizumab arm. This results in the second observed separation of the treatment arms.
- A similar pattern of T2 lesion volume reduction was observed in OLYMPUS.

Analyses within the subgroup of patients above or equal 51 years of age are difficult to interpret due to the very small number of patients.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 27 Summary of efficacy for trial WA21092

Title: A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif®) in patients with relapsing multiple sclerosis			
Study identifier	WA21092		
Design	Double-blind double-dummy RCT with an active control (interferon beta-1a) with an OLE.		
	Duration of main phase: Duration of Run-in phase:		96 weeks Screening was two weeks.
Hypothesis	Superiority for ocrelizumab (OCR) over active control		
Treatments groups	OCR + REBIF placebo		600 mg IV every 24 weeks (first dosing divided into 300 mg two weeks apart), 410 subjects randomised
	REBIF (Interferon beta-1a) + OCR placebo		Up-titration to 44 µg SC three times weekly (with option for down-titration to 22 µg SC three times weekly for tolerability reasons), 411 subjects randomised
Endpoints and definitions	Primary endpoint: Adjusted ARR		Hierarchical testing for primary endpoint and secondary endpoints
	Secondary endpoint no.1: Time to onset of CDP sustained for at least 12 weeks	Pre-specified pooling with Study WA21093	List of secondary endpoints is not exhaustive, and is here presented in hierarchical order.
	Secondary endpoint no.2: Total number of T1-Gd enhancing lesions at Weeks 24, 48 and 96		

	Secondary endpoint no. 3: Total number of new and/or enlarging T2 hyperintense lesions at Weeks 24, 48 and 96		
	Secondary endpoint no. 4: Proportion of patients with CDI sustained for at least 12 weeks	Pre-specified pooling with Study WA21093	
	Secondary endpoint no. 5: Time to onset of CDP sustained for at least 24 weeks	Pre-specified pooling with Study WA21093	
Database lock	29 May 2015		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Intent to treat		

Descriptive statistics of estimates	Treatment group	OCR	REBIF	
	Number of subject	410	411	
	Adjusted ARR	0.156	0.292	
	Sec. endpoint no.1; % pts at 96 weeks	9.75	15.18	
	Sec. endpoint no.2, mean no. of lesions per MRI scan <variability statistic>	0.016	0.286	
	Sec. endpoint no. 3, mean no. of lesions per MRI scan	0.323	1.413	
	Sec. endpoint no. 4, proportion of patients with improvement	20.7	15.64	

	Sec. endpoint no. 5, proportion (%) of patients with events at 96 weeks	7.58	12.03	
Effect estimate per comparison	Primary endpoint ARR	OCR/REBIFs		
		Adjusted ARR ratio	0.536	
		95% CI	0.400 – 0.719	
		P-value	<0.0001	
	*Sec. endpoint no.1; CDP 12 Weeks	OCR/REBIF		
		Hazard ratio	0.60	
		95% CI	0.45 – 0.81	
		P-value (Log-rank)	0.0006	
	Sec. endpoint no. 2, T1 Gd-enhancing lesions	OCR/REBIF		
		Rate ratio	0.058	
		95% CI	0.032 – 0.104	
		P-value	<0.0001	
	Sec. endpoint no. 3, new or enlarging T2 hyperintense lesions	OCR/REBIF		
		Rate ratio	0.229	
		95% CI	0.174 – 0.300	
		P-value	<0.0001	
	*Sec. endpoint no. 4, proportion of patients with improvement (CDI 12 weeks)	OCR/REBIF		
		Relative risk	1.33	
		95% CI	1.05 – 1.68	
		P-value	0.0194	
	*Sec. endpoint no. 5, CDP 24 weeks	OCR/REBIF		
		Hazard ratio	0.60	
		95% CI	0.43 – 0.84	
		P-value	0.0025	
Notes	*Results pooled (pre-specified) for Studies WA21092 and WA21093			

Table 28 Summary of efficacy for trial WA21093

Title: A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif®) in patients with relapsing multiple sclerosis		
Study identifier	WA21093	
Design	Double-blind double-dummy RCT with an active control (interferon beta-1a) with an OLE.	
	Duration of main phase: Duration of Run-in phase:	96 weeks Screening was two weeks.
Hypothesis	Superiority for ocrelizumab (OCR) over active control	
Treatments groups	OCR + REBIF placebo	600 mg IV every 24 weeks (first dosing divided into 300 mg two weeks apart), 417 subjects randomised

	REBIF (Interferon beta-1a) + OCR placebo		Up-titration to 44 µg SC three times weekly (with option for down-titration to 22 µg SC three times weekly for tolerability reasons), 418 subjects randomised
Endpoints and definitions	Primary endpoint: Adjusted ARR		Hierarchical testing for primary endpoint and secondary endpoints
	Secondary endpoint no.1: Time to onset of CDP sustained for at least 12 weeks	Pre-specified pooling with Study WA21092	List of secondary endpoints is not exhaustive, and is here presented in hierarchical order.
	Secondary endpoint no.2: Total number of T1-Gd enhancing lesions at Weeks 24, 48 and 96		
	Secondary endpoint no. 3: Total number of new and/or enlarging T2 hyperintense lesions at Weeks 24, 48 and 96		
	Secondary endpoint no. 4: Proportion of patients with CDI sustained for at least 12 weeks	Pre-specified pooling with Study WA21092	
	Secondary endpoint no. 5: Time to onset of CDP sustained for at least 24 weeks	Pre-specified pooling with Study WA21092	
Database lock	2015		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Intent to treat		
Descriptive statistics of estimates	Treatment group	OCR	REBIF
	Number of subject	417	418

	Adjusted ARR	0.155	0.290	
	Sec. endpoint no.1; % pts at 96 weeks CDP 12 Weeks	9.75	15.18	
	Sec. endpoint no.2, mean no. of T1 Gd-enhancing lesions per MRI scan	0.021	0.416	
	Sec. endpoint no. 3, mean no. of new/enlarging T2 lesions per MRI scan	0.325	1.904	
	Sec. endpoint no. 4, proportion of patients with improvement (CDI 12 Weeks)	20.7	15.64	
	Sec. endpoint no. 5, proportion (%) of patients with CDP 24 Weeks at 96 weeks	7.58	12.03	

Effect estimate per comparison	Primary endpoint ARR	OCR/REBIFs	
		Adjusted ARR ratio	0.532
		95% CI	0.397 – 0.714
		P-value	<0.0001
	*Sec. endpoint no.1; CDP 12 Weeks	OCR/REBIF	
		Hazard ratio	0.60
		95% CI	0.45 – 0.81
		P-value (Log-rank)	0.0006
	Sec. endpoint no. 2, T1 Gd-enhancing lesions	OCR/REBIF	
		Rate ratio	0.051
		95% CI	0.029 – 0.089
		P-value	<0.0001
	Sec. endpoint no. 3, new or enlarging T2 hyperintense lesions	OCR/REBIF	
		Rate ratio	0.171
		95% CI	0.130 – 0.225
		P-value	<0.0001
	*Sec. endpoint no. 4, proportion of patients with improvement (CDI 12 weeks)	OCR/REBIF	
		Relative risk	1.33
		95% CI	1.05 – 1.68
		P-value	0.0194
	*Sec. endpoint no. 5, CDP 24 weeks	OCR/REBIF	
		Hazard ratio	0.60
		95% CI	0.43 – 0.84

		P-value (Log-rank)	0.0025
Notes	*Results pooled (pre-specified) for Studies WA21092 and WA21093		

Table 29 Summary of efficacy for trial WA25046

Title: A Phase III, multicenter, randomized, parallel-group, double blinded, placebo controlled study to evaluate the efficacy and safety of ocrelizumab in adults with primary progressive multiple sclerosis.			
Study identifier	WA25046		
Design	Double-blind placebo controlled RCT (randomisation to OCR and placebo in a 2:1 ratio).		
	Duration of main phase: Duration of Run-in phase:		At least 120 weeks and planned total number of 253 events (CDP 12 weeks) Screening was four weeks.
Hypothesis	Superiority for ocrelizumab (OCR) over placebo		
Treatments groups	OCR		600 mg IV every 24 weeks (divided into 300 mg two weeks apart), 488 subjects randomised
	Placebo		As above, 244 subjects randomised
Endpoints and definitions	Primary endpoint: 12-Week CDP Proportion of patients with events at 120 weeks (Kaplan Meier estimate)		Hierarchical testing for primary endpoint and secondary endpoints
	Secondary endpoint no.1: 24-Week CDP Proportion of patients with events at 120 weeks (Kaplan Meier estimate)		
	Secondary endpoint no.2: Change in Timed 25-Foot Walk Relative Ratio to Baseline at Week 120 (MMRM)		
	Secondary endpoint no. 3: T2 Lesion Volume Relative Ratio to Baseline at Week 120 (MMRM)		

	Secondary endpoint no. 4: Percent Change from Week 24 to Week 120 in Total Brain Volume (MMRM)			
	Secondary endpoint no. 5: Change from Baseline in SF-36 PCS Score (MMRM)			
Database lock	2015			
Results and Analysis				
Analysis description	Primary Analysis			
Analysis population and time point description	Intent to treat			
Descriptive statistics of estimates	Treatment group	Ocrelizumab	Placebo	
	Number of subject	488	244	
	Primary endpoint, proportion of patients with CDP 12 Weeks at 120 weeks	0.302	0.340	
	Sec. endpoint no.1; proportion of patients with CDP 24 Weeks at 120 weeks	0.283	0.327	
	Sec. endpoint no.2, : Change in Timed 25-Foot Walk Relative Ratio to Baseline at Week 120 (MMRM)	38.933	55.097	
	Sec. endpoint no. 3, T2 Lesion Volume Relative Ratio to Baseline at Week 120 (MMRM), adjusted geometric mean (% change)	-3.366	7.426	

	Sec. endpoint no. 4, Percent change from Week 24 to Week 120 in Total Brain Volume (MMRM)	-0.902	-1.093	
	Sec. endpoint no. 5, Change from Baseline in SF-36 PCS Score (MMRM)	-0.731	-1.108	

Effect estimate per comparison	Primary endpoint CDP 12 Weeks	OCR/Placebo	
		Hazard ratio	0.76
		95% CI	0.59 – 0.98
		P-value (Log-rank)	0.0321
	Sec. endpoint no.1; CDP 24 weeks	OCR/Placebo	
		Hazard ratio	0.75
		95% CI	0.58 – 0.98
		P-value (Log-rank)	0.0365
	Sec. endpoint no. 2, Change in Timed 25-Foot Walk Relative Ratio to Baseline at Week 120 (MMRM)	OCR/Placebo	
		Relative reduction (%)	29.337
		95% CI	-1.618 – 51.456
		P-value	0.0404
	Sec. endpoint no. 3, , T2 Lesion Volume Relative Ratio to Baseline at Week 120 (MMRM),	OCR/Placebo	
		Rate ratio	
		95% CI	
		P-value (ranked ANCOVA)	<0.0001
	Sec. endpoint no. 4), Percent change from Week 24 to Week 120 in Total Brain Volume (MMRM)	OCR/Placebo	
		Relative risk reduction (%)	17.475
		95% CI	3.206 - 29.251
		P-value	0.0206
	Sec. endpoint no. 5, Change from Baseline in SF-36 PCS Score (MMRM	OCR/Placebo	
		Difference in Adjusted Mean	0.377
		95% CI	-1.048 – 1.802
		P-value (Log-rank)	0.6034
Notes			

Analysis performed across trials (pooled analyses and meta-analysis)

RMS

A Pooled Analysis Report was generated to report results of the efficacy and safety analyses performed using the pooled dataset collected in Studies WA21092 and WA21093 because of the pre-specified intent to pool the data from the two trials to maintain sufficient power to detect relevant treatment differences in the analysis of CDP and CDI endpoints.

Pooling criteria were pre-specified; to assess the validity of pooling data across Studies WA21092 and WA21093, demographics, baseline characteristics, ARR results, and 12-week CDP results were compared between the trials. Demographic and baseline characteristics were comparable across the two studies. No statistically significant treatment by study interaction effect was seen in the annualized protocol defined ARR between studies (p = 0.9538) showing that the treatment effect in this endpoint was similar in both studies. Finally, 12-week CDP was qualitatively similar, with both studies showing similar hazard ratios of the same size in favour of ocrelizumab compared to interferon beta-1a in patients treated with ocrelizumab than those treated with interferon beta-1a 44µg SC. Taken together, these data confirmed the patient population and treatment difference between OCR and IFN groups was broadly consistent between the two studies and that the prospectively-defined pooling criteria had been met to allow valid pooling of the data.

A total of 1656 patients were enrolled into Studies WA21092 and WA21093 (821 patients for WA21092 and 835 patients for WA21093). Enrolled patients were randomized 1:1 to interferon beta-1a 44 µg SC (N = 411 for WA21092 and N =418 for WA21093) or ocrelizumab 600 mg (N = 410 for WA21092 and N = 417 for WA21093).

Key Findings

- Ocrelizumab significantly and consistently reduced the ARR at Week 96 compared with interferon beta-1a in Studies WA21092 and WA21093.

Both studies achieved the primary endpoint; treatment with ocrelizumab led to consistently and statistically significant 46% and 47% reductions in the ARR compared with interferon beta-1a in WA21092 and WA21093, respectively. When data from the studies was pooled, ocrelizumab treatment resulted in a 47% reduction in ARR.

In Studies WA21092 and WA21093, treatment with ocrelizumab led to a suppression in the number of relapses experienced from a rate equivalent to one relapse approximately every 3.5 years in patients treated with interferon beta-1a (adjusted ARR of 0.292 and 0.290, respectively) to a rate equivalent to one relapse approximately every 6.5 years in patients treated with ocrelizumab (adjusted ARR of 0.156 and 0.155, respectively).

Ocrelizumab showed significant impact on measures of disability progression.

- Ocrelizumab consistently and significantly reduced the risk of 12- and 24-week CDP compared to interferon beta-1a in the pooled population of Studies WA21092 and WA21093, as well as the individual study results.

- Ocrelizumab significantly increased the proportion of patients with 12-week CDI compared to interferon beta-1a in the pooled population of Studies WA21092 and WA21093, as well as the individual results of Study WA21092, but had no significant effect on 12-week CDI in Study WA21093.

- Ocrelizumab significantly increased the MSFC score change from baseline to Week 96 when compared to interferon beta-1a in Study WA21093 and the pooled population of Studies WA21092 and WA21093, but had no significant effect on MSFC in Study WA21092.

The robustness of these results was demonstrated by the consistency of results between the sensitivity analyses and the ITT, particularly those including the initial event of neurological worsening during the double-blind treatment period as well as the SFU to 96 weeks, using 50% imputation and using 100% imputation, with hazard ratios of 0.57 - 0.60 in Study WA21092, 0.60 - 0.64 in Study WA21093 and 0.60 - 0.61 in the pooled population.

The MSFC scale is a neurological rating scale, which provides a global quantitative estimate of MS disability in three clinical dimensions (leg function/ambulation; arm/hand function; and cognitive function), and was a secondary endpoint in Studies WA21092 and WA21093. Treatment with ocrelizumab was associated with a significantly greater improvement in the MSFC z-score change from baseline to Week 96 compared with treatment with interferon beta-1a in Study WA21093 (difference in adjusted means 0.107, p = 0.0040) and the pooled populations (difference in adjusted means 0.077, p

= 0.0038), however, no significant difference between treatment groups was seen in Study WA21092 (difference in adjusted means 0.039, p = 0.3261).

Ocrelizumab showed significant suppression of MRI disease activity across all pre-planned MRI endpoints

- Ocrelizumab consistently and significantly reduced the total number of T1 Gd-enhancing lesions, the number of new and/or enlarging T2 lesions and the total number of new T1 hypointense lesions by Week 96 compared to interferon beta-1a in Studies WA21092 and WA21093 and in the pooled population.

- Ocrelizumab statistically significantly reduced the rate of whole brain volume loss from Week 24 to Week 96 compared to interferon beta-1a in the pooled population of Studies WA21092 and WA21093. While Studies WA21092 and WA20193 also reported a reduction in brain volume loss, the result in Study WA21093 was not statistically significant and the result in Study WA21092 is considered non-confirmatory

- NEDA was a pre-planned secondary endpoint to be analyzed only on the cohort of patients with a baseline EDSS score ≥ 2.0. It was a composite endpoint based on relapse, CDP and MRI activity. Patients were considered to have NEDA if they had experienced no protocol-defined relapses, no 12 week CDP event and no MRI showing disease activity (defined as Gd-enhancing T1 lesions or new and/or enlarging T2 lesions) during the 96-week treatment period.

The proportion of patients with baseline EDSS ≥ 2 who had NEDA during the double-blind treatment period was greater in the OCR group (46%) than in the IFN group (26%) in the pooled population from Studies WA21092 and WA21093, representing a 77% relative increase (p < 0.0001). Similar results were seen in the individual studies, however while p < 0.0001 in both studies, this was non-confirmatory as the endpoints followed a non-significant p-value in the hierarchical testing procedures.

In addition to the pre-specified secondary endpoint, NEDA was also analyzed for the ITT population (all patients independent of the baseline EDSS score) in the individual studies as well as in the pooled population of both studies. In the pool of both studies, a greater proportion of patients showed NEDA in the OCR group (48%) compared with the IFN group (27%), representing a 75% improvement for ocrelizumab versus the IFN group, p < 0.0001. The result of the pooled population was in line with the results of the individual studies

Efficacy in Subgroups of Different Disease Activity: Pooled Analyses

There are no agreed definitions of active and highly active disease activity in the European Union. The Sponsor took into account that patients with disease activity on treatment may have more active disease than those with disease activity off treatment, as well as labelling precedents and definitions established by other Sponsors as a guide. Based on these considerations the Sponsor pre-specified four subgroups (Table 35) of active and highly active disease containing both treatment naïve patients and patients who had inadequately responded to prior therapy in the WA21092/WA21093 SAP. The subgroups as defined are not mutually exclusive (i.e., are defined as minimum levels of disease activity).

Consistent with the final European MS guideline, which recommends that separate conclusions of the efficacy and safety in RMS patients both with low and high disease activity, to be provided at the time of benefit risk assessment (EMA/CHMP/771815/2011, Rev. 2), these data enable full understanding of the benefit/risk of ocrelizumab.

Table 30 Subgroup Definitions

Subgroup	Definition
Active Inadequate Responders	Treated with interferon or glatiramer acetate for at least 1 year and: had at least one relapse in the year prior to randomization **OR** had at least one baseline T1 Gd-enhancing lesion
Highly Active Inadequate Responders	Treated with interferon or glatiramer acetate for at least 1 year and: had at least one relapse in the previous year **AND** had at least nine T2 hyperintense lesions or at least one T1 Gd-enhancing lesion at baseline
Active Treatment Naive	Treatment-naïve (had not been treated with any MS medication in the 2 years prior to randomization) with at least two relapses in the previous 2 years and at least one relapse in the last year prior to randomization
Highly Active Treatment Naive	Treatment-naïve with at least two relapses in the last year prior to randomization and: had at least one baseline T1 Gd-enhancing lesion **OR** an increase in T2 hyperintense lesion count at baseline visit (changing from 0-5 to 6-9 lesions or from 6-9 lesions to > 9 lesions), as compared to the prior MRI

Gd = gadolinium.

For efficacy, all four subgroups were analyzed for the primary endpoint (ARR) and key secondary endpoints (12 and 24- week CDP, 12-week CDI at 12 weeks, T1 Gd-enhancing lesions and new and/or enlarging T2 hyperintense lesions). The pre-specified analyses for all subgroups pooled the Study WA21092 and WA21093 data to ensure at least 100 patients in each subgroup and enable adequate detection of treatment differences.

Overall, a treatment benefit of ocrelizumab compared with interferon beta-1a was observed in both active and highly active subgroups across all endpoints analyzed, including ARR and 12-week CDP, consistent with the findings in the ITT population (Figure 3 for ARR across subgroups and Figure 4 for 12-week CDP across subgroups). Importantly, consistency across all subgroups was observed between the 12-week and 24-week CDP result, which again is consistent with the 12- and 24-week CDP result in the ITT population.

Table 31 Annualized Relapse Rate by Week 96 by Subgroup – Inadequate Responder and Treatment-Naïve (ITT Population, Pooled Analysis of Studies WA21092 and WA21093)

Annualized Protocol Defined Relapse Rate by Week 96 (Negative Binomial Model) by Subgroups - Inadequate Responder and Treatment-Naive, Intent-to-Treat Population
Pooled: WA21092 and WA21093

Baseline Risk Factors	IFN beta-1a (N=829)			OCR 600mg (N=827)			Rate Ratio	95% CI	p-value	Forest plot
	No. in group	No. of Relapses	Patient years	No. in group	No. of Relapses	Patient years				OCR 600mg better / IFN Beta-1a better
All Patients	829	334	1339.16	827	194	1415.72	0.535	(0.435,0.659)	<.0001	
Active inadequate responder										
Yes	148	66	235.25	153	26	261.21	0.345	(0.204,0.585)	<.0001	
No	681	268	1103.91	674	168	1154.51	0.584	(0.466,0.733)	<.0001	
Active treatment naive										
Yes	311	137	510.95	323	89	557.40	0.556	(0.405,0.764)	0.0003	
No	518	197	828.22	504	105	858.32	0.506	(0.385,0.666)	<.0001	
Highly active inadequate responder										
Yes	140	64	223.56	143	23	243.07	0.317	(0.181,0.556)	<.0001	
No	689	270	1115.60	684	171	1172.65	0.589	(0.471,0.736)	<.0001	
Highly active treatment naive										
Yes	107	65	173.85	112	23	194.50	0.306	(0.180,0.518)	<.0001	
No	722	269	1165.31	715	171	1221.22	0.593	(0.473,0.743)	<.0001	

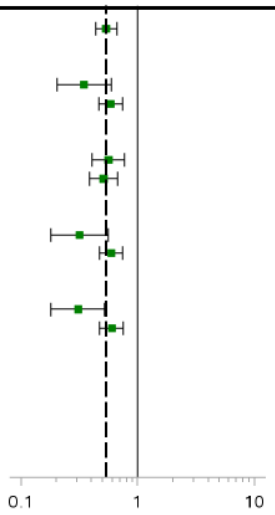
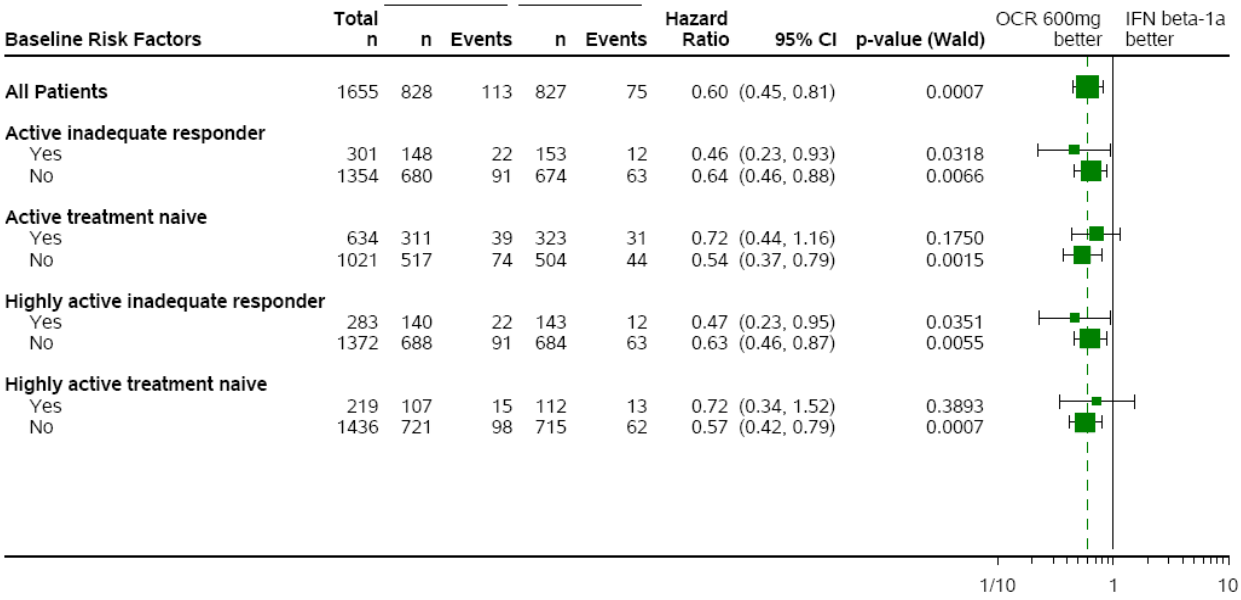


Table 32 Time to Confirmed Disability Progression Sustained for at least 12 Weeks by Subgroup – Inadequate Responder and Treatment Naïve (ITT Population, Pooled Analysis of Studies WA21092 and WA21093)

Time to Onset of CDP for at least 12 weeks during the Double-Blind Treatment Period by Subgroups - Inadequate Responder and Treatment-Naive, Intent-to-Treat Population
Pooled: WA21092 and WA21093

		IFN beta-1a (N=829)		OCR 600mg (N=827)				
Baseline Risk Factors	Total n	n	Events	n	Events	Hazard Ratio	95% CI	p-value (Wald)
All Patients	1655	828	113	827	75	0.60	(0.45, 0.81)	0.0007
Active inadequate responder								
Yes	301	148	22	153	12	0.46	(0.23, 0.93)	0.0318
No	1354	680	91	674	63	0.64	(0.46, 0.88)	0.0066
Active treatment naive								
Yes	634	311	39	323	31	0.72	(0.44, 1.16)	0.1750
No	1021	517	74	504	44	0.54	(0.37, 0.79)	0.0015
Highly active inadequate responder								
Yes	283	140	22	143	12	0.47	(0.23, 0.95)	0.0351
No	1372	688	91	684	63	0.63	(0.46, 0.87)	0.0055
Highly active treatment naive								
Yes	219	107	15	112	13	0.72	(0.34, 1.52)	0.3893
No	1436	721	98	715	62	0.57	(0.42, 0.79)	0.0007



Clinical studies in special populations

No such dedicated clinical studies were performed. The main studies included adult subjects up to the age of 55 years in RMS and PPMS. No clinical studies were performed in the paediatric population.

Supportive study(ies)

RMS

No stand-alone supportive clinical studies were claimed by the Applicant except for Study 21494 which has already been described in previous sections. However, the OLEs to studies WA21092 and WA21093 can be regarded as providing supportive data for persistence of efficacy:

The pooled population of patients enrolled in the OLE of Studies WA21092 and WA21093 who were originally in the OCR treatment group during the 96 week double-blind treatment period of the studies and who had completed an additional 46 weeks of open-label treatment with ocrelizumab showed an unadjusted ARR of 0.142 (see table below). This was consistent with the unadjusted ARR of 0.137 seen in the pooled population during the 96-week double-blind treatment period providing evidence for persistence of the efficacy of ocrelizumab on relapses in RMS for up to 3 years.

There are limited data on follow-up in OLE, therefore results should be interpreted with caution, however patients who were originally in the IFN group during the 96 week double-blind period of the studies also showed a benefit following switching to ocrelizumab in the OLE, with an ARR of 0.137 following 46 weeks of ocrelizumab treatment in the pooled population OLE population comparable to that seen in the pooled OCR group and lower than the rate of 0.249 seen in the pooled IFN group in the 96 week double-blind period of Studies WA21092 and WA21093.

The pooled population of patients enrolled in the OLE of Studies WA21092 and WA21093 who were originally in the OCR treatment group during the 96 week double-blind treatment period of the studies and who had completed an additional 46 weeks of open-label treatment with ocrelizumab showed a low rate of MRI lesion activity with 95.3% experiencing no new and/or enlarging T2 lesions. This provides evidence for persistence of the efficacy of ocrelizumab on an objective and quantifiable marker of disease activity in RMS up to 3 years.

Patients who were originally in the IFN group during the 96 week double-blind treatment period of the studies also showed a benefit following switching to ocrelizumab in the OLE, with 80.1% experiencing no new and/or enlarging T2 lesions following 46 weeks of ocrelizumab treatment in the pooled population of the OLE of Studies WA21092 and WA21093. This was in line with the time course of the effect of ocrelizumab on new and/or enlarging T2 lesions seen in the double blind period.

PPMS

No new stand-alone supportive studies were claimed by the Applicant and the OLE from Study 25046 has not been reported at the time of this report. However, the Applicant argued that the Studies 21092 and 21093 in RMS can be regarded as supportive to the PPMS Study 25046. The Applicant therefore made a comparison of outcomes for endpoints that were shared between the PPMS Study 25046 and the RMS Studies 21092/21093, inter alia 12-week CDP, 24-week CDP and timed 25-foot walk. However, the effect size seen in the RMS trials for these clinical endpoints favoured numerically RMS over PPMS although the RMS trials had a shorter duration and used an active control (in the PPMS trial the control was placebo).

Clinical Progression Primary Endpoint

Confirmed Disability Progression Sustained for at Least 12 Weeks:

Treatment with ocrelizumab in the Study WA25046 in PPMS patients led to a 24% reduction in the risk of 12-week CDP compared with placebo. Similarly, the results of the pooled data analysis of Studies WA21092 and WA21093 in RMS indicate that ocrelizumab treatment leads to a significant 40% decrease in risk of 12-week CDP from baseline to week 96 when compared with the interferon beta-1a, with significant reductions of 43% and 37% also seen in the individual studies.

Clinical Progression Secondary Endpoints

Confirmed Disability Progression Sustained for at Least 24 Weeks:

The analysis of the time to onset of CDP for at least 24 weeks in Study WA25046 in PPMS was consistent with the primary endpoint, where treatment with ocrelizumab led to a 25% reduction in the risk of 24-week CDP compared with placebo. In support of this, the pooled data analysis of Studies WA21092 and WA21093 in RMS patients indicates that ocrelizumab treatment leads to a significant 40% decrease in 24-week CDP compared with interferon beta-1a, with significant reductions of 43% and 37% also seen in the individual studies.

Timed 25-foot Walk:

Ocrelizumab treatment resulted in a 29% relative reduction in the percent progression in T25-FW over 120 weeks compared with placebo in the Study WA25046 in PPMS. The pooled analysis results of the T25-FW exploratory endpoint in the RMS Studies WA21092 and WA21093 supports this effect, with ocrelizumab leading to an 83% relative reduction in T25-FW over 96 weeks compared with interferon beta-1a (Pooled summary). The results seen in the individual studies were inconsistent (22% and 117% reductions, respectively).

Subclinical Progression Secondary Endpoints

MRI: Change in Brain Volume:

Treatment with ocrelizumab in Study WA25046 in PPMS patients reduced the rate of brain volume loss over the interval from Week 24 to Week 120 by 17.5% relative to placebo. Similarly, the pooled data analysis of the RMS Studies WA21092 and WA21093 indicated that treatment with ocrelizumab led to 18.8% relative reduction in mean percent brain volume loss from Week 24 to Week 96 in an RMS population, compared with interferon beta-1a treatment, with 23% and 15% reductions shown in the individual studies, respectively.

Exploratory MRI Endpoint

MRI: T2 Hyperintense Lesion Volume:

In the PPMS Study WA25046 ocrelizumab significantly decreased the total volume of T2 hyperintense lesions from baseline to Week 120 by 3.4%, compared with an increase the total volume by 7.4% in patients treated with placebo. The exploratory analyses of T2 hyperintense lesion volume in the Studies WA21092 and WA21093 showed that treatment with ocrelizumab also leads to a 7.3% and 7.0% decrease, respectively, in the total volume of T2 hyperintense lesions at 96 weeks in the RMS population in these studies, compared with a 2.5% and 2.1% decrease, respectively, in the groups treated with interferon beta-1a.

MRI: New and/or Enlarging T2 Lesion Count:

In an exploratory analysis of Study WA25046, treatment with ocrelizumab resulted in a 91.9% relative reduction in new and/or enlarging T2 hyperintense lesions per scan compared with placebo in a PPMS population over 120 Weeks. Similarly, the pooled data analysis of the RMS Studies WA21092 and WA21093 indicated that treatment with ocrelizumab led to 80% relative reduction in the number of new and/or enlarging T2 hyperintense lesions to Week 96 in the pooled RMS population of Studies WA21092 and WA21093, compared with interferon beta-1a, a drug that potentially reduces T2 lesions in its own right. 77% and 83% relative reductions were seen in the individual studies, respectively.

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Five different versions of the test product ocrelizumab were used in the clinical studies 21493, 21092, 21093, and 25046 (OLEs inclusive). The ADCC potency of the material used in Phase II Study 21493 (used for dose finding) was different from the ADCC potency of the version (0.4) used in Phase III. From a quality point of view, the version intended to market is similar to version 0.4 used in the Phase III studies.

RMS

Confirmatory clinical efficacy data were derived from two efficacy superiority trials in adults (≤55 years of age) with identical design (Study 21092 and Study 21093). These two main studies were RCTs with duration of 96 weeks that were overall appropriately designed, and used an appropriate study RMS population with active disease. Based on the inclusion criteria, patients with relapsing forms of MS were included in studies WA21092 and WA21093. Patients with SPMS were also included in RMS studies WA21092 and WA21093. However, the physician's assessment of whether the patient was in the relapsing-remitting or in the secondary progressive course of the disease was not collected at baseline. In order to identify SPMS patients, the Applicant retrospectively established a new baseline for EDSS, T25-FW, and 9-Hole peg test for each patient 30 days after the onset of each protocol-defined relapse - for accounting for any residual disability due to a relapse event - and requiring progression in the absence of relapse. Moreover, in addition to the ITT population, the treatment effect of OCR was estimated in the subgroup matching the definition of SPMS identified using the MSBase cohort (disability progression independent of relapses, baseline EDSS ≥4.0 and Pyramidal FFS ≥2) (Lorscheider et al. 2016). Post-hoc analyses on relapse-independent disability progression were performed during the treatment period on the pooled data of studies WA21092 and WA21093 and were limited to the 96 week double-blind treatment period. Disability progression was measured by using the composite disability endpoint (increase in EDSS that is sustained for at least 12/24 weeks, or a

20% increase in the timed 25-foot walk [T25-FW] that is sustained for at least 12/24 weeks, or a 20% increase in the 9-HPT that is sustained for at least 12/24 weeks [12/24-week composite endpoint]) in order to better characterize aspects of disease progression potentially missed with EDSS alone (e.g. arm function) and to increase the sensitivity of detecting events of disease progression over EDSS alone.

The studies included no placebo control but the active comparator was interferon beta-1a (Rebif®) SC (randomisation ratio 1:1) and this active control was dosed according to its labelling recommendations. The choice of active control was agreed as adequate. The test compound ocrelizumab was investigated for one fixed dose level (600 mg every 24 weeks) and the choice not to investigate a higher dose level was not questioned since the supportive dose response study 21493 did not reveal any efficacy advantages with a dose level of 2,000 mg. It remains unclear whether a lower dose would have also been beneficial.

Re-treatment criteria (i.e. any significant or uncontrolled medical condition or treatment-emergent, clinically significant laboratory abnormality; active infection; absolute neutrophil count < 1.5 × 103/µL; CD4 cell count < 250/µL; hypogammaglobulinemia IgG < 3.3 g/L; ongoing pregnancy) were pre-specified by the Applicant in the protocol, based on a biological plausibility considering the OCR mechanism of action, in order to allow doses to be delayed should one of these criteria be fulfilled. An association between lymphopenia and the decrease of CD4 and CD8 T cells below the LLN (lower limit of normal) and neutropenia and an increased risk of serious infection in OCR patients was found and therefore this should be taken into consideration.

The chosen primary endpoint (ARR) was appropriate and so were the secondary clinical and subclinical endpoints. The only shortcoming was that the secondary endpoints did not comprise an assessment of clinical global impression of change as recommended in the relevant EMA guideline. However, this was only considered a minor issue. The primary endpoint and the secondary endpoints were to be tested in a hierarchical manner to deal with the issue arising from multiplicity in the testing. The secondary endpoint CDP 12 Weeks preceded the secondary endpoint CDP 24 Weeks in the hierarchical testing. The hierarchical testing procedure was agreed as appropriate. The pre-specified methods to deal with missingness for the primary endpoint ARR and the secondary endpoints CDP 12 Weeks, CDI 12 Weeks and CDP 24 Weeks were overall considered as appropriate. The pre-specified pooling of outcomes from the studies 21092 and 21093 for the primary analysis of the secondary endpoints CDP 12 Weeks, CDI 12 Weeks and CDP 24 weeks was accepted. The pre-planned approach to pool efficacy data from the main studies 21092 and 21093 for the primary endpoint ARR and the secondary endpoint CDP was acknowledged. The subgroup analyses based on pre-baseline RMS disease intensities, inadequate responders to previous DMT (based on response to previous use of glatiramer acetate and/or interferon) and treatment naïve subjects was also accepted.

No stand-alone supportive clinical studies were submitted by the Applicant (except the supportive proof-of-concept and dose finding study 21493). The main studies (Study 21092 and Study 21093) had OLEs with no parallel comparator and these OLEs can potentially be regarded to provide supportive evidence of persistence of efficacy beyond Week 96 (dependent on the outcome) with the limitations inherent to the design of such OLEs.

The supportive phase II dose-response study 21493 in adults with RRMS investigated in its placebo controlled double-blind 24-weeks phase 600 mg OCR (divided into two equal doses of 300 mg two weeks apart) with 2,000 mg OCR (divided into two equal doses of 1,000 mg two weeks apart) and used an appropriate primary endpoint and secondary endpoints for such a dose response study with an acceptable time point of 24 Weeks for the primary analyses. Since no correction for multiplicity testing was planned the trial does not qualify as pivotal.

A European PIP was agreed with the PDCO for the condition treatment of MS. The PIP includes a waiver for SPMS and PPMS patients, in addition to RRMS patients below 10 years of age. The PIP also includes a deferral to provide results in paediatric RRMS patients from 10 to <18 years of age. It is therefore appropriate that the submitted clinical studies do not encompass subjects under the age of 18 years.

The clinical studies submitted did not enrol subjects with an age above 55 years. Efficacy results from adults ≤ 55 years of age cannot readily be extrapolated to adults > 55 years of age and the elderly as the disease changes with time and the effect size might be smaller. Moreover, data on patients with moderate and severe renal impairment are not available, however, this has been adequately reflected in the SmPC.

PPMS

Confirmatory clinical efficacy data was derived from one efficacy superiority trial in adults (⩽55 years of age) with PPMS (Study 25046) with a disability grade corresponding to EDSS 3.0 to 6.5 points. This main study was a RCT (randomisation to OCR or placebo in a 2:1 ratio) with a placebo control but no active control. The lack of active control is justified since no DMT for PPMS has been licenced, and there is a clear medical need for DMT. The study duration was appropriate with at least 120 weeks for each individual subject and a planned number of 253 events for the primary outcome variable CDP 12 Weeks. The diagnosis criteria for PPMS were in accordance with the revised McDonald criteria 2005. The test compound OCR was only investigated for one fixed dose level (600 mg [divided into two equal doses of 300 mg two weeks apart] every 24 weeks) and the lack of investigating of a lower dose level and a higher dose was questioned since no preceding dose response study was performed in a study population with PPMS (only in RMSS, see above). Efficacy results from Studies WA21092, WA21093, and WA25046 presented by exposure (Cmean) quartiles seem to suggest that beneficial effects are mainly seen with Cmeans above the median value. This supports that the dose used could be the lowest effective dose. There are no data available to elucidate whether a higher dose would result in even better efficacy.

A total of 82% of patients in both treatment groups had not received previous treatment with steroid medication. Of the 18% who had received steroid treatment, the majority (17% of patients in the placebo group and 16% in the OCR group) received treatment with methylprednisolone. Only 2 in each group (OCR 0.4%, placebo 0.8%) received steroids for reasons related to “MS relapse”.

The primary endpoint CDP was appropriate and so were the secondary clinical and subclinical endpoints although the secondary endpoints did not comprise an assessment of clinical global impression of change as recommended and cognitive performance as recommended in the relevant EMA guideline, but this is a minor issue as for the RMS trials. The primary endpoint and the secondary endpoints were to be tested in a hierarchical manner to deal with the issue arising from multiplicity in the testing. CDP 12 Weeks was the primary endpoint, and preceded the first secondary endpoint CDP 24 Weeks in the hierarchical testing. The hierarchical testing procedure was appropriate.

No stand-alone supportive study was submitted in support of the PPMS indication. Instead the Applicant has referred to and compiled clinical and subclinical progression endpoints from the RMS Studies 21092 and 21093 and compared these outcomes with outcomes for the corresponding endpoints in the PPMS Study 25046. Such data can only be regarded as remotely supportive since they originate from a MS disease entity other than PPMS. The Applicant also presented data from the extended controlled treatment period of Study WA25046 (approximately 2½-6 additional months of blinded treatment). The studies in RMS and PPMS study did not enrol subjects with an age above 55 years. Efficacy results from adults ⩽ 55 years of age cannot readily be extrapolated to adults > 55 years of age and the elderly as the disease changes with time and the effect size might be smaller.

Efficacy data and additional analyses

RMS

The main study 21092 met its primary endpoint; treatment with OCR significantly reduced the ARR by 46.4% at 96 Weeks compared with interferon beta-1a ($p < 0.0001$) and consistent estimates of treatment effect were observed in all pre-specified sensitivity analyses of the primary endpoint (e.g. patients who withdraw early without an ongoing relapse were imputed for 100% of the patients to have had a relapse at the time of withdrawing). The demonstrated effect size is considered clinically relevant. The rates of overall early withdrawal were acceptable (14% out of 821 randomised patients) and favoured numerically the ocrelizumab treatment group compared to IFN. For this reason, the

sensitivity analyses were not considered completely reassuring of not introducing some overestimation of the treatment effect so, a more conservative approach was required. The tipping point analysis was provided by the Applicant and showed that the statistical significance is lost only in the very extreme scenario. The continued hierarchical statistical testing for the secondary endpoints CDP 12 weeks (pre-specified pooled results with Study 21093), most MRI endpoints, CDI 12 Weeks (pre-specified pooled analysis) and CDP 24 Weeks (pre-specified pooled analysis) revealed statistically significant findings. The secondary endpoint MSFC was not met, and therefore the hierarchical statistical testing for the remaining secondary endpoints MRI Brain volume ($p = 0.0042$) and NEDA ($p < 0.0001$) was non-confirmatory, whilst the statistical significance testing for SF-36 PCS was clearly negative. Still the results for change in Brain volume and NEDA are encouraging. The study in itself also had statistically significant outcomes for CDP 12 Weeks and CDP 24 Weeks, but not for CDI 12 weeks. In the main analysis, missingness for CDP 12 Weeks, CDP 24 Weeks and CDI 12 Weeks was handled appropriately, and with positive results, with a conservative definition of non-CDI for subjects who withdrew prematurely, but more conservative imputation assumptions were required in the sensitivity analyses for CDP 12 Weeks and CDP 24 Weeks. The positive changes seen for CDP 12 Weeks and CDP 24 Weeks are regarded as clinically relevant in terms of effect size and the additional sensitivity analyses provided by the Applicant showed the consistency of the results.

The other main study 21093 also met its primary endpoint; treatment with ocrelizumab significantly reduced the ARR by 46.8% at 96 Weeks compared with interferon beta-1a ($p < 0.0001$) and in this main study, there were consistent estimates of treatment effect observed in all pre-specified sensitivity analyses of the primary endpoint. As for Study 21092, this effect size is also judged as clinically relevant although a more conservative approach in sensitivity analysis was requested for the primary endpoint. The tipping point analysis was provided by the Applicant reassuring on robustness and consistency of results of the main analysis. The rates of overall early withdrawal was somewhat higher than in Study 21092 (19% out of 835 randomised patients) and even more strongly favoured numerically the ocrelizumab treatment group compared to IFN. Most secondary endpoints were met following a hierarchical statistical significance testing, including pooled analyses of CDP 12 Weeks, CDI 12 Weeks and CDP 24 Weeks except for one study specific MRI endpoint (Brain volume). The study in itself also had, as in Study 21092, statistically significant outcomes for CDP 12 Weeks and CDP 24 Weeks, but not for CDI 12 weeks. In the main analysis, missingness for CDP 12 Weeks, CDP 24 Weeks and CDI 12 Weeks was handled appropriately, and with positive results, with a conservative definition of non-CDI for subjects who withdrew prematurely, but additional and more conservative sensitivity analyses for CDP 12 Weeks and CDP 24 Weeks were requested and showed robustness of the results. The positive changes seen for CDP 12 Weeks and CDP 24 Weeks are regarded as clinically relevant in terms of effect size. Step. no. 9 in the hierarchical testing chain, change in Brain volume, did not show any statistically significant difference versus the active control ($p = 0.09$) and the subsequent hierarchical testing was therefore broken and non-confirmatory (SF-36 PCS, $p=0.0404$; NEDA, $p<0.0001$). Still, the results for NEDA are encouraging.

As regard to the Per-Protocol (PP) sensitivity analyses, the Applicant gave some clarifications about the distribution of protocol deviations by treatment group: overall, the number of patients with any protocol deviation (both major and minor) was comparable between the two treatment groups (IFN beta-1a and OCR) with a trend towards an overall higher proportion of patients with protocol deviations in study WA21093 compared to study WA21092. As regarding the major protocol violations leading and not leading to exclusion from PP analysis, some slight differences between OCR and IFN beta-1a were observed in study WA21092. However, the results of the requested more conservative and strict PP analyses including any major protocol deviation (i.e. those leading and not leading to exclusion from the initial PP analysis) were comparable and consistent with those of the analyses performed on the ITT population.

Subgroups analyses across the main studies 21092 and 21093 did not identify a subgroup clearly yielding more or less treatment benefit when disease activity (“active” disease or “highly active disease” arbitrarily defined) was combined with treatment naïve subjects and non-responders (also arbitrarily defined). However, for ARR, patients who were active or highly active inadequate responders or highly active treatment naïve appeared to have a borderline better treatment effect than those who were not. However, in every subgroup ocrelizumab showed superior efficacy compared to IFN. For CDP

12 Weeks, treatment naïve subjects with active and highly active disease activity tended numerically to have less treatment benefit.

Patients who weigh <75 kg and those with a BMI <25 were less likely to have a CDP sustained for 12 weeks and 24 weeks during the 96 double-blind treatment period. The Applicant discussed the potential explanations for the different effect of body weight/BMI and therefore drug exposure on ARR and disability in terms of 12-week and 24-week CDP. Data on an exposure – response analyses exploring the correlation between four exposure (Cmean) quartiles with the key study endpoints were subsequently provided and showed that for ARR no substantial differences across the quartiles in the OCR group were observed, consistently with the subgroup analyses by body weight and BMI. Conversely, for the secondary endpoints 12-week and 24-week CDP, patients with higher exposure (i.e. lower body weight) received more benefit from the treatment with OCR compared to patients with lower exposure (i.e. higher body weight). A hypothesis involving the potential role of the two-stage process of RMS (i.e. first stage driven by inflammation; second stage driven by both inflammation and neurodegeneration) and the degree of blood-brain barrier (BBB) alterations influencing the OCR penetration into the brain was advanced by the Applicant. Although this hypothesis might have some biological plausibility, it cannot be supported according to the PK/PD data, because, first, no information is available with regards to OCR concentration in brain or cerebral spinal fluid following OCR administration in humans or in animals; second, monoclonal antibodies and other large-molecule biotherapeutics are known to have limited diffusion across BBB with a brain concentration ratio of approximately 0.1% relative to circulating serum concentrations (Yu and Watts 2013); third, a study (Study 14-3756) in healthy monkeys showed that OCR does not significantly penetrate the brain and peak values of activity within 24 hours after injection of [111-In] ocrelizumab in the brain that were <1% of the injected dose were found. In patients with MS for whom there is evidence of BBB disruption, it is actually not known which could be the degree of brain penetration of OCR but, based on the above mentioned PK data, it can be argued that it might be not such high. Therefore, no definite conclusions can be drawn on this issue. However, it cannot be excluded that in RMS patients or particularly in RMS patients who start to accumulate disability or are in advanced disease stage an influence of body weight/drug exposure on the effect of OCR on disability burden might exist.

The Applicant has provided additional subgroup analyses (pooled data from Study 21092 and 21093) for the subgroup of non-treatment-naïve subjects and treatment-naïve subjects, respectively, regardless of pre-study disease activity. Treatment benefit was observed in both treatment-naive and non-treatment-naive subgroups for the primary endpoint ARR. For 12-week CDP and 24-week CDP, the treatment benefit in non-treatment-naive patients was numerically on par with the benefit in treatment-naive patients but statistical significance was lost for the non-treatment-naive subgroup probably due to small numbers.

The results of the requested subgroup analyses on primary and key secondary endpoints by disease duration by symptom onset and MS diagnosis showed that overall for ARR, the effect of OCR seems not to be influenced by the disease duration, although in study WA21093 a trend favouring OCR effect in patients with longer disease duration was observed. The results on the secondary disability endpoints (12-week and 24-week CDP) are more heterogeneous and therefore it is not possible to individuate a specific pattern of treatment response and to draw definite conclusions on the influence of disease duration on OCR effect.

Regarding the above mentioned subgroup analyses on SPMS, the retrospective identification of these patients based on not pre-specified definitions, allowed the identification of a number of patients within the ITT population in a range from 1.9% to 10.2%. Therefore, the numbers are very small and the ITT population of RMS studies WA21092 and WA21093 resulted in predominantly (~90% or greater) RRMS patients. Overall, it is acknowledged that in the subgroup of patients with SPMS, the direction of the effect in terms of HR and risk reduction favoured OCR as compared to IFN beta-1a. However, statistical significance in terms of both 95% CIs and p values was not always achieved for all the single components of the composite disability endpoint used across each SPMS definition adopted. The analyses on SPMS have some limitations: post-hoc nature of the analyses; retrospective identification of SPMS based on not pre-specified definition; pooled data analyses; small number of patients with a probable diagnosis of SPMS; the 30-day period used for accounting for any residual disability due to a

relapse event that may be not sufficient; statistical issues regarding the intrinsic characteristics of the composite endpoints to detect smaller effect as significant. Therefore, the results of these analyses are difficult to interpret and prevent from drawing definite conclusions on the effect of OCR on SPMS independent of acute inflammatory events. In particular, they do not allow to exclude that the effect of OCR on disability may be driven by its effect on inflammation and on inflammation-related disability accumulation more than on the pure neurodegeneration-related disability.

Moreover, for the SPMS patients identified in the two studies WA21092 and WA21093, it would have been interesting to have data on MRI-related disease activity such as Gd-enhancing lesions and new or enlarging T2 lesions, by treatment groups, overall and by relapse-independent disability progression. Finally, the clinical relevance of these results on SPMS should have been discussed, for example, in terms of actual difference in progression delay between the two treatment groups, absolute difference in the proportion of patients who had disability progression, and time for performing the T25-FW. However, the above mentioned limitations of the analyses on SPMS would have remained.

The EMA guidelines on MS stated that "In trials intended to evaluate the relapse rate, it is recommended not to include SPMS subjects with superimposed relapses as this might complicate trial design and hamper the interpretation of the effect on relapses and disability". However, it is also stated: "It is reasonable to assume that relapses in RRMS and SPMS have the same underlying inflammatory pathophysiology and therefore efficacy on relapses in RRMS patients may be extrapolated to efficacy on relapses in SPMS. However, extrapolation of the effect on disability will not be considered appropriate as pathophysiology is different". Therefore, as the anti-inflammatory effect of OCR has been demonstrated by the results on ARR in both studies WA21092 and WA21093, for reasons related to biological plausibility, this drug could be considered effective in preventing relapses not only in patients with RRMS but also in those with SPMS. Nevertheless, it should be taken into account that in those patients who are in the conversion phase from RRMS to SPMS, the efficacy of a treatment on relapses is not necessarily translated into a reduction of the disability burden, particularly of the disability accumulation related to neurodegenerative mechanisms.

The Study 21092 and the Study 21093 tested only one dose level of ocrelizumab (600 mg every 24 weeks; first dosing as 300 mg two weeks apart). A lower therapeutic optimal dose has not been unambiguously identified whilst 2,000 mg ocrelizumab (given as 1,000 mg two weeks apart) in the phase II trial 21493 did not convey any efficacy advantages over 600 mg.

PPMS

The only main study, study 25046, met its primary endpoint (time to event) but not with a compelling p value; treatment with ocrelizumab led to a 24% reduction in the risk of 12-week CDP compared with placebo (hazard ratio 0.76 [95% CI: 0.59, 0.98], p=0.0321). In the CHMP interactions at the time before the MAA, it was highlighted that statistical evidence stronger than $p<0.05$ on the primary endpoint would be required to account for the fact that a single trial in PPMS was to be conducted.

The Kaplan-Meier survival curves for time to onset of 12-week CDP showed separation starting from 12 weeks but the separation did not seem to increase thereafter. However, there was a lower proportion of patients in the ocrelizumab group with CDP compared to placebo group throughout the treatment period. A similar pattern for the Kaplan-Meier survival curves was seen for CDP 24 Weeks. The absolute difference for proportion of patients with a 12 –Week CDP at Week 120 was just around 4% implying an NNT of 25 subjects. A similar absolute difference was seen for CDP 24 Weeks.

The robustness of the results of the primary endpoint was analysed by performing various sensitivity analyses. Sensitivity analyses were consistent with the primary analysis in terms of treatment effect. With regard to imputation of initial disability progression events for patients with early treatment discontinuation, the approach of ignoring these events resulted in a reduced treatment effect (HR 0.82 [95% CI: 0.63, 1.07], p=0.1477). However, multiple imputation (HR 0.78 [95% CI: 0.60, 1.02]) and imputation by efficacy related reason for withdrawal / withdrawal by subject (HR 0.77 [95% CI: 0.60, 1.00], p=0.0490) resulted in consistent estimates of the treatment effect. The premature discontinuation rate (25% out of 732 randomised patients) was somewhat higher than the assumptions for the sample size estimate (20%). Premature discontinuation rates numerically clearly

favoured ocrelizumab treatment compared to IFN. The continued hierarchical statistical testing for the secondary endpoints time to CDP 24 weeks (p =0.0365), change in timed walk from baseline to week 120 (p = 0.0404), two MRI endpoints related to change in total T2 lesion volume and Brain volume (p < 0.0001 and p = 0.0206, respectively) were met. The last secondary endpoint SF-36 PCS for the hierarchical testing was not met.

During the scientific assessment of the MAA the Applicant modified the indication to 'early PPMS', and better reflect the results of the performed trial. The intention was to align the indication with the patient population studied in Study WA25046 (median age 46 years [range 18-56 years], median duration of disease 5.5-6 years, median time since diagnosis 1.3-1.6 years). However, no specific age limit - or other limit - was introduced. The Applicant argued for a positive B/R balance in the narrow indication 'early PPMS' by presenting WA25046 subgroup analyses showing more convincing effect in young patients whereas side effects were not more pronounced in them. A pre-specified subgroup analysis of the primary endpoint suggested that patients who are younger may receive a greater treatment benefit than patients who are older (≤ 45 years: HR 0.64 (0.45, 0.92), >45 years: HR 0.88 (0.62, 1.26). Similarly, a Forest plot illustrates age-dependence of the effect on 'Time to Onset of CDP' with a HR of 0.59 (p=0.0323) in the first age quartile (18-39 years), a HR of 0.71 (p=0.1984) in the second age quartile (40-46 years) etc. To some degree this is further supported by post-hoc subgroup analyses of the rituximab OLYMPUS study where the HR for 'Time to CDP (12 Weeks)' was 0.49 (p=0.0032) for patients 51 years or younger whereas there appeared to be no treatment effect for patients older than 51 years.

New analyses performed by the Applicant suggest that not only age but also T1-Gd enhancing lesions may modulate the effect of OCR on disability progression.
In particular, systematic analyses of all available baseline covariates (age, T1 Gd-enhancing lesions, time since MS symptoms onset, time since MS diagnosis, and EDSS score that were pre-specified subgroups, as well as additional covariates such as T2 lesion count, T2 lesion volume, non-enhancing T1 hypointense lesion volume, time since MS diagnosis and MSSS) associated with maturity of the disease as well as MRI activity have been submitted. The treatment effect of OCR has been estimated within all subgroups as the hazard ratio (HR) for delaying the time to onset of 12-week CDP (primary endpoint) as well as 12-week composite CDP (pre-specified exploratory endpoint) during the double-blind treatment period. The use of the HR to describe the effect size instead of a comparison at time point Week 120, pre-specified for the primary endpoint, is considered acceptable for a summary report of subgroup analyses. In any case, as regards HR data, even though no "subgroup by treatment interaction" resulted statistically significant, "age" and "presence of T1-Gd enhancing lesions" showed a favorable trend for the primary outcome, 12-week CDP. Results on the pre-specified exploratory endpoints 12-week composite CDP and the individual components T25-FW and 9-HPT showed a consistent trend for age but a less consistent trend for the MRI parameters.
Moreover, in both studies WA02546 and OLYMPUS more than 60% of patients with T1 Gd-enhancing lesions at baseline were below the respective study median age, suggesting that younger age correlated with more MRI activity. The interaction between age and T1 Gd enhancing lesions at baseline with regard to predicting OCR treatment effect was also investigated by estimating the hazard ratio for delaying the time to onset of 12-week CDP (primary endpoint) during the double-blind treatment period within all four possible subgroup combinations.
On the basis of the results of these analyses, the Applicant drew the following conclusions: i. age has the greatest influence as the determining factor for subgroup efficacy, with young patients deriving substantial treatment benefit from ocrelizumab, independent of T1 Gd-enhancement status; ii. the presence of T1 Gd-enhancing lesions at baseline only contributes to the magnitude of the treatment effect within the two age groups; iii. age and presence of gadolinium-enhancing lesions at baseline are overlapping and independent effects.
However, based on analyses by strata and data description used by the Applicant it is difficult to draw conclusions on whether age is the variable that drives an increase of the effect size independent of the presence of T1 Gd-enhancing lesions (or viceversa) and, in addition, on whether there is an interaction effect or independence between these two variables (at least as a trend).

The summary 2x2 table below, derived by the data provided by the Applicant, can be helpful to better understand the trend in treatment effect modification (in terms of HR) for the primary outcome, 12-week CDP, within the different components.

Patient population	Age <=45 (HR)	Age >45 (HR)	All (HR)
T1 Gd+	0.52	0.85	0.65
T1 Gd-	0.74	0.93	0.84
All	0.64	0.91	0.76

As the above table highlights, it is indeed difficult to identify only in age the main driver of treatment effect. The only way to understand the effect of each single component independently of the other ones, would be by building a multivariate Cox regression model with the description of the effect by each single component independently of the other ones and by interaction components.

Although subgroup analyses should not be over interpreted, it seems that younger patients with T1 Gd-enhancing lesions at baseline have a better treatment effect [≤ 45 years: HR 0.52 (0.27-1.00); ≤ 46 years (median age of the WA25046 study); HR 0.48 (0.25-0.92); <51 years: HR 0.53 (0.31-0.89)]. This supports an indication in early PPMS early with imaging features characteristic of inflammatory activity.

In the double-blind period the treatment effect appeared modest and could be interpreted as a delay of a few months in 12 week-CDP progression. The Applicant argued that EDSS progression (of 1.0 or 0.5 EDSS points depending on baseline score) - and consequently any measurable delay in progression - is clinically relevant. Furthermore, based on extrapolations of data including the extended controlled period, a delay in median time to progression of 1.3 years was calculated. For the EDSS 7 milestone post-hoc analyses suggest an expected delay in reaching this of 8.8 years. However, such extrapolations should be interpreted with caution. This is particularly true if it is taken into account that in some cases extrapolation was carried on ahead in time (i.e. even until 4 or 5 times the time of observed data). Moreover, these extrapolations incorporate the terminal part of the KM curve, including the extended controlled period, which represents an area of statistical uncertainties due to already previously discussed reasons (i.e., effect sizes similar to those obtained during the controlled treatment period with smaller p values due to the increase in the number of events for CDP endpoint; apparent increase in the separation between the two KM curves starting from Week 144 with an apparent augmentation of the absolute difference between OCR and placebo and a consequent decrease of the NNT; the period after 144 weeks coincides with the actual starting of the gradual switch to the open label extension, there are too many graphically reported censored patients compared to the period before week 144 with a strong decrease in the number of patients at risk; use of composite endpoints for data presentation with their intrinsic ability in case of time to event data to detect small effects).

Furthermore, as previously pointed out, the extrapolation of efficacy results from RMS studies to PPMS population performed by the Applicant in support of the one pivotal study WA2546, had several limitations (i.e., post-hoc nature, retrospective identification of SPMS patients, pooled data analyses, small number of patients, the 30-day period used for accounting for any residual disability due to a relapse event, and the intrinsic ability of composite endpoints adopted to detect smaller effects) and therefore are not definitely reliable.

For the primary and secondary endpoints, time to onset of CDP sustained for at least 12 and 24 weeks, the possible reasons underlying the lower effect of OCR in females was discussed. Data on the frequency of Gd-enhancing lesions at baseline in males and females were provided. This showed a slight imbalances in the female subgroup (OCR 29.4% and placebo 21.8%) compared with the male subgroup (OCR 25.7% and placebo 27.7%) with more Gd-enhancing lesions at baseline observed in female patients receiving OCR. In terms of biological plausibility, the figures on the potential influence of Gd-enhancing lesion distribution on the effect of OCR by sex reported in descriptive, univariate and

multivariate analyses would not substantially explain the lower treatment effect observed in female PPMS patients. The same reduction of OCR efficacy in females is not seen in RMS. Uncertainties on these subgroups remained, however, it was acknowledged that no definite conclusions could be drawn due to the lack of power of the study for subgroup analyses and interaction testing and the heterogeneity and inconsistency of results across the different endpoints. As regards to the PP sensitivity analysis, it should be considered that a total of 157 major protocol deviations occurred in 68 patients of the study (75 deviations of the inclusion or exclusion criteria and 82 deviations during study conduct). However, based on the submitted data, it seemed that there were some discrepancies between the numbers of major protocol violations initially reported and those provided by treatment group. This has subsequently been clarified, and it was acknowledged that the discrepancy was relatively small.

The remainder of the secondary endpoints were met in the hierarchical testing except for change from Baseline in SF-36 PCS Score but MMRM was used to handle missingness. As MMRM was not regarded as being sufficiently conservative method in dealing with missingness, the Applicant subsequently presented analyses for change in Total Brain Volume using a pattern mixture model with imputation based on copy reference. This imputation method was regarded as conservative by CHMP because it assumed that there was no residual drug effect on brain volume loss after withdrawal from treatment. The results were to some degree consistent with the primary analysis. However, statistical significance was lost (treatment difference 0.150, p=0.0645) using this method instead of MMRM (treatment difference 0.192, p=0.0206).

For timed 25-foot walk and L2 lesion volume, LOCF analyses were presented. Results were in line with those obtained with MMRM.

The Study 25046 tested only one dose level of ocrelizumab (600 mg [divided into two equal doses of 300 mg two weeks apart] every 24 weeks). The proposed posology in the SmPC is 600 mg x 1. However, since B-cell depletion is associated with AUC and not Cmax, there should be no difference in expected treatment effect with the 600 mgx1 and the 300 mgx2 regimens.

A potentially lower or higher therapeutic optimal dose has not been investigated in the PPMS population, whilst 2,000 mg ocrelizumab (divided into two equal doses of 1,000 mg two weeks apart) in the phase II trial 21493 in a RRMS population did not convey any efficacy advantages over 600 mg. Efficacy results from Studies WA21092, WA21093, and WA25046 presented by exposure (Cmean) quartiles seem to suggest that beneficial effects are mainly seen with Cmeans above the median value. This supported that the dose used could be the lowest effective dose. There were no data available to elucidate whether a higher dose would result in even better efficacy.

Additional expert consultation

Minutes and answers from the Scientific Advisory Group (SAG) Neurology Meeting for OCREVUS on 8 June 2017

1. The SAG experts are invited to comment on the clinical relevance of the observed results in the study WA25046 in PPMS patients. The experts should focus on the clinical interpretation of the observed effect size and what it represents for these patients, as well as on the minimal clinically important difference that could be meaningful for such patients in the timeframe of the study duration.

Most of the experts considered the trial population to be an atypical PPMS cohort, consisting mainly of younger patients likely to have a more “active” disease. Therefore, they considered that the results from the trial will have to be cautiously interpreted and that extrapolation of these results to the whole PPMS population may be questionable.

Additional data in PPMS patients in the later stages of their disease would be useful in determining the best population in which to use ocrelizumab. The population was not stratified for disease activity. The

experts considered that any data looking into a potential link between baseline disease activity (in terms of clinical and MRI activity) and the observed clinical effect would be welcome.
Of note, one expert considered that the rationale for including younger patients is supported as in a neurodegenerative disease like PPMS the target should be the “early” population where the expectation of achieving the best result is most prominent.

Given the above considerations over the PPMS trial population, some experts considered that, despite the modest effect seen in the whole population, the positive results might be driven by a strong signal for efficacy in a sub-population of PPMS patients. These experts were of the positon that the observed effect could be relevant for a subpopulation of patients with PPMS, possibly dependent on the disease stage or the inflammatory activity. With regard to the results from the secondary outcomes, it was felt that they may be considered as supportive but should not be given confirmatory weight with regard to the expected proof of efficacy.

Limitations in the robustness of the efficacy data were mentioned. In particular, the differences between genders with respect to the results for the primary endpoint were noted, (not significant for females while significant for males). Similarly, the absence of significance in the results for patients aged over 45 years was considered as a concern.
Nonetheless, it was acknowledged that the study was not powered for subgroup analyses and thus results may be difficult to interpret with regards to patient selection/restriction of approval.

The SAG experts also noted that the preferable, more conservative significance level ($P<0.01$) in the power calculation was not reached and agreed that for a single pivotal trial the requirements for this should be stricter than the demonstrated level of $P<0.05$. Based on this point, and on the very small effect size, one expert considered that the WA 25046 study cannot be considered as fully successful, despite the demonstrated significance level. Some experts emphasized that in a slowly progressive disease, using an ordinal scale such as the EDSS that mainly relies on motor function as a measure of efficacy; a large effect size should not be expected during the proposed observational period of the clinical study.

The patient representatives supported the position that the effect size is small, but consistent as the results from most of the secondary endpoints point in the same direction and they represent the important aspects of everyday life for the PPMS patient. Additionally, they stressed the importance of the positive effects observed in the HRQoL (Health Related Quality of Life) scales, emphasising that after a certain level of progression (EDSS~7.0) the effects on non-motor aspects of disability (e.g. cognition) become even more important than EDSS progression.

Regarding what may constitute a minimal clinically important difference (MCID), the SAG experts could not reach a consensus on a specific effect size in a relevant outcome measure that could be agreed as MCID throughout the spectrum of PPMS. The patient representatives supported the position that any effect in this population should be considered relevant and important.

2. Having in mind the latest scientific developments and the up-to-date knowledge about the pathogenic mechanisms in MS, the CHMP would like to ask the SAG experts whether there is a scientific/mechanistic rationale to use some of the available data from the SPMS patients in the studies in Relapsing MS patients as supportive in the context of the evaluation of the results from the study WA25046 in PPMS.

The SAG experts agreed that RMS and PPMS are more likely to be two phenotypes of a single pathological process rather than different diseases. However, the experts were divided on how supportive the RMS data are in the present case, as the different pathophysiological components involved in RMS and PPMS, although similar, may nevertheless differ substantially in importance and chronology. Furthermore, the SAG experts considered that that the study design and the power calculation were likely to have been developed according to results from of other programmes that had failed, increasing the number of patients included and choosing a “time to event” outcome design to

increase the chances of showing a positive clinical effect for a slowly progressive disease such as PPMS on the EDSS scale.

Most of the experts considered that the RMS data could not be supportive as PPMS – as usually defined in clinical practice - is such a distinct and specific MS phenotype that in the present case, generation of separate efficacy data in a more representative population is required.

Other experts considered that the data from the RMS development programme for Ocrevus should be considered supportive as the different types of MS represent a disease continuum, rather than different diseases. This position was supported by the patient representatives.

Finally, some of the experts considered that the Ocrevus RMS data could be considered as supportive for efficacy in a sub-group of PPMS patients with proven inflammatory activity (i.e. the younger population with more active disease).

3. The CHMP would like to ask the experts about their view on the potential mechanism of action of ocrelizumab in PPMS, and how do they see the results in trial WA25046 in the context of the failures of all the other programmes by drugs targeting similar epitopes.

The majority of the SAG experts considered that the ocrelizumab trial in PPMS recruited a significantly different cohort of PPMS patients compared to the other trials in this population and to the patients usually encountered in clinical practice. In particular, as mentioned above, it recruited a population consisting of younger patients with potentially more active disease than the “classic” PPMS population.

As an additional comment, some experts noted the observed “cluster of malignancies” (breast cancer) registered in the development programme. They expressed the opinion that these data deserve to be considered carefully in the discussion of the B/R profile of the product, and should be taken into account in the discussion on a broad vs restricted indication in the PPMS population and in the risk management plan and monitoring.

2.5.3. Conclusions on the clinical efficacy

Confirmatory clinical efficacy data from two identically designed pivotal studies in RMS were provided. In both trials the primary endpoint and most secondary endpoints were met. The effect of OCR treatment in the RMS patients is statistically significant, clinically relevant, and consistent across the majority of study endpoints. During the assessment, in order to better reflect the conclusions on the observed efficacy and safety, the Applicant narrowed the indication to “active RMS”. This was considered acceptable as consistent efficacy had been shown in patients with active and highly active disease.

The development programme in PPMS consisted of a single pivotal study. The primary endpoint and most of the secondary endpoints of the study were met. Most sensitivity analyses were in line with the primary analysis and give reassurance on the reliability of results. Although results are not statistically compelling for an application based on one single pivotal trial, supportive data are derived from the Olympus trial, which support that a subgroup of PPMS patients that could benefit from ocrelizumab treatment exists.

The magnitude of the effect is indeed modest, smaller than what hypothesized in the calculation of the sample size. It should be however taken into account that the mechanism of action of ocrelizumab is anti-inflammatory in nature and that extraordinarily complex processes other than inflammation can be responsible for the neurodegeneration in PPMS. These processes may become predominant in more advanced stages of the diseases. Moreover, mechanisms other than those involving B cells could participate to chronic inflammation, on which ocrelizumab may have no effect. Until our knowledge on

the pathology progresses further, it will indeed be difficult to successfully target all main pathological mechanisms that underline disease progression in PPMS.

The clinical relevance of treatment effect cannot be denied, as a minimal clinical benefit cannot be defined at present and it is considered that any positive effect, even small, is of benefit as no other approved disease modifying treatments are available.

The identification of the patient population that may benefit the most from the drug was based on the provided sub-group analyses. Despite their limitations, it is clear that subjects in the early stage of disease and with the presence of acute inflammation as per MRI activity tend to benefit more. This was the reason for the amended indication in PPMS patients with “early” disease.

The CHMP agreed with the Applicant’s proposal to continue investigating the long term safety and efficacy in the whole PPMS population in a randomized, double blind, placebo controlled study including also older (>55 years) patients and patients more advanced in their disease course.

2.6. Clinical safety

Safety data from a total of 2147 MS patients are available from two pivotal Phase III studies in relapsing forms of multiple sclerosis (RMS) (WA21092 and WA21093), one Phase III study in primary progressive multiple sclerosis (PPMS) (WA25046), and a supporting dose-finding Phase II study in relapsing remitting MS (RRMS) (WA21493). Ocrelizumab doses in the MS program ranged between 600 mg and 2000 mg, although in the pivotal Phase III studies only the 600 mg dose was used.

Additional supportive safety data are available from 2926 patients (7324 patients years) exposed to ocrelizumab in a dose range of 20 mg to 2000 mg in a terminated development programme in patients with rheumatoid arthritis (RA). Further safety data are available from a limited number of patients with Systemic lupus erythematosus (SLE) and lupus nephritis (LN). These programmes were terminated due to similar safety issues (serious and opportunistic infections) and insufficient efficacy.

Different process versions (0.2, 0.3 and 0.4), but the same formulation (formulation 2) of ocrelizumab were used in the phase II study WA21493. In the rest of the phase III RMS and PPMS studies presented version 0.4 was used. However, the intended-to-market version is 1.0. This version is currently used in the ongoing open label extension. In addition, in the RA development program versions 0.1, 0.2 and 0.3 were used. Formulation 1 was also used in study WA18230 (Phase I/II, RA).

Patient exposure

In order to provide a complete assessment of the safety of ocrelizumab in RMS and PPMS, the data was pooled and analyzed as described below.

Pool A: Phase III RMS Controlled Treatment

Pool B: MS All Exposure (RMS, RRMS, and PPMS)

Pool C: Phase III RMS All Exposure

PPMS (WA25046): Phase III PPMS Controlled Treatment

Pool D: Phase II and Phase III RA Controlled Treatment

Pool E: RA All Exposure

Table 33 Overview of Safety Data Pools for the Ocrelizumab Clinical Development Program:

Pool	Type	Population	Studies	Duration	Patient N	OCR Exposure
A	Phase III RMS Controlled Treatment	RMS	WA21092 WA21093	96 week controlled treatment	OCR: 825 IFN: 826	1448 PY
B	MS All Exposure [a]	RMS RRMS PPMS	WA21493 WA21092 WA21093 WA25046	Controlled and OLE periods	OCR: 2147	4485 PY
C	Phase III RMS All Exposure [a]	RMS	WA21092 WA21093	Controlled and OLE periods	OCR: 1448	2305 PY
PPMS	Phase III PPMS Controlled Treatment	PPMS	WA25046	Controlled treatment for at least 120 weeks	OCR: 486 placebo: 239	1416 PY
D	RA Controlled Treatment	RA	7 Studies	Controlled treatment ranging from 24 to104 weeks	OCR + DMARD: 2341 placebo + DMARD: 981	2007 PY
E	RA All Exposure [a]	RA	9 Studies	Controlled, OLE and SFU periods	OCR + DMARD: 2926	7324 PY

DMARD = immunosuppressant disease – modifying anti – rheumatic drugs; IFN = interferon beta-1a;; OCR = ocrelizumab; OLE = open-label extension; PPMS = primary progressive multiple sclerosis; PY = patient years; RA = rheumatoid arthritis; RMS = relapsing multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SFU = safety follow-up.

[a] All exposure is defined as all patients who received any dose of ocrelizumab (includes both controlled treatment period and open-label extension periods).

Source: ISS Table 1.

At least 1173 MS patients have been exposed to the proposed dose 600 mg dose for more than 95 weeks.

Demographics:

- RMS population

Baseline demography and disease characteristics of the patients recruited into the two pivotal studies were matched across treatment groups and reflected an active RMS population. Patients were mainly white (approximately 90%) and female (approximately two-thirds), and median age 37-38 years. Around half of the patients had been diagnosed within 2 years, and almost all patients (96-98%) had experienced at least one relapse within 1 year, prior to randomization. Approximately 40% of patients had one or more T1 Gd enhancing lesions at baseline. Patients were at a relatively early disability stage of RMS as evidenced by the median baseline EDSS scores of 2.5.

- PPMS population

Baseline demography and disease characteristics of the patients recruited into the study were matched across treatment groups and reflected a PPMS population. The population enrolled in the study showed comparable proportions of patients by sex (approximately 51% male and 49% female), which is consistent with the known epidemiology of PPMS. Other baseline characteristics reflective of a PPMS population, were mean age of approximately 45 years, mean EDSS approximately 4.7, and normalized brain volume of approximately 1467 cm3. No patients had any prior relapse.

- RA population

The majority of patients were female (80% of patients) and white (69.5% of patients). The median age was 53 years (range 18-90 years and median weight was 72 kg (range 28-200 kg). The median duration since RA diagnosis was 5.69 years and 8.1% of patients were MTX-Naïve at baseline. Biologic and non-biologic DMARDs had been previously received by 38.1% and 59.2% of patients, respectively, and 37.4% of patients had previously received anti-TNFs.

Adverse events

The most common AEs by PT were IRR, headache, influenza-like illness, upper respiratory tract infection, and nasopharyngitis. Influenza-like illness, headache, injection site erythema, and injection site reaction were more frequently reported in the IFN group. Infusion related reactions (IRRs), upper respiratory tract infection, and nasopharyngitis were more common in the ocrelizumab group. Compared to placebo the same overall differences in frequencies of adverse events was observed.

Table 34 Summary of ADRs Associated with Ocrelizumab (in RMS or PPMS) with an Incidence of ≥ 2% and Higher than the Comparator:

ADR SOC and PT	RMS (Pool A)		PPMS		Frequency Category for OCR
	OCR N = 825	IFN N = 826	OCR N = 486	Placebo N = 239	
Injury, Poisoning and Procedural Complications					
Infusion-related reactions	283 (34.3%)	80 (9.7%)	194 (39.9%)	61 (25.5%)	Very common
Infections and Infestations					
Upper respiratory tract infection	125 (15.2%)	87 (10.5%)	53 (10.9%)	14 (5.9%)	Very common
Nasopharyngitis	122 (14.8%)	84 (10.2%)	110 (22.6%)	65 (27.2%)	Very common
Sinusitis	46 (5.6%)	45 (5.4%)	19 (3.9%)	7 (2.9%)	Common
Bronchitis	42 (5.1%)	29 (3.5%)	30 (6.2%)	12 (5.0%)	Common
Oral herpes	24 (2.9%)	17 (2.1%)	11 (2.3%)	1 (0.4%)	Common
Respiratory tract infection	19 (2.3%)	17 (2.1%)	11 (2.3%)	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%)	6 (1.2%)	2 (0.8%)	Common
Influenza	-	-	56 (11.5%)	21 (8.8%)	Very common
Psychiatric Disorders					
Insomnia	46 (5.6%)	38 (4.6%)	27 (5.6%)	12 (5.0%)	Common
Respiratory, Thoracic and Mediastinal Disorders					
Cough	25 (3.0%)	12 (1.5%)	29 (6.0%)	8 (3.3%)	Common
Catarrh	-	-	10 (2.1%)	2 (0.8%)	Common

ADR – adverse drug reaction; IFN – interferon beta 1-a; OCR – ocrelizumab; PPMS – primary progressive multiple sclerosis; PT – preferred term; RMS – relapsing multiple sclerosis; SOC – system organ class.

Pool A – controlled treatment period of Studies WA21092 and WA21093. PPMS – controlled treatment period of Study WA25046.

Table 35 Overview of Safety Profile of Ocrelizumab during Controlled Treatment Period (Pool A and PPMS):

	Phase III RMS Controlled Treatment Population (Pool A)		Phase III PPMS Controlled Treatment Population	
	IFN Beta-1a 44 µg SC (N=826)	OCR 600 mg IV (N=825)	Placebo (N=239)	OCR 600 mg IV (N=486)
Number of patients with:				
Any AE	688 (83.3%)	687 (83.3%)	215 (90.0%)	462 (95.1%)
Serious AE	72 (8.7%)	57 (6.9%)	53 (22.2%)	99 (20.4%)
Death	2 (0.2%)	1 (0.1%)	1 (0.4%)	4 (0.8%)
AE leading to withdrawal from treatment	51 (6.2%)	29 (3.5%)	8 (3.3%)	20 (4.1%)
IRR	80 (9.7%)	283 (34.3%)	61 (25.5%)	194 (39.9%)
Serious IRR	1 (0.1%)	1 (0.1%)	0	5 (1.0%)
IRRs leading to withdrawal from treatment	0	11 (1.3%)	1 (0.4%)	2 (0.4%)
Infection (SOC)	433 (52.4%)	482 (58.4%)	162 (67.8%)	339 (69.8%)
Serious infection (SOC)	24 (2.9%)	11 (1.3%)	20 (8.4%)	34 (7.0%)
Malignancies	2 (0.2%)	4 (0.5%)	2 (0.8%)	11 (2.3%)

AE adverse event ; IFN interferon beta-1a ; IRR infusion related reaction ; OCR ocrelizumab ; SOC MedDRA system organ class .

Analysis of Adverse Events by Organ System or Syndrome

Infusion related reactions (IRRs)

To reduce the risk of IRRs, all patients (including those in the placebo and IFN comparator groups) received IV methylprednisolone 100 mg prior to infusion. The addition of oral antihistamine to methylprednisolone pre-treatment for each dose was associated with at least a 2 – fold lower Incidence in IRRs compared with pre-treatment with methylprednisolone alone.

In all MS Phase III trials the initial ocrelizumab dose of 600 mg was administered as a divided dose (two 300 mg infusions administered 14 days apart). In the PPMS study administration of ocrelizumab continued as a divided dose (2 x 300 mg) regimen through the entire treatment period, whereas in the RMS studies subsequent doses were administered as single 600 mg infusions. From Dose 2 onwards there appears to be no benefit with regard to IRR for PPMS patients in administering ocrelizumab using the divided dose regimen (2 x 300 mg infusions, 14 days apart).

The most common symptoms associated with IRRs in the OCR group (in ≥ 10% of patients with IRRs) included pruritus, rash, throat irritation, and flushing.

RMS population:

IRRs occurred with a higher incidence in patients treated with ocrelizumab compared with those receiving IFN (IFN 9.7% of patients and OCR 34.3% of patients). The higher incidence of IRRs in patients receiving ocrelizumab was most evident at the first infusion (Infusion 1, Dose 1) (IFN 6.5% versus OCR 27.5%) and persisted for all infusions, albeit with decreasing incidence with subsequent dosing. Overall, IRRs were reported in the highest proportion of patients (IFN 46.3% and OCR 80.6%) during the infusion or while the patient was still in the clinic.

The majority of IRRs in both treatment groups (IFN 98.8% and IFN 92.6% of patients with IRRs) were of Grade 1 or 2 in intensity. Grade 3 IRRs were reported in one (0.1%) patient in the IFN group compared with 20 (2.4% of patients) patients in the OCR group.

PPMS population:

IRRs in the PPMS population occurred with higher incidence in patients treated with ocrelizumab relative to those in the comparator group (placebo 25.5% of patients and OCR 39.9% of patients).

There were 5 patients (1.0%) with a single occurrence of a serious IRR associated with an ocrelizumab infusion

Infections

The rate of infections was higher in RMS patients treated with ocrelizumab (84.5 per 100 patient years [PY]) compared with patients treated with interferon beta-1a (67.8 per 100PY) However, the rate of serious infections in RMS patients treated with IFN was higher (1.79 events per 100PY) compared with patients treated with ocrelizumab (0.83 per 100PY).

The rate of infections in PPMS patients treated with ocrelizumab was similar to the placebo group (71.7 per 100PY and 73.8 per 100PY, respectively). The rate of serious infections in PPMS patients was balanced between the placebo (2.88 per 100PY) and ocrelizumab (2.97 per 100PY) groups. This higher rate of serious infections in both arms of the PPMS study, compared with RMS patients, likely reflects the relative greater severity of PPMS.

The majority of infections were of Grade 1 or 2 intensity. There were no fatal infections in RMS patients treated with ocrelizumab. In the PPMS study, fatal infection was reported in two patients (0.4%) in the ocrelizumab group during the controlled treatment period (one case of pneumonia and one case of pneumonia aspiration).

Table 36 Serious Infections (broad definition) by Outcome – Clinical Studies in Multiple Sclerosis:

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

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

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

At the time of data cut-off there were no opportunistic infections in any MS patient treated with ocrelizumab including hepatitis B reactivation. One case of PML has been reported with the use of ocrelizumab, however, the patient had previously been treated with natalizumab. No fevers of unknown origin were identified. No disseminated herpetic infections were reported. However, herpes and candida infections did occur with slightly higher frequencies in the ocrelizumab groups than in the IFN and placebo groups.

Association of Neutropenia with Infections

Mean and median neutrophil levels did not change during treatment with ocrelizumab and the overall incidence of Grade 3 (<1.0-0.5 10^9 cells/µL) and Grade 4 (<0.5 10^9 cells/µL) neutropenia was low.

Marked (i.e., changes from baseline below a certain threshold), low neutrophil counts was reported in a higher percentage of patients in the OCR group compared with PBO group during controlled treatment in PPMS patients (4.6% vs 1.7%) and a higher percentage of Grade 2 or above neutropenia was seen in OCR group (4.3%, 21 patients) compared to placebo group (1.3%, 3 patients). Marked

low neutrophil counts in OCR treated patients were observed with similar frequencies also in OCR treated RMS population, Pool A (36 patients, 4.4%).

In the Phase III MS all exposure population (modified Pool B) Grade 4 neutropenia was reported in 8 ocrelizumab patients (2 in RMS, 5 in PPMS, and 1 in Phase 2 study WA21493 in RRMS) compared with none in the comparator (IFN/placebo) groups.

Regarding prolonged neutropenia, the current available data in MS programs did not allow for a proper assessment of the duration of the decrease in neutrophil counts due to wide intervals of scheduled assessments. Caution is needed as the review of the neutropenic SAEs revealed that in 2 of the 3 cases the patients received GCSF treatment. GCSF treatment was for 2 SAEs (febrile neutropenia and agranulocytosis) in 2 PPMS patients.

The clinical relevance of low neutrophil counts in relation to serious infection was assessed by comparing the rate per 100PY of serious infections reported during the episodes when neutrophil counts were confirmed to be below the LLN (< 1.96 x 109/L for at least two consecutive measurements) and the rate of serious infection per 100PY when neutrophil counts were confirmed to be below the LLN. Based on the results of these analyses, in the Phase III MS all exposure population (modified Pool B), an increase in the rate per 100PY of serious infections during confirmed neutrophils below LLN (3.24 [; 95% CI: 0.39, 11.70) was observed as compared with those without confirmed neutrophils below LLN (1.85 95% CI: 1.49, 2.28). Conversely, no association with serious infections was observed in the decreased neutrophil counts in RMS and in PPMS controlled treatment population.

The rheumatoid arthritis OCR development program indicated a higher risk of neutropenia with OCR (OCR 400 mg: 6.2%; OCR 1000 mg: 7.4) compared to PBO (2.9%).

Association of Immunoglobulin Levels with Infections

Table 37 Association of Levels of Immunoglobulins with Infections - MS All Exposure Population (Pool B):

	All Patients N = 2147 4484.5 PY	Pts with IgA <LLN N = 61 170.1 PY	Pts with IgG <LLN N = 121 410.2 PY	Pts with IgM <LLN N = 426 1190.8 PY
Infections				
No. of events	3486	125	285	895
Events per 100PY	77.7	73.48	69.48	75.16
95% Confidence Interval	75.2, 80.4	61.16,87.55	61.65, 78.04	70.31, 80.25
Serious Infections				
No. of events	104	8	14	36
Events per 100PY	2.32	4.70	3.41	3.02
95% Confidence Interval	1.90, 2.81	2.03, 9.27	1.87, 5.73	2,12, 4.19

PY = patient years; LLN = lower limit of normal.

Infections in RA Studies and other populations

In contrast to observations in the MS population, an imbalance in serious and opportunistic infections was observed in the RA population, including, but not limited to atypical pneumonia and pneumocystis jirovecii pneumonia, varicella pneumonia, tuberculosis and histoplasmosis. In rare cases, some of these infections were fatal. The rate of serious infections was higher in the immunosuppressant plus ocrelizumab1000 mg group (7.28 per 100PY) compared with the immunosuppressant plus 400 mg (5.18 per 100PY) or immunosuppressant plus placebo (3.99 per 100PY) group.

Serious infections were reported in 3 patients in the SLE trial (WA20499) and in 64 patients in the LN trial (WA20500). Among the 3 patients from the SLE trial, two patients developed opportunistic infections (cytomegalovirus [CMV] retinitis and pneumocystis jiroveci pneumonia) and both died (due to upper respiratory infection and pneumocystis, respectively). The third patient had an SAE of pneumonia, which resolved without sequelae. Among the 64 patients in the LN trial who developed a serious infection, eight patients died from the serious infection (due to Legionella infection, pneumonia, sepsis, urosepsis and septic shock).

Of the 10 fatal infection cases, all patients were treated with concomitant immunosuppressants which likely contributed to their fatal outcome.

Malignancies

RMS Pool A

The rate per 100PY of malignancy was 0.14 (95% CI: 0.02, 0.52) for the IFN group and 0.28 (95% CI: 0.08, 0.71) for the OCR group. These were reported in two (0.2% of patients) patients in the IFN group (PTs of mantle cell lymphoma and squamous cell carcinoma) and 4 (0.6%) patients in the OCR group (PTs of renal cancer, malignant melanoma, and two cases of invasive ductal breast carcinoma).

PPMS

The rate per 100PY of malignancy events was 0.30 (95% CI: 0.04, 1.10) for the placebo group and 0.92 (95% CI: 0.49, 1.57) for the OCR group.

Table 38 Incidence Rates per 100PY of Malignancy in MS Patients (Pool B) Compared with Literature Reports:

Type	ISS (PY = 4467)	3-Month Safety Update (PY = 5684)	Comparator (IFN and placebo)[a]	Pooled MS CT data (placebo)[b]	Epidemiology
Malignancies	0.425 (0.256, 0.664)	0.440 (0.285, 0.649)	0.195 (0.053, 0.499)	0.50 (0.36, 0.67)	0.67 (0.63, 0.71)[c]
Malignancies without NMSC	0.336 (0.188, 0.554)	0.317 (0.188, 0.500)	0.097 (0.012, 0.352)	0.33 (0.20, 0.50)	0.37 (0.32, 0.43)[d]
Breast Cancer (female)	0.261 (0.105, 0.538)	0.233 (0.101, 0.459)	0 (0-0, 293)	0.16 (0.06, 0.32)	0.21 (0.18, 0.23)[c] 0.14 (0.11, 0.16)[d]
NMSC	0.090 (0.024, 0.229)	0.123 (0.050, 0.254)	0.097 (0.012, 0.352)	0 to 0.42 (0, 0.9)[b,e]	0.19 (0.15, 0.24)[d]

CT = clinical trials; IFN = interferon beta-1a; MS = multiple sclerosis; NMSC = non-melanoma skin cancer; OCR = ocrelizumab; PPMS = primary progressive multiple sclerosis; PY = patient years; RMS = relapsing forms of multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis.

Note: Pool B = MS all exposure population (OCR data from Phase III RMS studies WA21092, WA21093; Phase II RRMS Study WA21493, and Phase III PPMS Study WA24056).

The Incidence rate reported for NMSC using pooled MS CT data (placebo) presented in the ISS (ISS Table 105) was incorrect due to typographical error. The value (as shown above) has been corrected for the 3-month Safety Update Report.

RA Population

The rate per 100PY of malignancy was comparable between placebo (1.11; 95% CI: 0.53, 2.04), OCR 400 mg(0.90; 95% CI: 0.41, 1.70) and OCR 1000 mg(1.32; 95% CI: 0.68, 2.31) groups. There was no other particular type of malignancy which occurred in more than 2 patients in any group.

Autoimmune disorders

Across the MS development program (Pool B), AEs related to autoimmune disorders were reported in 12 patients (0.6%) receiving OCR. Multiple sclerosis was the most common autoimmune disorder reported as an AE (0.3%, 7 patients) with few reports of other PTs (single cases of immune thrombocytopenic purpura, autoimmune uveitis, alopecia areata and 2 cases of autoimmune thyroiditis).

Suicide and Depression

Suicide and Depression Events by Class and PT – Phase III RMS Controlled Treatment Population (Pool A):

Summay of Suicide & Depression Event by Body System Class and Preferred Term, Pool A: Phase III RMS Controlled Treatment Population
Protocol(s) : WA21092 / WA21093

MedDRA System Organ Class MedDRA Preferred Term	IFN beta-1a (N=826)	OCR 600mg (N=825)
Total number of patients with at least one adverse event	65 (7.9%)	70 (8.5%)
Overall total number of events	76	78
PSYCHIATRIC DISORDERS		
Total number of patients with at least one adverse event	65 (7.9%)	70 (8.5%)
Total number of events	76	78
DEPRESSION	54 (6.5%)	64 (7.8%)
DEPRESSED MOOD	9 (1.1%)	3 (0.4%)
SUICIDAL IDEATION	4 (0.5%)	2 (0.2%)
COMPLETED SUICIDE	1 (0.1%)	1 (0.1%)
DEPRESSION SUICIDAL	2 (0.2%)	0
MAJOR DEPRESSION	1 (0.1%)	0
SUICIDE ATTEMPT	0	1 (0.1%)

Investigator text for AEs encoded using MedDRA version MedDRA v18.0
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately.
Suicide and depression are identified using Adverse events falling into the Standard MedDRA Query 'Depression, suicide, self-injury (narrow)'.

Program: /opt/BIOSTAT/prod/cdt3422z/t_ae.sas
Output: /opt/BIOSTAT/prod/cdt3422s/s03422a/reports/t_ae_SUIC_spa.out
09OCT2015 19:45 Page 1 of 1

Suicide and Depression Events by Class and PT – Phase III PPMS Controlled Treatment Population:

Suicide and Depression Event by Body System Class and Preferred Term. Controlled Treatment Period, Safety-Evaluable Population
Protocol: WA25046

MedDRA System Organ Class MedDRA Preferred Term	Placebo (N=239)	OCR 600mg (N=486)
Total number of patients with at least one adverse event	33 (13.8%)	47 (9.7%)
Overall total number of events	37	50
PSYCHIATRIC DISORDERS		
Total number of patients with at least one adverse event	33 (13.8%)	47 (9.7%)
Total number of events	37	50
DEPRESSION	30 (12.6%)	37 (7.6%)
DEPRESSED MOOD	3 (1.3%)	8 (1.6%)
SUICIDE ATTEMPT	0	2 (0.4%)
DEPRESSION SUICIDAL	0	1 (0.2%)
DYSTHYMIC DISORDER	1 (0.4%)	0
SUICIDAL IDEATION	0	1 (0.2%)

Suicide and depression are identified using Adverse events falling into the Standard MedDRA Query 'Depression, suicide, self-injury (narrow)'.
Investigator text for AEs encoded using MedDRA version MedDRA v18.0.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdt3422z/z25046a/t_ae.sas
Output: /opt/BIOSTAT/prod/cdt3422h/u25046a/reports/t_ae_SUIC_CNTR_SE_046.out
23NOV2015 14:57 Page 1 of 1

Serious adverse event / deaths / other significant events

Serious adverse events

Pool A RMS:

The rate of SAEs estimated per 100PY (SAEs per 100PY) was numerically higher in the IFN group with overlapping CIs (IFN 6.29; 95% CI: 5.05, 7.75 and OCR 5.39; 95% CI: 4.26, 6.72).

Table 39 Serious Adverse Events Reported in ≥1% of Patients by System Organ Class – Phase III RMS Controlled Treatment Population (Pool A):

System Organ Class	IFN (N = 826)	OCR (N = 825)
Infections and Infestations	24 (2.9%)	11 (1.3%)
Nervous System Disorders	11 (1.3%)	8 (1.0%)
Injury, Poisoning, and Procedural Complications	10 (1.2%)	6 (0.7%)

IFN = interferon beta-1a; N = number of patients; OCR = ocrelizumab. Note: Results represent: N of patients (% based on N in the column heading).

PPMS :

The rate per 100PY of SAEs overall was similar between treatment groups (placebo 11.7; 95% CI: 9.21, 14.6 and OCR 10.2; 95% CI: 8.64, 12.1). The rates of SAEs varied by dose throughout the

controlled treatment period with no clear trend in rates between placebo and OCR group or with subsequent dosing

Table 40 Serious Adverse Event Reported in ≥1% of Patients by System Order Class – Phase III PPMS Controlled Treatment Population:

System Organ Class	Placebo (N = 239)	OCR (N = 486)
Infections and Infestations	14 (5.9%)	30 (6.2%)
Injury, Poisoning, and Procedural Complications	11 (4.6%)	6 (3.9%)
Nervous System Disorders	9 (3.8%)	18 (3.7%)
Neoplasms Benign, Malignant and Unspecified	7 (2.9%)	8 (1.6%)
Gastrointestinal Disorders	3 (1.3%)	10 (2.1%)
Musculoskeletal and Connective Tissue Disorders	6 (2.5%)	6 (1.2%)
General Disorders and Administrative Site Conditions	3 (1.3%)	6 (1.2%)
Renal and Urinary Disorders	3 (1.3%)	5 (1.0%)

Deaths:

Death was reported in 11 patients (3 patients who were receiving or had received placebo or IFN and 8 patients who were receiving or had received ocrelizumab). In Pool A, there were 3 death reported: two patients in the IFN group (suicide, mechanical ileus) and one patient in the OCR group (suicide). In PPMS during the controlled treatment period, there were 5 deaths reported: one patient (0.4%) in the placebo group (road traffic accident) and 4 patients (0.8%) in the OCR group (pulmonary embolism, pneumonia, pancreatic carcinoma metastatic, pneumonia aspiration).

Laboratory findings

RMS Pool A:

The most common marked laboratory abnormalities were increases in liver enzymes including alanine aminotransferase (ALT) and aspartate aminotransferase (AST) which occurred at higher frequencies in the IFN than in the OCR group (ALT: IFN 17.7% and OCR 5.1% patients with abnormalities and AST: IFN 10.1% and OCR 2.2% patients with abnormalities.

The proportion of patients with marked decreases in neutrophils was higher in the IFN (18.2%) than in the OCR (4.4%) group. In the majority of patients in the OCR group, marked decreases in neutrophils were single occurrences with only 0.1% of patients reporting replicated marked decreases in neutrophils. In the IFN group, 7.0% of patients had marked decreases in neutrophils that were replicated.

CD19+ B Cells

Treatment with ocrelizumab led to a rapid depletion of CD19+ B cells in blood with near complete depletion at Week 2. The median time to repletion (return to baseline or LLN, whichever was lower) of B cells was 72 weeks (range 27 to 175 weeks) after the last infusion.

Other FACS Analyses (CD3+, CD4+, CD8+, CD16+56+Cells)

Following the first infusion of ocrelizumab, there was a small initial decrease in CD3+, CD4+ and CD8+ T cell counts. Thereafter, mean cell counts remained stable until week 96. Larger decreases were observed in the CD3+, CD4+ and CD8+T cell counts in the IFN group through 96 weeks.

There was no impact of treatment with ocrelizumab on NK lymphocyte counts across the controlled treatment period. Treatment with interferon beta-1a resulted in significant decreases in NK lymphocyte counts at Week 12, which then stabilized at this level and remained stable over the controlled treatment period.

Immunoglobulins

The proportion of patients, at baseline, reporting IgG, IgA and IgM below the lower limit of normal (LLN) in the ocrelizumab group was 0.5%, 1.5% and 0.1% respectively. Following treatment, the proportion of ocrelizumab-treated patients reporting IgG, IgA and IgM below the LLN at 96 weeks was 1.5%, 2.4% and 16.5%, respectively.

PPMS:

The proportion of patients with marked increases in AST or ALT was similar to placebo. The proportion of patients that presented with markedly low levels of neutrophils was higher in the OCR group (4.6%) than in the placebo group (1.7%). However, only 0.6% of ocrelizumab-treated patients (none in the placebo group) had markedly decreased levels of neutrophils that were replicated.

The pattern was similar to the RMS Pool A population with regards to immunoglobulins, (CD3+, CD4+, CD8+, CD16+56+-Cells), and CD19+ B Cells, except placebo did not have an effect on these parameters.

Safety in special populations

Weight

The rate of adverse events and SAEs including infections were higher in patients with a baseline body weight ≥ 75 kg.

Age

Ocrelizumab has not been studied in patients younger than 18 years and older than 55 years.

Safety in Subgroups of Different Disease Activity

The adverse event profile within each of the four subgroups was consistent with the adverse event profile of the overall safety population. This includes the total number of patients who experienced an AE, SAE, or serious infection.

Table 41 Subgroups of Different Disease Activity – Adverse Event profile:

	Subgroup 1 Active Inadequate Responders		Subgroup 2 Active Treatment Naive		Subgroup 3 Highly Active Inadequate Responders		Subgroup 4 Highly Active Naive		RMS Safety population in Controlled Treatment Period)	
	IFN N=148	OCR N= 153	IFN N= 311	OCR N= 322	IFN N= 140	OCR N= 143	IFN N= 107	OCR N= 112	IFN N=826	OCR N= 825
Total number of patients with at least 1 AE	121 (81.8%)	129 (84.3%)	260 (83.6%	266 (82.4%)	114 (81.4%)	119 (83.2%)	92 (86.0%	94 (83.9%)	688 (83.3%)	687 (83.3%)
Total number of patients with at least 1 SAE	12 (8.1%)	10 (6.5%)	26 (8.4%)	22 (6.8%)	12 (8.6%)	9 (6.3%)	11 (10.3%)	5 (4.5%)	72 (8.7%)	57 (6.9%)
Total number of patients with at least 1 serious Infection (SOC)	4 (2.7%)	5 (3.3%)	8 (2.6%)	1 (0.3%)	4 (2.9%)	4 (2.8%)	5 (4.7%)	0	24 (2.9%)	11 (1.3%)

AE adverse event; IFN interferon beta-1a; OCR ocrelizumab; SAE serious adverse event; SOC MedDRA system organ class.

Concomitant Steroid Use (yes/no)

The rate per 100PY of AEs in patients who received steroids was higher in both the IFN and OCR groups. Within each subgroup, the rate of AEs was similar between IFN and OCR treatments.

In the OCR group, SAEs were reported at a higher rate per 100PY in patients receiving steroid treatment (8.87; 95% CI: 5.74, 13.1) compared with those not on steroid treatment (4.55; 95% CI: 3.41, 5.95). In the IFN group, SAE rates were similar between steroid (6.82; 95% CI: 4.53, 9.86) and non-steroid (6.07; 4.63, 7.81) subgroups. In the OCR group, infections were also reported at a higher rate per 100PY in patients receiving steroid treatment (102; 95% CI: 91.0, 115) compared with those not on steroid treatment (81.3; 95% CI: 76.2, 86.7). In the IFN group, infection rates were similar between steroid (76.7; 95% CI: 68.5, 85.7) and non-steroid (65.9; 95% CI: 60.9, 71.1) subgroups.

When patients were stratified by regional subgroups (EU/Switzerland/Norway, Latin America, Non-EU/Israel/Africa, or USA/Canada/Australia), the rate per 100PY of AEs was highest in the USA/Canada/Australia subgroup compared with all other subgroups

Diabetes (yes/no)

The rate per 100PY of AEs was higher in diabetic patients (321; 95% CI: 292, 352) compared with non-diabetic patients (251; 95% CI: 247, 256). There was also a higher rate of SAEs in diabetic patients (12.6; 95% CI: 7.46, 19.9) compared with non-diabetic patients (6.79; 95% CI: 6.04, 7.62).

Regional Subgroups

When patients were stratified by regional subgroups (EU/Switzerland/Norway, Latin America, Non-EU/Israel/Africa, or USA/Canada/Australia), the rate per 100PY of AEs was highest in the USA/Canada/Australia subgroup compared with all other subgroups.

Use in Pregnancy and Lactation

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

B cell levels in human neonates following maternal exposure to ocrelizumab have not been studied in clinical trials. There are no adequate and well-controlled data from studies in pregnant women; however transient peripheral B cell depletion and lymphocytopenia have been reported in infants born

to mothers exposed to other anti-CD20 antibodies during pregnancy. A search of the Roche Global Safety Database using the pregnancy flag and the Standardized MedDRA Query (SMQ) Pregnancy and neonatal topics identified a total of 46 patients administered at least one OCR infusion who became pregnant during clinical study participation (15 MS patients [1.1% of female patients in Pool B], 21 RA patients [0.9% of female patients in Pool E], and 10 LN patients [4.3% of female LN patients]). An abnormal pregnancy/ fetal or neonatal finding was reported in 20 cases. This includes 11 cases reporting a spontaneous fetal loss (spontaneous abortion, missed abortion, anembryonic pregnancy, or fetal death) in 10 patients (since one patient experienced two sequential spontaneous abortions 1.5 years apart), and nine cases of premature delivery and/or an abnormal finding in a live born baby. The rates of spontaneous foetal loss and premature birth reviewed in this dataset were similar or lower than the rates reported in the literature.

In total, six cases with an abnormal finding in the baby were reported; among these, there were three cases reporting the following four adverse events classified as a structural malformation: small renal cyst, benign nasopharyngeal neoplasm, congenital positional feet contracture and limited hips abduction. As regards to the finding reported as benign nasopharyngeal neoplasm, since neither the results of the histopathological analysis nor a final diagnosis was provided, a full assessment of this case is impossible. However, as the last OCR infusion was administered approximately 6 months prior to conception, this embryo/foetus is not considered to have been exposed to OCR in utero and a causal relationship of the event to OCR unlikely. The second case with events that the MAH classified as structural malformations reported a full term new born baby with congenital positional feet contracture and limited hips abduction. Conception occurred approximately three months after the last OCR infusion given for RA. The mother had concomitantly taken methotrexate, a known teratogen, (during four weeks) up to four months prior to the conception. Due to the temporal association, the MAH considers it unlikely that either drug played a contributory role for the abnormal findings. The third case with a structural malformation is a report of a small renal cyst. Since the last OCR infusion for LN was administered three years before conception, this foetus is not considered in utero exposed to OCR and the event assessed as unrelated to OCR. Among the six cases reporting an abnormal finding in a live born baby, there was a case of infection (sepsis) in a newborn baby. Since conception occurred nearly 10 months after the last OCR dose, this foetus is not considered to have been transplacentally exposed to OCR. However, an embryo/foetus considered not transplacentally exposed to OCR may still be affected indirectly by the OCR induced B-cell depletion in the pregnant mother. The sixth case with an abnormal finding was a normal baby with low birth weight (2.31 kg, length 48.3 cm) at 39-week gestation. CD-19 cell counts tested in the baby were not available in any of the reviewed cases.

The overall rate of birth defects (defined as any abnormality affecting body structure or function), in this dataset is 12.5% (6/48), which is higher than the 3.3% reported by the CDC in the general population. No appropriate publications could be found in the literature that describes the rate of birth defects in MS, RA or SLE patients. The rate of events classified by the MAH as structural malformations in this dataset is 6.25% (3/48), which is higher than that reported for the general population (2–3%), but within the range of malformations reported in published studies in the MS population treated with other DMTs. However, this classification may be very conservative and it is of note that none of the three embryos/foetuses are considered to have been exposed to OCR in utero. A multi-source non-interventional PASS will assess and characterize pregnancy and infant outcomes of women with MS exposed to OCR during the six months before the estimated date of conception or at any time during pregnancy.

A patient (#1930433, from study WA21093 site 209771, PI: Prof Azra Alajbegovie, were GCP non compliance have been reported) became pregnant during the study conduct and delivered a stillborn baby under unclear circumstances, and a report was duly filed with the Bosnian Competent Authority.

Safety post last dose of OCR (Phase III MS All exposure, Pool B excluding Phase II

There are limited data regarding safety post-last dose. Section 5.1 of the SmPC provides information on the long lasting pharmacodynamics effect of ocrelizumab and as such, the prescriber is presented with the knowledge currently available.

Table 42 Number of Patients and Patient-Years Available after First Infusion of Last Dose - Phase III MS All Exposure Population (Pool B excluding Phase II):

Number of Patients and Patient-Years from First Infusion of Last Dose, Pool B: Phase III MS All Exposure Population
Protocol(s) : WA21092 / WA21093 / WA25046

Ocrelizumab	All Exposure (N=146)
Total number of patients post the last infusion	146
Total patient years of observation time post last infusion	159.305

Number of patients and observation time in patient years	n	Patient years
<=24 weeks	11 (7.5%)	3.232
>24 to <=48 weeks	40 (27.4%)	27.946
>48 to <=72 weeks	60 (41.1%)	67.060
>72 to <=96 weeks	21 (14.4%)	31.328
>96 to <=120 weeks	11 (7.5%)	21.558
>120 to <=144 weeks	2 (1.4%)	4.672
>168 to <=192 weeks	1 (0.7%)	3.509

Only patients who entered safety follow up period are included in the analysis.
Percentages are based on number of patients that entered safety follow-up.
Exposure in patient-years during safety follow up is counted from first infusion of last Dose up to the last known alive date while reporting.

Table 43 Serious Adverse Events in 100 Patient Years During Safety Follow-up - Phase III MS All Exposure Population (Pool B excluding Phase II):

	Intervals of Safety Follow-up in Weeks					
Weeks	**< 24**	**> 24- ≤ 48**	**> 48- ≤ 72**	**> 72- ≤ 96**	**> 96- ≤ 120**	**> 120- ≤ 144**
Patient N	146	135	95	35	14	3
PY	65.3	53.2	28.0	8.8	2.7	0.53
Overall						
Patients with at least one event	26 (17.8%)	4 (3.0%)	2 (2.1%)	1 (2.9%)	0	0
Number of Events	30	4	2	1	0	0
Rate per 100PY	45.9	7.51	7.15	11.4	0.0	0.0
SOC with most frequent SAEs (Patients with at least one event)						
Infections and Infestations	8 (5.5%)	0	1 (1.1%)	0	0	0
Benign Neoplasm and Malignancies	6 (4.1%)	0	1 (1.1%)	0	0	0
Nervous System Disorders	5 (3.4%)	0	0	1 (2.9%)	0	0
Serious Infections based on broader definition[1]						
Patients with at least one event	9 (2.6%)	1 (0.7%)	1 (1.1%)	0	0	0
Number of Events	12	1	1	0	0	0
Rate per 100PY	18.4	1.88	3.58	0.0	0.0	0.0

PY = patient years; SAE = serious adverse event; SOC = system organ class.

[1]Infections falling into MedDRA class infections or any SAE for which a pathogen was identified. Serious is defined as indicated serious on the CRF by the investigator or based on whether or not IV anti-infective was given.

Immunological events

Hypersensitivity

No cases fulfilled the criteria for anaphylactic reactions or DRESS.

Antibody Titers

Ocrelizumab did not appear to have an effect on specific humoral immunity to common bacterial and viral antigens over the 96-week study period (*S. pneumonia*, mumps, rubella, varicella zoster). The proportions of patients with positive antibody titers against rubella, mumps and varicella at Week 96 were similar to the proportions at baseline.

Anti-Drug Antibodies

The baseline prevalence of ocrelizumab ADAs in both treatment groups was <1%, and the titers of these ADAs did not increase post treatment.

In the RMS population, 0.4% (3 patients) showed positive (treatment-induced and –enhanced) ocrelizumab ADAs. Of these, one patient tested positive for neutralizing antibodies to ocrelizumab. No IRRs or other relevant adverse events such as hypersensitivity reactions were observed in the patient who developed neutralizing antibodies.

In the PPMS population 9 patients (1.9%) showed positive (treatment-induced and –enhanced) ocrelizumab ADAs. Of these, one patient tested positive for neutralizing antibodies to ocrelizumab. The patient who developed neutralizing antibodies did not experience an IRR or hypersensitivity reactions.

Nine patients (3.8%) in the placebo group tested ADA positive for ocrelizumab post-baseline. These results reflect the fact that the ADA tests were designed to have an untreated positive rate of 5% in the screening assay and 1% in the confirmatory assay.

Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction studies have been performed, as no drug-drug interactions are expected via the CYP and other metabolizing enzymes or transporters for a monoclonal antibody like ocrelizumab.

Discontinuation due to adverse events

RMS Pool A

The incidence was higher in the IFN group (6.2%; 51 patients) compared with the OCR group (3.5%; 29 patients). The primary AEs leading to withdrawal reported with a higher incidence in the IFN group were influenza-like illness, fatigue, injection site reaction, liver function test abnormalities, and abnormalities in creatine phosphokinase levels (increased) or in platelet or leukocyte counts, neutropenia or leukopenia.

In the OCR group, the primary AE leading to withdrawal occurring with a higher incidence compared with IFN was IRR; reported in 11 patients in the OCR group and none in the IFN group.

PPMS

The proportion of patients withdrawn from study treatment due to an AE was similar between groups (placebo 3.3% and OCR 4.1%). The primary AEs by SOC leading to withdrawal were balanced between the placebo and OCR group with the exception neoplasm Benign, Malignant and Unspecified (placebo 1 patient [0.4%] and OCR 7 patients [1.4%]), infections and Infestations (placebo 3 patients [1.3%] and OCR 4 patients [0.8%]). AEs in all other SOCs were balanced between the placebo and OCR groups. The AEs leading to withdrawal by PT reported in more than one patient were invasive ductal breast carcinoma (placebo 0 patients [0%], OCR 2 patients [0.4%]), MS relapse (placebo2 patients [0.8%], OCR 1 patient [0.2%]) and IRR (placebo 1 patient [0.4%], OCR 2 patients [0.4%]).

Post marketing experience

N/A

2.6.1. Discussion on clinical safety

A sufficiently large safety database is available. It includes 825 RMS patients from two pivotal Phase 3 studies (1448 patient years of exposure, Pool A); 486 PPMS patients from one pivotal Phase 3 study (1416 patient years of exposure; PPMS) and 2147 patients in the MS all exposure population which also includes a Phase 2 study in RMS patients and the open-label extension periods of the studies mentioned (4485 patient years of exposure; Pool B). At least 1173 MS patients have been exposed to the proposed dose 600 mg dose for more than 95 weeks. However, long-term exposure data do not

allow conclusive evaluation of the risk of malignancies as well as rare risks, such as PML. The RMS and PPMS patient population included in the controlled MS trials is a selected patient population, not entirely representative of the MS patient population target of the two claimed indications. For instance median age of PPMS enrolled patients was 46 years and the baseline EDSS score of patients included in the studies was up to 6.5 in PPMS and 5.5 in RMS. Patients with a history of recurrent or chronic infections or immunodeficiency, and patients with a history of ischemic cerebrovascular disorders were excluded. Cardiovascular disease was not among exclusion criteria, but there was only one enrolled patient with a history of cardiovascular disease (SMQ cardiac failure).

There is no information regarding patients older than 55 years. The absence of safety data in patients ≥55 years of age requires a more cautious approach with regard to the observed imbalance in malignancies, including breast cancer, observed in OCR-treated patients relative to comparator (IFN or placebo), as it is well known that the risk of malignancies increases with age.

Additional supportive safety data are available from 2926 patients (7324 patients years) exposed to ocrelizumab in a dose range of 20 mg to 2000 mg in a terminated development programme in patients with rheumatoid arthritis (RA). Further safety data are available from a limited number of patients with Systemic lupus erythematosus (SLE) and lupus nephritis (LN). These programmes were terminated due similar safety issues (serious and opportunistic infections) and insufficient efficacy. Following CHMP request, the Applicant extensively discussed possible explanations for the unfavourable safety profile observed in the ocrelizumab RA clinical development program compared to rituximab, which is used in clinical practice in combination with methotrexate in the same setting as the one of ocrelizumab RA Phase III trials [treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARD) including one or more tumour necrosis factor (TNF) inhibitor therapies]. The Applicant stated that given the many differences between the OCR and RTX RA development programs (including differences in patient populations, use of concomitant medications, functional differences between the two molecules [conferring different activity in vitro], and dose and dose regimen differences), it is difficult to draw any definitive conclusions in regard to the different safety profiles. Even though both RTX and OCR target CD20, these are different molecules, with functional differences [conferring different activity in vitro]. These differences between RTX and OCR warrant a cautious approach in using the rituximab clinical data to exclude the relevance of safety issues that emerged from the OCR clinical development program, such as the imbalance in malignancies between the active and the control group.

Comparing ocrelizumab to IFN treatment, the discontinuation rate was lower in the ocrelizumab group (3.5%) than in the IFN group (6.2%). The number of patients to experience an AE including a serious adverse event was similar in the IFN beta-1a group and the ocrelizumab group. As expected adverse event such as influenza like symptoms, injection site reactions, myalgia, pruritus, increased hepatic transaminase and headache were common in the IFN beta-1a group and occurred more frequently than in the ocrelizumab group.

In the PPMS trial, slightly more patients experienced adverse events in the ocrelizumab compared to placebo (95% vs. 90%). The frequency of adverse events by Grade were similar in the two treatment groups. The rate of discontinuation was slightly higher in the ocrelizumab group compared to placebo.

Analysis of safety in subgroups with different disease activity did not show any difference, although the number of events in some subgroups were low which precludes firm conclusions.

The main safety issues with the use of ocrelizumab are infusion related reactions (IRR), an increased risk of infections and a higher frequency of malignancies in the ocrelizumab groups. IRRS occurred more frequently in the ocrelizumab group (34.3%-39.9%) compared to IFN (9.7%) and placebo (25.5%). All patients were pretreated with 100 mg methylprednisolone to reduce the risk of IRRs. Patients who also received antihistamines had a twofold reduced risk of IRRs. Pretreatment with antihistamines is considered mandatory**.** The IRR symptoms observed with ocrelizumab treatment were primarily pruritus, rash, throat irritation and flushing. Most were Grade 1 or 2 in intensity and only one patients had a Grade 4 IRR in the RMS studies. There were 5 serious IRRs in the PPMS study. Most

IRRs occurred with the first infusion and the incidence subsequently decreased. Splitting the 600 mg dose into two with a two weeks separation in the PPMS trial did not reduce the overall risk of IRRs. Most IRRs were manageable which is reflected in the discontinuation rate; 0.4% in the PPMS trial and 1.3% in the RMS studies discontinued due to IRRS in the ocrelizumabs groups. In most IRR events (78% in the Phase 3 RMS controlled treatment population, Pool A and in 77% in PPMS) symptomatic therapy for the management of IRR symptoms in addition to the slow down or interruption of the infusion was administered. In the remaining 22% of the IRR events in Pool A (23% in PPMS) no additional intervention was necessary and the slow down or interruption of the infusion was sufficient to resolve the IRR event. The need to reduce the infusion rate in case of IRR is adequately reflected in the SmPC in section 4.2.

Muscle spasticity was observed in one case of serious IRR. However, muscle spasticity as a symptom of IRR was only reported in 2 PPMS patients as of 20 January 2016, across all PPMS, RMS and RA populations, thus it was concluded not to consider muscle spasticity as a true symptom of IRR. During the controlled treatment period 12 patients were ADA positive and two patients also tested positive for neutralizing antibodies. The information provided in the SmPC for the prescriber, that the impact of treatment-emergent ADAs on safety and efficacy cannot be assessed given the low incidence of ADA associated with Ocrevus is considered adequate.

Infections occurred more frequently (rates per 100PY) with ocrelizumab (85.4; 95% CI: 80.7, 90.3) than with IFN (69.1; 95% CI: 64.8, 73.5). The largest difference was seen in viral infections, 26.5% vs. 20.5%, although bacterial infections also occurred more frequently in the ocrelizumab group, 21.6% vs. 18.6%. However, serious infections including non-serious infection requiring IV anti-infective treatment occurred more frequently in the IFN group, 3.8% vs. 1.8% in the ocrelizumab group, and was primarily of bacterial origin. While the rate of serious infections in the overall RMS population was higher in patients treated with IFN (1.79 events per 100 PY) compared with patients treated with OCR (0.83 per 100 PY), in the subgroup of subjects with lymphocytes confirmed to be <LLN (defined as counts < LLN for at least 2 consecutive measurements), higher rates of serious infections were observed in OCR treated patients (4.22) compared to IFN treated patients (0).
Similarly to what was observed in the RMS population, while the rate of serious infections in the overall PPMS population was similar in patients treated with OCR (2.97 events per 100 PY) and in patients treated with PBO (2.88 per 100 PY), in the subgroup of subjects with lymphocytes confirmed to be <LLN, higher rates of serious infections were observed in OCR treated patients (7.93) compared to PBO treated patients (0).

Even though the number of events is low, and thus the confidence intervals partially overlap, these data have a strong biological plausibility: in patients that are B cell depleted, if also the overall number of lymphocytes decrease, these patients are at increased risk of infections.

Furthermore, more patients in the ocrelizumab group experienced Grade 4 (1.6% vs. 0.4%), and Grade 5 (death) (0.4% vs. 0%) infections. The higher frequency of life threatening serious infections and of serious infection leading to death in OCR treated patients compared to comparators was confirmed in the 3-month safety update (CCOD 20 January 2016) (OCR: 12/ 1311, 0.9% vs PBO/IFN: 1/1065, 0.09%). A worse outcome of serious infections is a concern with a B cell depleting therapy, as it is well known that in a real world setting a higher frequency of serious infection will be observed, and this will potentially lead to a higher mortality. The Applicant has introduced a specific warning statement in the SmPC regarding increased risk of life-threatening infections associated with the development/presence of dysphagia. It is noteworthy that the rate of infections leading to withdrawal was slightly lower in the ocrelizumab group than in the placebo group. This means that that most of the infections which occur with ocrelizumab use is not treatment limiting.

Opportunistic infections, herpes and candida infections, in the RMS studies occurred more frequently in the ocrelizumab group. The overall rate of events per 100PYwas 2.79 (95% CI: 1.98, 3.81) in the IFN group and 5.25 (95% CI: 4.14, 6.57) in the ocrelizumab group. However, in the PPMS trial the overall rate of events per 100PY was 3.03 (95% CI: 1.85, 4.68) in the placebo group and 2.33 (95% CI: 1.60, 3.27) in the ocrelizumab group. There were no hepatitis B reactivation. One case of PML has been reported with the use of ocrelizumab, however, the patient had previously been treated with

natalizumab In one case of neutropenic sepsis available data do not allow neither to confirm nor to exclude the opportunistic nature of the event due to insufficient information.

At the CCOD for the 3-month safety update, the incidence of serious infection (including non-serious infections requiring IV antiinfectives) in Pool C (Phase 3 RMS All Exposure population), increased from 2.1% (37 events in 31 patients reported in the ISS) to 3.5% (62 events in 51 patients). This increase was due primarily to more serious pneumonia events reported in 7 additional patients. Increased rates of serious infection were observed in RMS patients and in Pool B over time (beginning at Dose 5). To assess if the increase in serious infection over time was related to duration of ocrelizumab exposure, the rate of serious infection was assessed in those Pool C patients who were initially randomized to the OCR group before entering open-label ocrelizumab treatment compared with those patients initially randomized to the IFN group who began open-label ocrelizumab treatment after completion of the 96-week controlled treatment period. By dose, the rate of serious infection increased, specifically beginning at Dose 5, in those patients initially randomized to the OCR group. In those patients randomized to the IFN group, the rates of serious infection remained stable over time and similar to those reported with Dose 1 through Dose 3 in patients randomized to the OCR group in the ISS. An increase in the rate of serious infections was observed in RMS between Years 2 and 3, but not in subsequent years. No increase was observed in PPMS.

Neutropenia (including prolonged neutropenia) is listed as an important identified risk for rituximab. Marked low neutrophil counts was reported in a higher percentage of patients in the OCR group compared with PBO group during controlled treatment in PPMS patients (4.6% vs 1.7%) and a higher percentage of Grade 2 or above neutropenia was seen in OCR group (4.3%, 21 patients) compared to placebo group (1.3%, 3 patients). Marked low neutrophil counts in OCR treated patients were observed with similar frequencies also in the RMS controlled treatment population (36 patients, 4.4%). In the Phase III MS all exposure population (modified Pool B) Grade 4 neutropenia was reported in 8 ocrelizumab patients (2 in RMS, 5 in PPMS, and 1 in Phase 2 study WA21493 in RRMS) compared with none in the comparator (IFN/ placebo) groups. In the Phase III MS all exposure population (modified Pool B), an increase in the rate per 100PY of serious infections during confirmed neutrophils < LLN (< 1.96 x 109/L for at least two consecutive measurements) (3.24 [; 95% CI: 0.39, 11.70) was observed compared with without confirmed neutrophils < LLN (1.85 95% CI: 1.49, 2.28). Conversely, no association with serious infections was observed in the decreased neutrophil counts in RMS and in PPMS controlled treatment population. Also the rheumatoid arthritis OCR development program indicated a higher risk of neutropenia with OCR (OCR 400 mg: 6.2%; OCR 1000 mg: 7.4) compared to PBO (2.9%). Regarding prolonged neutropenia, the current available data in MS programs do not allow a proper assessment of the duration of the decrease in neutrophil counts due to wide intervals of scheduled assessments. Caution is needed as the review of the neutropenic SAEs revealed that in 2 of the 3 cases the patients received GCSF treatment. GCSF treatment was for 2 SAEs (febrile neutropenia and agranulocytosis) in 2 PPMS patients. In light of the above, a statement regarding neutrophils has been amended to section 4.8 of the SmPC and neutropenia has been included in the Table of adverse reactions.. In the majority of patients, IgM levels decreased significantly. There was only a slight transient decrease in IgA and IgG levels. IgM levels appear to be normalised in the majority of patients within 24 weeks based on data from the Phase II study. In Pool B (MS All exposure) rates of serious infections per 100PY in patients with levels of IgA, IgG and IgM below the LLN at any timepoint were higher than the rate in the overall population, even though the limited number of cases and the limitations of the method due to the visits schedule, do not allow to draw definitive conclusions. Decrease in serum immunoglobulins (Ig) has appropriately been added as an important identified risk. Other risks associated with development of infections were high BMI and previous infections. There was no impact on NK lymphocyte count in the ocrelizumab groups. In the IFN group, there was a decrease in CD3+, CD4+ and CD8+T cell count as well as NK lymphocyte count. CD19+ B cell count was near complete depletion at Week 2 and the median time to repletion (return to baseline or LLN, whichever was lower) of B cells was 72 weeks (range 27 to 175 weeks) after the last infusion. In all safety Pools, following the first infusion of OCR, there was a decrease in mean levels of the different subsets of T cells (CD3, CD4, CD8). After this initial decrease, levels of these T cell subsets remained stable with small fluctuations throughout treatment. In order to better understand the possible clinical relevance of the observed decrease in subsets of T cells (CD3, CD4, CD8), following CHMP request to

provide all available data on the possible correlation between serious infections and outcome of serious infections and decrease in T cells (CD3, CD4 and CD8) , the Applicant conducted an analyses on the association between confirmed drops in T cells below LLN over two consecutive measurements and serious infections; this analyses showed that decreases in CD4 and CD8 T cells below the LLN were associated with an increased risk of serious infections within MS ocrelizumab treated patients, compared to patients without CD4 and CD8 T cells below the LLN. Even though the number of events is low, and thus the confidence intervals partially overlap, these data have a strong biological plausibility: in patients that are B cell depleted, if also T cells are decreased, these patients are at increased risk of infections. Similar findings were observed also for confirmed low lymphocyte counts (defined as counts <LLN for at least 2 consecutive measurements): higher rate of serious infections were observed in patients with confirmed low lymphocyte counts compared to patients without lymphocyte counts <LLN. From the above, it appears that measuring lymphocyte counts can be a method to identify OCR treated patients at increased risk of serious infection. The Applicant accepted to add a paragraph on Lymphocyte counts in paragraph 4.8 of the SmPC, in the section description of selected adverse reaction/ Laboratory abnormalities.

The risk of serious infections and opportunistic infections in the MS population differ from RA population. In the RA studies, the risk of serious infections and opportunistic infections was clearly increased. The opportunistic infections included herpes and candida infection, which were also disseminated in some cases, tuberculosis, pneumocystis jiroveci, histoplasmosis and hepatitis B. However, the RA and MS population differ. The RA population was on average older, had different co-morbidities, higher doses of ocrelizumab was used in some patients and they were also treated with DMARDs i.e. other immunosuppressants. In the SLE and LN populations concomitant immunosuppression was also used which resulted in a high frequency of serious infections. 6% (SLE) and 3% (LN) of the patients enrolled in these studies died due to an infection.

Concomitant steroid use for MS relapse was associated with a higher frequency of adverse event including infections. Following CHMP request, the Applicant has presented analyses taking into account the temporal association between the use of corticosteroids and the onset of infections allowing only a temporal window for infections from the onset of MS relapse to 30 days after the end of the relapse. With this analysis, within the OCR group, higher rates of infections or serious infections were not observed in the subgroup of MS relapses treated with corticosteroids compared with the subgroup of MS relapses not treated with corticosteroids. It cannot be excluded due to small numbers, that there is an increased risk of infections when using concomitant glucocorticosteroids for symptomatic treatment of relapses. This is appropriately reflected in the SmPC.

Across both RMS and PPMS indications of the Phase III pivotal clinical trials with Ocrelizumab in MS, a total of 15 patients received prior DMTs other than IFN and GA. For all these patients, the time elapsed from the end of DMT until the start of OCR were in line with the protocol requirements as per the exclusion criteria. Available data do not allow any evaluation of the possible additive immune effect that could occur when switching patients from another DMT with immunosuppressive effect to OCR, possibly leading to a worse safety profile. The pharmacodynamics of other disease modifying MS therapies should be taken into consideration when prescribing OCR, which is reflected in Section 4.4 of the SmPC.

In light of the relevance of gathering additional safety data on OCR safety in patients previously treated with a DMT with immunosuppressive effect, the Applicant committed to collect information on type and duration of DMT used prior to switching to OCR in the post–authorization safety study (PASS) on long-term surveillance of MS patients treated with OCR.

There is a higher frequency of malignancies in the ocrelizumab groups compared to IFN and placebo; rate of malignancy per 100PY, ocrelizumab RMS 0.28 (95% CI: 0.08, 0.71) vs. IFN 0.14 (95% CI: 0.02, 0.52) and ocrelizumab PPMS 0.92 (95% CI: 0.49, 1.57) vs. placebo 0.30 (95% CI: 0.04, 1.10). The difference appear to primarily driven by more cases of breast cancer in the ocrelizumab groups. There were no cases of breast cancer in the IFN or placebo groups whereas there were 3 cases in the RMS ocrelizumab group and 4 cases in the PPMS ocrelizumab group. One further case of breast cancer

occurred in a RRMS patient from study WA21493 (treated with OCR 2000 mg) and one further case of breast cancer occurred in a patient switched to OCR in the open label phase of study WA21093.
Even though this pattern was not seen in the RA population, the RA ocrelizumab programme is not considered adequate to evaluate a long-term risk. In the RA ocrelizumab development program the median number of ocrelizumab doses received by the patients was only 2 in the controlled treatment period and only 3 in the uncontrolled pool. Of note, one case of male breast cancer_was reported (Patient WA20495-141462-90803) in a 67 year old Japanese male previously treated with infliximab, diagnosed with breast cancer one year after the start of the treatment with OCR 200 mg. Breast cancer is a very rare disease in males.
Age-standardised comparison of incidence rates of breast cancer revealed that compared to epidemiological data the 95% confidence intervals overlapped. Furthermore, with additional data as of 30 June 2016 the standardized incidence rate per 100PY of female breast cancer was 0.227 (95% CI: 0.096, 0.498). This rate was consistent with that reported at the 20 January 2016 CCOD (0.240; 95% CI: 0.096, 0.544) and with that reported in the SCS (0.281; 95% CI: 0.104, 0.666). The results across all CCODs remained within the 95% CIs for the standardized incidence rates reported for the SEER database (0.124; 95% CI: 0.124, 0.125). This could indicate that the risk is not higher than in the general population.
Baseline risk factors for the development of breast cancer other than age and gender was not recorded. The suppression of B-cells lasted for more than 2 years. B cells are known to play a significant role in tumor surveillance; however, there is conflicting evidence as how it influences tumor development. Non-clinical xenograft models (breast cancer) suggest that B cell depletion slow tumor progression while other xenograft models have been associated with enhanced tumor growth. Available data do not allow to definitely confirm nor rule out a causal relationship between B cell depletion and the development of the specific subtypes of breast cancers observed in the ocrelizumab trials.
Furthermore, 11 years of follow-up data for rituximab, which is also a CD20 monoclonal antibody, do not seem to suggest any increased risk of malignancy. However, also this argumentation may not be considered conclusive, because even though both rituximab and OCR target CD20, these are different molecules that may carry different safety profiles.
The Applicant has proposed a post-marketing *Long-Term Surveillance of Ocrelizumab-Treated Patients with Multiple Sclerosis* study. In the PASS study, baseline and on-treatment tumour surveillance should be planned. This should be able to clarify if ocrelizumab is associated with an increased risk of malignancies including breast cancer.
As requested, in section 4.4, in the subparagraph ”Malignancies” of the proposed SmPC, information on the imbalances observed compared to placebo, including the cluster in breast cancer, has been provided. The need to exclude from treatment patients with active malignancy and perform individual benefit risk assessment in patients with known risk factors for malignancies or actively monitored for recurrence of malignancy has also been included.
There were three deaths in the RMS trials, two in the IFN group and one in the ocrelizumab group. None were considered related to the treatments. In the PPMS trial group 1 patient in the placebo group died (road traffic accident). In the ocrelizumab group 4 patients (0.8%; AE PTs of pulmonary embolism, pneumonia, pancreatic carcinoma metastatic, pneumonia aspiration) died. Two of the cases in the ocrelizumab group (pneumonia cases) could have been related to ocrelizumab.

Three additional deaths were reported after the SCS up to 30 September 2016, all 3 considered unrelated to study drug by the investigator: one case of adenocarcinoma of the oesophagus (in a 52-year old female), one case of acute coronary insufficiency (in a patient with multiple CV risk factors) and one event with an unknown cause of death (40 years old male, from a site in Switzerland; the patients was found dead in his residence; according to the first results the death was due to an epileptic event; as per the “Forensic medical assessment of death” report, the cause of death remains unclear after autopsy, although an epileptic seizure process with consequent failure of central regulation was conceivable.

The Applicant clarified that the term Crohn’s disease is not part of the narrow basket to detect immune disorders (ocrelizumab specific MedDRA Term selection, that contains approximately 100 PTs) used by the Applicant for the Summary of Clinical Safety. However, the PT Crohns disease is part of the standard MedDRA Query (SMQ) “Pre-malignant tumours (narrow)” which was used to detect pre-

malignancies, and using this basket one case of Crohn disease was identified at the Summary of Clinical Safety CCOD. With the 3 months safety update submitted with this response (with a cut-off date of 20 Jan 2016), 3 new cases of Crohn's disease were detected (cumulatively 4/2279 patients exposed to OCR, 0.2%).

The Applicant states that the limited information available for these 3 new cases, precludes an evaluation of whether or not the disease might have been pre-existent. In order to increase sensitivity to detect a potential signal of autoimmune diseases associated with ocrelizumab treatment, a broad basket of approximately 400 terms was applied; in addition to the four cases of Crohn's disease mentioned above, four more cases mapping to the System Order Class (SOC) Gastrointestinal Disorders (one case of ulcerative colitis and three cases of chronic gastritis) were identified by applying the broad screening basket for autoimmune diseases in the ocrelizumab all exposure population as of the 20 January 2016 CCOD (for the 3-month safety update). The proportion of patients with AEs related to autoimmune disorders identified with the broad basket to detect immune disorders at the CCOD for the 3 months safety update in Pool B was 5.0% (114 patients). The event rate of autoimmune disorders (broad basket) per 100 patient-years observed with ocrelizumab in MS (2.22; 95% CI: 1.85, 2.65) falls within the range reported in placebo-exposed patients in other MS studies (0 to 5.48; 95% CI: 3.85, 7.12). In order to better evaluate a potential signal of autoimmune diseases associated with ocrelizumab treatment, the frequencies of autoimmune diseases (using the broad basket of approximately 400 terms) in OCR MS controlled pools (Pool A and PPMS) was provided by the Applicant. At present, there is insufficient data to warrant inclusion of autoimmune disorders in general, or of any particular autoimmune disorder in the ocrelizumab SmPC. Autoimmune disorders will be monitored though routine pharmacovigilance in upcoming PSURs.

The Applicant has been requested to further discuss the possible reasons for the higher rates of AEs, SAEs and infections reported in patients from the USA region. No definitive conclusion may be drawn for this finding. However, the higher reporting rate of AEs including infections in the USA, has also been observed with IFN, as well as in the pooled placebo from OCR RA controlled treatment studies, which the Applicant states is consistent with other reported data in autoimmune indications (Mabthera for Rheumatoid Arthritis). For both IFN and OCR groups, the difference in infection by preferred term (PT) between both regions was driven by a higher reporting proportion of patients with nasopharyngitis, urinary tract infection, sinusitis, and bronchitis in USA vs ROW. Based on the above, the higher reporting rate of AEs, SAEs and infections in the USA with OCR in MS is not considered a safety concern.

Depression and suicidal ideation are known to occur with increased frequency in the MS population and in association with interferon use. In RMS trials, current severe depression and/or suicidal ideation was an exclusion criteria. In Pool A similar frequencies and rates of suicide and depression events occurred in OCR and IFN groups [OCR: 8.5% vs IFN 7.9%; rate per 100 PY: 5.39 (95% CI: 4.26, 6.72) for the OCR group and 5.43 (95% CI: 4.28, 6.80) for the IFN group]. In PPMS, a high proportion of patients reported Psychiatric Disorders (mostly depression) in both treatment groups (PBO 13.8%; OCR 9.7%). 4 events related to suicide (0.8%) occurred in the OCR group (2 suicide attempts, 1 each depression suicidal and suicidal ideation), compared to no events in the PBO group. Suicide events were reported in 12 ocrelizumab-treated patients (0.5%) in the MS trials (MS OCR all exposure population; N = 2279 patients) and this rate is considered low based on the epidemiological data (lifetime prevalence of 28.6% with suicide intent and 6.4% with attempted suicide). Overall, the Applicant's conclusion not to include suicide attempt/ suicidal ideation in Section 4.8 of the SmPC is acknowledged, because a causal association between exposure to ocrelizumab and suicide attempt/ suicidal ideation cannot be established based on available data.

Both RMS and PPMS patients with congestive heart failure (NYHA III or IV functional severity) were not eligible in the OCR MS clinical development program, because infusion-related reactions (IRRs) in this patient population could theoretically lead to serious CV consequences, including fatal outcome; the absence of data in patients with a history of congestive heart failure (New York Heart Association III & IV) is reported in section 4.4 in the currently proposed SmPC. Furthermore the Applicant states that

the exclusion criteria “history of ischemic cerebrovascular disorders (e.g. stroke, transient ischemic attack)” was implemented to minimize the risk of drop-out for other health issues.

In the Phase 3 controlled MS treatment population six CV related SAEs considered drug related by the investigator were reported in 5 OCR treated patients (peripheral arterial occlusive disease and dry gangrene reported in one patient with hyperlipidemia and smoke as other risk factors; cardiac failure congestive, in a patient with overweight as other risk factor; chest pain, in a patient with chest tightness and pain with glatiramer acetate injection; acute MI in a 43 old female with no known risk factors and oedema peripheral in a 54 year old female with no known risk factors) compared to 1 event in the PBO group (atrial fibrillation, in a patient with obesity and arterial hypertension).

In the MS all exposure population (Population Pool B), based on the cardiac SMQ retrieval strategy, 19 CV related SAEs were reported in 18 patients. Most of these patients had CV disease risk factors. Myocardial infarction and acute myocardial infarction preferred terms were the most common term retrieved (7/18 patients). The rates of myocardial infarction (MI) reported in Pool B was consistent with epidemiological data in MS reported by the Applicant.

On the basis of the above, the Applicant’s conclusion not to include in section 4.8 of the OCR SmPC as ADRs the PT myocardial infarction, cardiac failure congestive, chest pain, dry gangrene and peripheral arterial occlusive at this time, nor the addition of information on the absence of data in patients with cardiovascular disorders due to OCR trials exclusion criteria is acknowledged.

Further explanation on a serious adverse event of autoimmune uveitis has been requested. The Applicant clarified that there were no reports of uveitis or autoimmune uveitis during the controlled treatment period in any OCR MS and RA clinical studies. In the MS population, after completion of the controlled treatment periods and up to the updated CCOD 20 January 2016, 4 cases of uveitis/ autoimmune uveitis were reported. For all patients uveitis was not due to an infection. One patient had an alternative explanation (history of recidivant pan-uveitis since 2004). It is acknowledged that an association between uveitis and multiple sclerosis –regardless of treatment- has been reported and that a causal association between exposure to ocrelizumab and uveitis cannot be definitely established based on the above four cases.

No reports of Immune Thrombocytopenic Purpura (ITP) occurred during the controlled treatment period in any OCR MS clinical studies. In the MS population, after completion of the controlled treatment periods and up to the updated CCOD 20 January 2016, 2 cases of ITP (one life threatening, considered remotely related to OCR 2000 mg received in the first cycle of study WA21493, even though occurring more than 1.5 years after the last OCR 600 mg dose; and one grade 1, considered not drug related by the investigator) and one event of purpura (not reported as ITP) were reported. No cases of ITP were reported with placebo in MS studies with other molecules (Laser Analytical Report). Based on the Laser Analytical report the event rate per 100 PY of ITP observed with OCR in MS is below the ranges reported for other MS treatments. At present available data do not allow a definite conclusion regarding a causal relationship with ocrelizumab. Idiopathic thrombocytopenic purpura will be monitored through routine pharmacovigilance in upcoming PSURs. One case of Systemic Inflammatory Response Syndrome (SIRS) which resulted in death occurred in the Phase 2 study WA21493. The aetiology of this SIRS case could not be fully clarified and its underlying cause remains unknown. The investigator assessed the event as probably related to ocrelizumab. In addition, one of the two experts consulted by the Applicant considered the event as possibly related to experimental therapy. Based on the above, a causal relationship with OCR for this case is at least a reasonable possibility. The Applicant has included the case of Systemic Inflammatory Response Syndrome (SIRS) in section 4.8 of the SmPC and in section 4.9 (Overdose), with cross reference to section 4.8.

Marked increased GGT (GGT > 160 U/L and a change from baseline value of at least 50%) was observed in a higher percentage of patients treated with OCR (6.9%) compared to PBO (4.6%) in the PPMS study (WA25046). However no imbalance was observed in increased ALT and AST between treatments and no symptomatic hepatic events were observed in patients with increased GGT. The percentage of AEs related to abnormal liver function tests was similar in the OCR group compared with PBO (25 patients, 5.1% vs 12 patients, 5%). 10/ 25 events (in 9 patients) in the OCR group were considered treatment related by the investigator (compared to none in the PBO group) and 6 AEs (in 5

patients) resulted in modification/interruption of the study treatment in the OCR group (compared with none in the PBO group). In RMS patients, a lower percentage of OCR treated patients reported marked increased GGT (4.3%; 35 patients) compared to the IFN group (9.1%, 75 patients). On the basis of the above, it is agreed that the inclusion of increased GGT or of abnormal liver function tests in Section 4.8 of the SmPC is not considered warranted at this time.

Though in PPMS patients (Study WA25046) a higher percentage of marked low hemoglobin (hemoglobin <110 g/L and a change from baseline value of at least 15%) was observed in the OCR group compared with the PBO group (3.3%; 16 patients vs 1.7%, 4 patients), the percentage of patients with replicated marked low values were similar between the two groups (OCR 2.1 vs PBO 1.7%). Similarly, no difference in the percentages of AEs related to low hemoglobin were observed between OCR (3.7%, 18 patients) and PBO groups (3.8%, 9 patients). In RMS, marked low hemoglobin was reported in a lower percentage of patients in the OCR group compared to the IFN group (2.7 vs 3.4%), as well as marked low haemoglobin levels which were replicated (1.6% vs 1.9%). Similarly, the percentage of patients in which anemia-related events were reported was more than 2-fold higher in the IFN (3.5%; 29 patients) group compared with OCR group (1.5%; 12 patients). Thus the Applicant's conclusion that the inclusion of low haemoglobin in section 4.8 of the SmPC is not warranted at this time is acknowledged.

In the PPMS controlled treatment population, the percentage of patients in which low lymphocyte counts were reported as a laboratory abnormality was more than 2-fold higher in the OCR group (26.3%) compared with the placebo group (11.7%). The imbalance in low lymphocyte counts between the OCR and placebo groups was driven primarily by Grade 1 (13.1% vs 5.0%) or Grade 2 lymphopenia (12.1% vs 5.4%) in ocrelizumab treated patients compared to PBO. No imbalance was observed between the two treatment groups for Grade 3 lymphopenia (1.0% vs 1.3%) and no cases of Grade 4 lymphopenia in either group. Also when considering marked lymphopenia (<0.7 x 10e9/L or a change from baseline values of at least 30%, defined by the Applicant as clinically relevant), a higher percentage of PPMS ocrelizumab treated patients reported marked lymphopenia compared with PBO group (6.8% vs 5.0%). In most patients (28/32 PPMS) the value normalized while on study treatment. In the RMS controlled treatment population (Pool A), the percentage of patients in which low lymphocyte counts were reported as a laboratory abnormality was higher in the IFN group (32.6%) compared with the OCR group (20.7%). This is not unexpected as lymphopenia is known to be associated with interferon beta-1a treatment. The majority of the lymphocyte count abnormalities in ocrelizumab treated patients were Grade 1 (10.9% IFN vs 9.4% PBO) and Grade 2 in intensity (18.9% vs 10.4%). Grade 3 abnormalities were reported in 2.8% of patients in the IFN group and 0.9% of patients in the OCR group. No cases of Grade 4 lymphopenia were reported in either group. Also when considering marked lymphopenia, a higher percentage of IFN treated patients reported marked lymphopenia compared with OCR group (12.8% vs 5.3%). In most patients (34/ 39 RMS Pool A) the value normalized while on study treatment. Even though B lymphocyte count depletion is an expected therapeutic effect of OCR, the available data indicate that the decreased total lymphocytes count which is observed only in a subset of OCR treated patients is not driven by B cell depletion (otherwise we would observe it in the vast majority of OCR treated patients). Furthermore, available data indicate that lymphopenia (defined as lymphocytes counts defined to be <LLN for at least two consecutive measurements) is of clinical relevance as it is associated with a higher risk of serious infections. An independent statement regarding lymphocytes in section 4.8 of the SmPC has been introduced.

The Applicant analysed the 8 events of amylase or lipase increased which occurred in 4 patients OCR treated patients in the PPMS population, compared to no events in the PBO group. Of these 4 patients, 1 patient had increased amylase levels at screening, which were sustained during the study; one of these patients had a concurrent salivary gland adenoma. All events of lipase increase were associated in time with one of the amylase increase events. All 4 patients were asymptomatic during the increase of these enzymes and did not receive any treatment for the events. All events resolved. The patients remained on study treatment with ocrelizumab. No imbalance in adverse events of amylase or lipase increase was observed in the RMS and RA populations. 7 events of pancreatitis (5 serious and 2 non serious) occurred in 5 patients receiving OCR (2 RMS and 3 PPMS patients), compared to no events in the control groups (IFN or PBO).The onset latency was reported from Day 70 to Day 743. The two non-serious events in one PPMS patient were reported as drug related by the investigator, while the 5

SAEs were reported as not related to study treatment. Risk factors that may have contributed to the onset of pancreatitis in three patients included gallstones, cholelithiasis, and high level of triglycerides.

In the OCR dataset the overall rate of birth defects (6/48, 12.5%) and that the rate of events classified by the MAH as structural malformations (3/ 48, 6.25%) was higher than the one reported for the general population (respectively 3.3% and 2–3 %).

The Applicant argued that there may be differences in counting a birth defect as a major or minor congenital malformation according to the classification used. The Applicant argued that the statement that the rate of events classified by the applicant as structural malformations (6.25%; 3/ 48 pregnancies) was higher than that for the general population (3.3%) is not considered appropriate since the rate may in fact be equal or lower, depending on the major malformation definitions applied. The Applicant's argumentation is not entirely clear. In fact, as far as the same classification is used to assess the frequencies of structural malformations both in the ocrelizumab clinical development program and in the general population a comparison should be possible. However, the argumentation provided by the Applicant that the conservative rate observed with ocrelizumab is within the range of malformations reported in published studies in the MS population treated with other DMTs is acknowledeged. Unfortunately appropriate publications could not be found in the literature that describes the rate of birth defects in MS, RA or SLE patients, regardless of treatment. Furthermore, the Applicant argues that extensive data available in-house for rituximab, which is another anti-CD 20 monoclonal antibody, do not suggest that rituximab may cause structural malformations, growth alterations, functional deficits, premature births, miscarriages, stillbirths, or any other events not in line with the known mode of action and safety profile in non-pregnant adults. In this regard it must be emphasized that even though both Rituximab and OCR target CD20, these are different molecules, with different mechanisms of action that may carry different safety profiles. Overall the Applicant's argumentations for not including at present in section 4.6 of the SmPC the information on the higher rate of birth defects and structural malformations compared to the ones reported in the general population is acknowledged. The request to extend the use of effective contraception from 6 to 12 months after the last OCR infusion has been accepted by the Applicant and implemented in the label. As regards to patient WA21093-209771-1930433 many information are lacking; the patient started open label ocrelizumab on 26 September 2016 and received the last OCR infusion on 28 August 2015. Concomitant drugs were sertraline and bromazepam. On an unspecified date in 2015 she became pregnant. On 28 January 2016 she was admitted to the hospital and her pregnancy ended with a stillborn baby on the same day. The results of the autopsy performed on the child were not reported and the reason for the death was unknown. During subsequent steps in the procedure, the requested data regarding the autopsy and additional circumstances concerning the pregnancy and stillbirth was provided by the Applicant. Available data do not allow the drawing of definite conclusions regarding the stillbirth, the autopsy report of the foetus concluded that the morphological changes in the lungs and heart speak in favor of severe asphyxia, after attempts of inhaling air. The death outcome occurred due to short-term inhalation of fluid. The premature childbirth is a consequence of the occurred retroplacental haematoma and multiple infarctions within the placenta, which was also confirmed by the pathohistological finding. No infection was reported before and after the delivery of stillbirth.

A PASS with the title "Multi-source surveillance study of pregnancy and infant outcomes in ocrelizumab-exposed women with multiple sclerosis" (BA39732) will be conducted to assess and characterize pregnancy outcome.

There are limited data regarding safety post last dose. The Applicant stated that the most unbiased body of data in which to consider safety post last dose is the planned treatment free period in the Phase II study WA21493, where 90% of patients exposed to any ocrelizumab dose (196 out of the total of 218 randomized patients) entered the TFP. No increased risk of SAEs or serious infections post-last dose was observed in the TFP of the Phase II study WA21493. Among patients exposed to OCR in the Phase 3 trials, only 178 (8.6%) patients entered the SFU. Also in these updated safety data (CCOD

20 January 2016) the rates of SAEs (26.1; 95% CI: 19.69-34,02) and of serious infections (10.5; 95% CI: 6.55, 15,83) per 100 PY post last dose are higher than the rates reported in the 3 month safety update for the overall all exposure population of Pool C (that includes all safety data from the pivotal RMS studies (SAEs: 5.78; 95% CI: 4.98- 6.68; serious infections: 1.92, 95% CI: 1.47-2,46). The majority of SAEs and Serious infections were reported within the first 24 weeks post-last dose. The Applicant has committed to continue to collect and analyse data regarding high risk of SAEs and serious infections post last dose of ocrelizumab as the data currently available to assess ocrelizumab safety after the last dose is limited. Section 5.1 already provides information on the long lasting pharmacodynamics effect of ocrelizumab and as such, the prescriber is presented with the knowledge currently available.

2.6.2. Conclusions on the clinical safety

The CHMP considers the following measures necessary to address issues related to safety:

In order to evaluate the long term safety of the product, two PAS studies were recommended to be performed, one of which will include a wider PPMS population.

The main safety issues with ocrelizumab are the risk of infusion related reactions and infections. With regards to IRRs the majority were manageable. Further, the risk of serious infections was lower than with IFN and comparable to placebo but more patients in the ocrelizumab groups with serious infections had a worse outcome than in the comparator groups. Furthermore, both in RMS (Pool A) and in PPMS, in the subgroup of subjects with lymphocytes confirmed to be <LLN, higher rates of serious infections were observed in OCR treated patients compared to IFN/ PBO treated patients. Increased rates of serious infection were observed in RMS patients and in Pool B over time (beginning at Dose 5).

In addition, there is a small imbalance with regards to malignancies, which seem to be driven by a cluster breast cancer. However, available data do not allow to definitely establish nor rule out a clear causality to ocrelizumab treatment. The Applicant has proposed a post-marketing *Long-Term Surveillance of Ocrelizumab-Treated Patients with Multiple Sclerosis* study. In the PAS study, baseline and on-treatment tumour surveillance should be planned. Furthermore, in section 4.4, subparagraph malignancies of the proposed SmPC adequate information and recommendations for prescribers have been provided. The Applicant has proposed a restriction of the indication to active RMS due to the uncertainties related to the imbalance in malignancies, which is supported.

Compared to IFN, ocrelizumab causes neutropenia or increased levels of hepatic transaminases with lower frequencies. However, Grade 4 neutropenia occurred in OCR treated patients compared to no Grade 4 events in IFN group. Furthermore 2 PPMS patients received GCSF treatment for neutropenic SAEs.

Relevant safety issues have adequately been identified an added to the RMP.

2.7. Risk Management Plan

Safety concerns

Table 44: Summary of Safety Concerns

Important identified risks	• Infusion-related reactions • Infections
Important potential risks	• Hypersensitivity reactions • Malignancies including breast cancer • Impaired immunization response • PML • Serious Infections related to decrease in immunoglobulins (particularly in patients previously exposed to immunosuppressive/ immunomodulatory drugs or with pre-existing hypogammaglobulinaemia
Missing information	• Use in pregnancy and lactation • Use in pediatric population • Use in patients over 55 years old (including elderly) • Long-term safety of ocrelizumab treatment • Concomitant use of any immunosuppressive/ immunomodulating medication other than steroids for acute relapses • Safety of ocrelizumab following immunosuppressive/ immunomodulating DMTs other than beta interferons and glatiramer acetate • Safety of immunosuppressive/ immunomodulating DMTs following ocrelizumab

Pharmacovigilance Plan

Table 45: On-going and Planned Additional Pharmacovigilance Studies / Activities in the Pharmacovigilance Plan

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
Study BN29739: Title: *A Phase IIIb, Multicentre, Randomized, Parallel-Group, Open-Label Study To Evaluate The Effects Of Ocrelizumab On Immune Responses In Patients With Relapsing Forms Multiple Sclerosis* (Interventional, Category 3)	This multicenter, randomized, open-label Phase IIIb study will evaluate the immune response to vaccines (tetanus toxoid, 23-valent pneumococcal polysaccharide vaccine, influenza vaccine, and KLH) after administration of a dose of ocrelizumab in participants with RMS.	Impaired immunization response	Ongoing	Primary CSR: Q4 2017 Final CSR: Q1 2023
Study BA39732 Title: *Multi-Source Surveillance Study of Pregnancy and Infant Outcomes in Ocrelizumab-Exposed Women with Multiple Sclerosis* (Non-interventional, Category 3)	To estimate the frequency of selected adverse pregnancy outcomes in women with MS exposed to ocrelizumab during the defined exposure window (i.e., spontaneous abortions, stillbirths, elective abortions, and preterm births) To estimate the frequency of selected adverse fetal/neonatal/infant outcomes at birth and up to the first year of life of infants from pregnancies in women with MS exposed to ocrelizumab (i.e., congenital malformations, adverse effects on immune system development [e.g., severe infectious disease in the first year of life], and low birth weight) To compare the frequency of each safety event of interest between ocrelizumab-exposed pregnant women with MS and two comparison cohorts: (a) pregnancies in women with MS who have not been exposed to ocrelizumab (overall, and in two strata: pregnancies exposed to non-ocrelizumab DMTs, and pregnancies not exposed to DMTs), and (b) pregnancies in women without MS who have not been exposed to ocrelizumab	Use in pregnancy and lactation	Protocol synopsis submitted with RMP	Final CSR: March 2024

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
Study BA39730 Title: *Long-Term Surveillance of Ocrelizumab-Treated Patients with Multiple Sclerosis* (Non-interventional, Category 3)	To assess and characterize the long-term safety data from the use of ocrelizumab in patients with MS. The primary objective is to estimate the event rates of SAEs, including malignancy and infections, following ocrelizumab treatment in patients with MS The secondary objective is: to compare the incidence of each serious safety event between ocrelizumab-exposed patients with MS and patients with MS exposed to other approved DMTs (overall and by individual DMTs if possible), within the same data source. If sufficient data are available, an exploratory objective of this study is to compare the safety profile of patients with MS exposed to ocrelizumab to the safety profile of patients with MS not exposed to any DMTs.	Long-term safety of ocrelizumab treatment Infections Malignancies including breast cancer PML Safety of ocrelizumab following immunosuppressive/ immunomodulating DMTs other than beta interferons and glatiramer acetate	Protocol synopsis submitted with RMP	Interim reports: biannually; summarized in the next PSUR/ PBRER due. The study duration will be 10 years. The final report will be submitted after study end in line with regulatory requirements.
Study WA40404: A Phase IIIb Multicenter, Randomised, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Ocrelizumab in Adults with Primary Progressive Multiple Sclerosis Later in their Disease Course* (category 3)	To evaluate the safety and efficacy of ocrelizumab (Ocrevus®) compared with placebo in patients EDSS 3 to 8 using 9HPT as the primary efficacy outcome, and 12 week confirmed disability progression as a key secondary endpoint. Baseline assessment of features characteristic of imaging inflammatory activity (T1 Gd-enhancing MRI lesions and/or new/enlarging T2 lesions) will be undertaken to explore treatment effect in subgroups with different inflammatory profiles.	Use in patients between 55 and 65 years old. Use in more disabled patients (EDSS 6.5 to 8) Long-term (5 years or more) safety of ocrelizumab treatment	Planned	Final report June 2024
Monkey Study 17-1133 (Non-clinical Category 3)	To assess immunization status of babies born to mother's treated with ocrelizumab in cynomolgus monkeys	Use in pregnancy & lactation	Planned	Final report, Dec 2019

CSR = Clinical Study Report; DMT = disease-modifying therapy; FPI = First Patient In; LPLV = Last Patient Last Visit; OLE = open-label extension; PBRER = Periodic Benefit-Risk Evaluation Report; PSUR = Periodic Safety Update Report; SFU = safety follow-up.

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important identified risks		
Infusion-related reactions	Advice in Section 4.2 of the EU SmPC (Posology and method of administration) Special warning and precaution in Section 4.4 of the EU SmPC (Special warnings and precautions for use) Listed as an ADR in Section 4.8 (Undesirable effects)	None proposed
Infections	Contraindication in Section 4.3 of the EU SmPC (Contraindications) Special warning and precaution in Section 4.4 of the EU SmPC (Special warnings and precautions for use) Listed as ADRs in Section 4.8 (Undesirable effects)	None proposed
Important potential risks		
Hypersensitivity reactions	Contraindication in Section 4.3 of the EU SmPC (Contraindications) Special warning and precaution in Section 4.4 of the EU SmPC (Special warnings and precautions for use)	None proposed
Malignancies including breast cancer	Contraindication in Section 4.3 of the EU SmPC (Contraindications) Special warning and precaution in Section 4.4 of the EU SmPC (Special warnings and precautions for use) Section 5.3 (Preclinical safety data) includes a statement that no preclinical carcinogenicity or mutagenicity studies were conducted	None proposed
Impaired immunization response	Contraindication in Section 4.3 of the EU SmPC (Contraindications) Special warning and precaution in Section 4.4 of the EU SmPC (Special warnings and precautions for use)	None proposed
PML	Special warning and precaution in Section 4.4 of the EU SmPC (Special warnings and precautions for use)	None proposed
Serious infections related to decrease in immunoglobulins (particularly in patients previously exposed to immunosuppressive /immunomodulatory drugs or	Contraindication in Section 4.3 of the EU SmPC (Contraindications) Special warning and precaution in Section 4.4 of the EU SmPC (Special warnings and precautions for use)	None proposed

with pre-existing hypogammaglobulinaemia		
Missing information		
Use in pregnancy and lactation	Advice in Section 4.6 of the EU SmPC (Fertility, pregnancy and lactation) Advice in Section 5.3 of the EU SmPC (Preclinical safety data)	None proposed
Use in pediatric population	Advice in Section 4.2 of the EU SmPC (Posology and method of administration)	None proposed
Use in patients over 55 years old (including elderly)	Advice in Section 4.2 of the EU SmPC (Posology and method of administration)	None proposed
Long-term safety of ocrelizumab treatment	None proposed	None proposed
Concomitant use of any immunosuppressive/ immunomodulating medication other than steroids for acute relapses	Special warning and precaution in Section 4.4 of the EU SmPC (Special warnings and precautions for use)	None proposed
Safety of ocrelizumab following immunosuppressive/ immunomodulating DMTs other than beta interferons and glatiramer acetate	Special warning and precaution in Section 4.4 of the EU SmPC (Special warnings and precautions for use)	None proposed
Safety of immunosuppressive/ immunomodulating DMTs following ocrelizumab	Special warning and precaution in Section 4.4 of the EU SmPC (Special warnings and precautions for use)	None proposed

Conclusion

The CHMP and PRAC considered that the RMP version 1.4 (dated 08 November 2017) is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant requested alignment of the PSUR cycle with the international birth date (IBD). The IBD is 28 March 2017. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The CHMP, based on the available data, considers ocrelizumab to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Significance of paediatric studies

N/A

2.11. Product information

2.11.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.11.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ocrevus (ocrelizumab) is included in the additional monitoring list as it is a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Ocrelizumab has been developed for the treatment of patients with relapsing forms of multiple sclerosis (RMS) and primary progressive MS (PPMS).

During the assessment process, the Applicant amended the indication initially applied for as follows:

"*Ocrevus is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features (see section 5.1).*

Ocrevus 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 (see section 5.1).

In approximately 85% of patients, MS begins as a relapsing, episodic disorder with gradual complete or incomplete recovery, relapsing remitting multiple sclerosis (RRMS). Remitting multiple sclerosis (RMS) is used to describe those patients with either RRMS or secondary progressive MS (SPMS) who continue to experience relapses. Patients accumulate disability as a result of incomplete recovery from acute relapses and/or gradual disease progression. The aim of the treatment is to suppress relapses and disease progression.

Primary progressive MS (PPMS) accounts for approximately 10% of all cases. It is characterized by a progressive course from disease onset, with infrequent superimposed discrete clinical attacks or relapses. The aim of the treatment is to delay disease progression.

3.1.2. Available therapies and unmet medical need

RMS

In addition to treatments for the symptoms of MS and treatment of relapses (such as corticosteroids), there are currently 12 disease modifying therapies (DMTs) approved for use in patients with RRMS and/or other forms of RMS in the EU. In a clinical setting, first line treatment is usually dimethyl fumarate, teriflunomide, glatiramer acetate or a medical product within the interferon beta class. Second or third line therapies are usually natalizumab, alemtuzumab or fingolimod.

PPMS –unmet medical need

No treatment has been demonstrated to significantly slow the progression of disability in patients with PPMS, including therapies approved for the treatment of RMS. Phase III RCTs evaluating glatiramer acetate, mitoxantrone, interferon beta-1a IM, interferon beta-1b, fingolimod and a Phase II/III study with rituximab did not demonstrate significant impact on clinical progression in the PPMS population. In the absence of any approved treatment for PPMS, a variety of unapproved agents including mycophenolate mofetil, cyclophosphamide, mitoxantrone, or rituximab, in addition to other therapies approved for the treatment of RMS, are used in clinical practice.

3.1.3. Main clinical studies

Study	WA21092 and WA21093		WA25046	
Indication	**RMS**		**PPMS**	
Arm	**Interferon beta-1a 44 μg SC / 3 x weekly**	**Ocrelizumab 600 mg IV /24 weeks**	**Placebo**	**Ocrelizumab 600 mg IV / 24 weeks**
Patient population	MS according to McDonald criteria 2010 (RRMS or SPMS with relapses) EDSS at screening from 0-5.5 Prior to screening: ≥2 relapses in 2 years or one relapse in the year before screening		MS according to McDonald criteria 2005 (PPMS) EDSS at screening from 3.0 to 6.5 points	
Primary Endpoint	ARR		12-week CDP	
Randomization	1:1 ocrelizumab: interferon beta-1a		2:1 ocrelizumab: placebo	
No of treated patients	411 (WA21092) 418 (WA21093)	410 (WA21092) 417 (WA21093)	239	486
Dose	44 μg SC 3x week	600 mg IV every 24 weeks	Placebo IV every 24 weeks	600 mg IV every 24 weeks
Controlled Treatment Duration	96 weeks		Minimum duration 120 weeks (120 weeks and minimum number of CDP events observed) Median follow-up time: ocrelizumab 3.0 years, placebo 2.8 years	
Blinding	Double-blind, double-dummy		Double-blind	
Open Label extension	Patients who completed the double-blind treatment period were offered enrollment into an optional OLE of the study to further characterize the long-term safety and efficacy of ocrelizumab			
Safety follow up	Patients who completed or withdrew prematurely from double-blind or open-label treatment were encouraged to enter a SFU period, and a B-cell monitoring period			

3.2. Favourable effects

RMS:

In study WA21092, the primary endpoint, annualized relapse rate (ARR) was met with a reduction 46.4% compared with interferon beta-1a. Adjusted ARR Ratio (95% CI), ITT population: 0.537, (0.400, 0719), p< 0001. Statistically significant outcomes for the secondary endpoints CDP 12 Weeks and CDP 24 Weeks were observed, however not for CDI 12 weeks.

The other main study WA21093 also met its primary endpoint as treatment with ocrelizumab significantly reduced the ARR by 46.8% at 96 Weeks compared with interferon beta-1a. Adjusted ARR Ratio (95% CI), ITT population: 0.532 (0.397 – 0.714), p <0.0001. Statistically significant outcomes for the secondary endpoints CDP 12 Weeks and CDP 24 Weeks were registered, however not for CDI at 12 weeks.

Results from individual studies were consistent with those from the pre-specified pooled analysis. The primary endpoint was met with a statistically significant reduction of the ARR of 47% compared with interferon beta-1a. The continued hierarchical statistical testing for the secondary endpoints CDP 12 weeks, most MRI endpoints, CDI 12 Weeks and CDP 24 Weeks revealed statistically significant findings. The secondary endpoint MSFC was not met, and therefore the hierarchical statistical testing for the remaining secondary endpoints MRI Brain volume (p = 0.0042) and NEDA (p < 0.0001) was non-confirmatory, whilst the statistical significance testing for SF-36 PCS was negative.

Subgroups analyses across the main studies did not identify a subgroup clearly yielding more or less treatment benefit. For ARR, patients who were active or highly active inadequate responders or highly active treatment naïve appeared to have a borderline better treatment effect than those who were not. However, in every subgroup ocrelizumab showed superior efficacy compared to IFN. For CDP 12 Weeks, treatment naïve subjects with active and highly active disease activity tended numerically to have less treatment benefit. For ARR, the effect of OCR seems not to be overall influenced by the disease duration, although in study WA21093 a trend favouring OCR effect in patients with longer disease duration was observed.

PPMS

The main study, study WA25046, met its primary endpoint (time to event). Treatment with ocrelizumab led to a 24% reduction in the risk of 12-week CDP compared with placebo (hazard ratio 0.76 [95% CI: 0.59, 0.98], p=0.0321). The Kaplan-Meier survival curves for time to onset of 12-week CDP showed separation from 12 weeks, with a lower proportion of patients in the ocrelizumab group with CDP throughout the treatment period.

The continued hierarchical statistical testing for the secondary endpoints time to CDP 24 weeks (p =0.0365), change in timed walk from baseline to week 120 (p = 0.0404), two MRI endpoints related to change in total T2 lesion volume and Brain volume (p < 0.0001 and p = 0.0206, respectively) were met. The last secondary endpoint SF-36 PCS for the hierarchical testing was not met.

Pre-specified non-powered subgroup analyses of the primary endpoint indicate that patients who are younger or those with T1 Gd-enhancing lesions at baseline receive a greater treatment benefit than patients who are older or without T1 Gd-enhancing lesions [≤ 45 years: HR 0.64 (0.45, .0.92), >45 years: HR 0.88 (0.62, 1.26); with T1 Gd-enhancing lesions at baseline: HR 0.65 (0.40-1.06), without T1 Gd-enhancing lesions at baseline: HR 0.84 (0.62-1.13)]. Moreover, post-hoc analyses suggested that younger patients with T1 Gd-enhancing lesions at baseline have the better treatment effect [≤ 45 years: HR 0.52 (0.27-1.00); ≤ 46 years (median age of the WA25046 study); HR 0.48 (0.25-0.92); <51 years: HR 0.53 (0.31-0.89)].

3.3. Uncertainties and limitations about favourable effects

RMS and PPMS

The clinical studies submitted did not enrol subjects with an age above 55 years. Efficacy results from adults ≤ 55 years of age cannot readily be extrapolated to adults > 55 years of age and the elderly as the disease changes with time and the effect size might be smaller. However, patients enrolled in the ongoing clinical trials continue to be dosed with 600 mg ocrelizumab every six months after they become 55 and older.

Persistence of efficacy beyond the results observed in the controlled period will only be available from the open label extension with limitation in the design of such.

RMS

Both main studies used MMRM as the method to handle missing data in the analysis of change in MSFC, SF-36 PCS and change in Brain volume. MMRM is not regarded as being sufficiently conservative method for this purpose.

NEDA showed in both main studies a non-confirmatory p-value of <0.0001, but for subjects who withdrew prematurely, only subjects who were withdrawn due to lack of efficacy or death were regarded to have disease activity.

The analyses on SPMS have some limitations, which prevent drawing definite conclusions on the effect of OCR on SPMS independent of acute inflammatory events. In particular, they do not exclude that the effect of OCR on disability may be driven by its effect on inflammation and on inflammation-related

disability accumulation more than on the pure neurodegeneration-related disability. Based on the EMA guidelines on MS, as the anti-inflammatory effect of OCR has been demonstrated by the results on ARR in both studies WA21092 and WA21093, for reasons related to biological plausibility, this drug could be considered effective in preventing relapses not only in patients with RRMS but also in those with SPMS.

PPMS

Only one study in PPMS patients has been conducted. It met the primary endpoint 12-week CDP, however not with a compelling p-value (HR 0.76 [95% CI: 0.59, 0.98], p = 0.0321). Statistical evidence stronger than $p<0.05$ on the primary endpoint would usually be required when a single trial is conducted.

The Applicant compiled clinical and imaging endpoints from the RMS Studies WA21092 and WA21093 and compared them with the outcomes for the corresponding endpoints in the PPMS Study. However, these data originate from a MS disease entity other than PPMS and, also as noted by the experts consulted during the scientific advisory group in neurology, it is uncertain to which extent they might contribute to the evidence for the PPMS indication.

Inclusion criteria of study WA25046 have led to the recruitment of a patient population that may not reflect the broad PPMS patient population neither with regard to age (age range limited to 18-55 years,) nor with regard to disability (the selected EDSS inclusion range excludes more advanced disease stages). Analyses performed by the Applicant suggest that not only age but also T1-Gd enhancing lesions may modulate the effect of OCR on disability progression. However, based on analyses by strata and data description used by the Applicant it was difficult to draw conclusions on whether age was the variable that drove the increase of the effect size independent of the presence of T1 Gd-enhancing lesions (or vice versa) and, in addition, on whether there was an interaction effect or independence between these two variables (at least as a trend). The only way to understand the effect of each single component independently of the other ones, would be by building a multivariate Cox regression model with the description of the effect by each single component independently of the other ones and by interaction components.As for MRI disease characteristics, T1 Gd-enhancing lesions were present in 25-27% of patients. It was difficult to establish whether this percentage is higher than what observed in the clinical practice setting because data on the presence of T1 Gd-enhancing lesions in PPMS are few, originate mostly from RCTs, and vary across trials(i.e., in the PROMiSE study on GA the percentage of patients with T1 Gd-enhancing lesions was 14%; in the INFORMS study on fingolimod, 13%; in the study with rituximab, 24.5%). Furthermore, in WA25046 study the information of “new or enlarging T2 lesions” (the other MRI criteria considered characteristic of inflammatory activity, besides T1 Gd-enhancing lesions) at baseline is missing.

The Kaplan-Meier survival curves for time to onset of 12-week CDP showed separation from 12 weeks but the separation did not seem to increase thereafter. A similar pattern for the Kaplan-Meier survival curves was seen for CDP 24 Weeks. The absolute difference for proportion of patients with a 12 –Week CDP at Week 120 was just around 4% implying an NNT of 25 subjects, whilst the sample size estimate assumed an absolute difference of 13%. A similar absolute difference was seen for CDP 24 Weeks.

With regard to imputation of initial disability progression events for patients with early treatment discontinuation, the approach of ignoring these events resulted in a reduced treatment effect (HR 0.82 [95% CI: 0.63, 1.07], p=0.1477). However, multiple imputation (HR 0.78 [95% CI: 0.60, 1.02]) and imputation by efficacy related reason for withdrawal / withdrawal by subject (HR 0.77 [95% CI: 0.60, 1.00], p=0.0490) resulted in consistent estimates of the treatment effect.

Although a statistical significant difference (p = 0.0404) was observed between OCR and placebo over 120 weeks in terms of the 25-foot walk (T25-FW) , the difference between unadjusted means of absolute changes from baseline was of only 3 seconds. Furthermore, when expressed as unadjusted median values of absolute changes from baseline, a more reliable estimate of treatment effect when

distribution of results is strongly skewed, the difference between OCR and placebo was even lower than 3 seconds (0.43 seconds).

Furthermore, the pre-specified rules for censoring/imputation of patients who withdrew from treatment, although reasonable, are not completely reassuring of not introducing some overestimation of the treatment effect, particularly in consideration of the high amount of withdrawals from treatment (about 25%) and the imbalance between the two treatment groups (placebo group, 33.6% vs. OCR, 20.7%).

During the assessment, data issues have been identified at several sites during a GCP inspection. An analysis was presented excluding 897 (24%) EDSS assessment as these were potentially done after infusion. This sensitivity analysis of Time to Onset of CDP for at Least 12 Weeks during the Double-Blind Treatment Period demonstrated a Hazard Ratio (95% CI) of 0.81 (0.63, 1.04). An analysis excluding 22 sites with a total of 197 subjects (a total of 732 patients were enrolled in the study), showed a slightly lower hazard ratio (00.69 compared to the original 0.76)) and a very minor loss in precision of the estimated 95% confidence interval of the hazard ratio, which was unexpected given the loss in data. However, further analyses of the primary endpoint in the 22 excluded sites showed that there was no difference between the two treatment groups. Analyses of the secondary endpoints lead to the conclusion that the most likely reason for not observing an effect for the primary endpoint in the 22 excluded trial sites was caused by poor conduct of the study with regards to adequately capturing the clinical endpoints. Thus, GCP findings and the exclusion of 22 trial sites did not change the results from the original analyses.

A total of 157 major protocol deviations occurred in 68 patients of the study (75 deviations of the inclusion or exclusion criteria and 82 deviations during study conduct). In a PP analysis repeated after exclusion of all patients with major protocol deviation the risk reduction with OCR compared to placebo decreased and statistical significance was not achieved even at the standard levels of 0.05.

Several other sensitivity analyses were performed, the results of which only partially confirmed the results of the primary analysis.

Results from subgroup analyses added further uncertainty to the overall understanding of treatment benefit. In particular, the apparent reduction of treatment effect in females with PPMS, not seen in RMS patients, was not understood and explained by the distribution of Gd-enhancing lesions at baseline.

3.4. Unfavourable effects

Infusion related reactions occurred (IRRS) more frequently in the ocrelizumab groups (34.3%-39.9%) compared to IFN (9.7%) and placebo (25.5%). Most were Grade 1 or 2 in intensity and one patient had a Grade 4 IRR in the RMS studies. There were 5 serious IRRs in the PPMS study. Most IRRs occurred with the first infusion and the incidence subsequently decreased. Splitting the 600 mg dose into two with a two weeks separation in the PPMS trial did not reduce the overall risk of IRRs. IRRs lead to a discontinuation rate of 0.4% in the PPMS trial and 1.3% in the RMS studies.

Infections occurred more frequently (rates per 100PY) with ocrelizumab (85.4; 95% CI: 80.7, 90.3) than with IFN (69.1; 95% CI: 64.8, 73.5). The largest difference was seen in viral infections, 26.5% vs. 20.5%, although bacterial infections also occurred more frequently in the ocrelizumab group, 21.6% vs. 18.6%. Infections including non-serious infection requiring IV anti-infective treatment occurred more frequently in the IFN group, 3.8% vs. 1.8% in the ocrelizumab group, and was primarily of bacterial origin. However, while the rate of serious infections in the overall RMS population was higher in patients treated with IFN (1.79 events per 100 PY) compared with patients treated with OCR (0.83 per 100 PY), in the subgroup of subjects with lymphocytes confirmed to be <LLN (defined as counts < LLN for at least 2 consecutive measurements), higher rates of serious infections were observed in OCR treated patients (4.22) compared to IFN treated patients (0).

In the PPMS study, the frequency of infections per 100PY in the placebo group and ocrelizumab group was similar; placebo 76.1; 95% CI: 69.6, 83.0 and ocrelizumab 76.5; 95% CI: 72.0, 81.2. Similarly to what observed in the RMS population, while the rate of serious infections in the overall PPMS population was similar in patients treated with OCR (2.97 events per 100 PY) and in patients treated with PBO (2.88 per 100 PY), in the subgroup of subjects with lymphocytes confirmed to be <LLN, higher rates of serious infections were observed in OCR treated patients (7.93) compared to PBO treated patients (0).
Even though the number of events is low, and thus the confidence intervals partially overlap, these data have a strong biological plausibility: in patients that are B cell depleted, if also the overall number of lymphocytes decrease, these patients are at increased risk of infections.
Furthermore, serious infection had a worse outcome in OCR-treated patients compared to control groups; more patients in the ocrelizumab group experienced Grade 4 (1.6% vs. 0.4%), and Grade 5 (death) (0.4% vs. 0%) infections. The higher frequency of life threatening serious infections and of serious infection leading to death in OCR treated patients compared to comparators was confirmed in the 3-month safety update (CCOD 20 January 2016) (OCR: 12/ 1311, 0.9% vs PBO/IFN: 1/1065, 0.09%).

The rate of infections leading to withdrawal was slightly lower in the ocrelizumab group than in the placebo group.

Increased rates of serious infection were observed in RMS patients and in Pool B over time (beginning at Dose 5).

Herpes and candida infections, in the RMS studies occurred more frequently in the ocrelizumab group. The overall rate of events per 100PYwas 2.79 (95% CI: 1.98, 3.81) in the IFN group and 5.25 (95% CI: 4.14, 6.57) in the ocrelizumab group. However, in the PPMS trial the overall rate of events per 100PY was 3.03 (95% CI: 1.85, 4.68) in the placebo group and 2.33 (95% CI: 1.60, 3.27) in the ocrelizumab group. One case of PML has been reported with the use of ocrelizumab, however, the patient had previously been treated with natalizumab.

Compared to IFN, ocrelizumab causes neutropenia with lower frequencies. However, Grade 4 neutropenia occurred in OCR treated patients compared to no Grade 4 events in IFN group. Furthermore 2 PPMS patients received GCSF treatment for neutropenic SAEs.

In the majority of patients, IgM levels decreased significantly. In Pool B (MS All exposure) rates of serious infections per 100PY in patients with levels of IgA, IgG and IgM below the LLN at any timepoint were higher than the rate in the overall population. Risk associated with development of infections were high BMI and previous infections. CD19+ B cell count was near complete depletion at Week 2 and the median time to repletion (return to baseline or LLN, whichever was lower) of B cells was 72 weeks (range 27 to 175 weeks) after the last infusion.

Higher rate of serious infections were observed in patients with confirmed low lymphocyte counts compared to patients without lymphocyte counts <LLN, as well as in patients with confirmed decreases in CD4 and CD8 T cells below the LLN, compared to patients without CD4 and CD8 T cells below the LLN. Even though the number of events are low, and thus the confidence intervals partially overlap, these data have a strong biological plausibility: in patients that are B cell depleted, if also T cells are decreased, these patients are at increased risk of infections. Even though B lymphocyte count depletion is an expected therapeutic effect of OCR, the available data indicate that the decreased total lymphocytes count which is observed only in a subset of OCR treated patients is not driven by B cell depletion (otherwise we would observe it in the vast majority of OCR treated patients).

There was a slight increase in the incidence of malignancies in the ocrelizumab groups compared to IFN and placebo - rate of malignancy per 100PY, ocrelizumab RMS 0.28 (95% CI: 0.08, 0.71) vs. IFN 0.14 (95% CI: 0.02, 0.52) and ocrelizumab PPMS 0.92 (95% CI: 0.49, 1.57) vs. placebo 0.30 (95% CI: 0.04, 1.10).

3.5. Uncertainties and limitations about unfavourable effects

More than 1173 MS patients were exposed to the proposed dose 600 mg dose for more than 95 weeks with a total of 4485 patient years of exposure to ocrelizumab in the MS population. However, even if this is a large safety database rare adverse events or adverse events likely to occur later might not have been captured. In particular, available long term exposure data do not allow to conclusively evaluate both the risk of malignancies as well as PML. Moreover, the exclusion of patients >55 years old, prevents the assessment of the safety profile of OCR in the elderly, in particular with respect to malignancies, the risk of which is known to increase with age.

Patients with a history of recurrent or chronic infections or immunodeficiency, and patients with a history of ischemic cerebrovascular disorders were excluded from the pivotal trials. Cardiovascular disease was not among exclusion criteria, but there was only one enrolled patient with a history of cardiovascular disease (SMQ cardiac failure). The safety of OCR in the presence of the above mentioned morbidities is thus not assessable at present.

Opportunistic infections, but not PML were seen in the RA population where ocrelizumab exposure corresponds to 7324 patients years albeit in dose levels ranging from 20 mg to 2000 mg. Opportunistic and serious infections was also seen in the SLE and LN population and 6% and 3%, respectively died in these population due to infections. It is uncertain if safety data from these patient populations can be extrapolated to the MS population as patients in the RA, SLE and LN population also received additional immunosuppressant treatment, had different comorbidities and the RA population was older than the MS population. It is thus unknown if prior or current immunosuppressant treatment in the MS population will increase the risk of infections. It is also unknown, had the safety database been as large as in RA, if cases of opportunistic infections would have occurred in the MS population.

Up to the 30 Jun 2016, there were in total 26 cases of malignancies reported in MS patients treated with ocrelizumab. There was an imbalance in the incidence of malignancies in the ocrelizumab groups compared to IFN and placebo with a cluster of breast cancers in the ocrelizumab groups. There were no cases of breast cancer in the IFN or placebo groups whereas there were 3 cases in the RMS ocrelizumab group and 4 cases in the PPMS ocrelizumab group. One further case of breast cancer occurred in a RRMS patient from study WA21493 (treated with OCR 2000 mg) and one further case of breast cancer occurred in a patient switched to OCR in the open label phase of study WA21093. It is uncertain why this imbalance was observed and currently the data from the RA development programme is not considered adequate to evaluate a long term risk, because in the RA ocrelizumab development program the median number of ocrelizumab doses received by the patients was only 2 in the controlled treatment period and only 3 in the uncontrolled pool. In randomised controlled trials only about 20% of randomized RA patients received more than 2 OCR doses and only 38 patients received up to 8 OCR doses in the open label part. The higher incidence of malignancies, with a cluster for breast cancer, observed in OCR-treated patients relative to comparator (IFN or placebo) is a cause of concern, particularly as age >55 years was an exclusion criteria.

Additionally, long-term safety has not been investigated, and for this reason the applicant will perform post-approval studies to address this issue.

3.6. Effects Table

Table 46 Effects Table for ocrelizumab in adult patients with RMS and PPMS.

Effect	Short Description	Unit	Ocrelizumab	Control	Uncertainties / Strength of evidence	References
Favourable Effects*						
RMS: Adjusted ARR	Rate ratio, primary endpoint		0.156	IFN: 0.291	Not identified (NI) / p <0.0001	Studies WA21092/3 pooled
RMS: 12-week CDP	Pts at 96 weeks, Hazard ratio (KM estimate)	%	9.75	IFN: 15.18	NI / p = 0.0006	Studies WA21092/3 pooled
RMS: 24-week CDP	Pts at 96 weeks, Hazard ratio (KM estimate)	%	7.58	IFN: 12.03	NI / p = 0.0025	Studies WA21092/3 pooled
RMS: 12-week CDi	Pts at 96 weeks with improve-ment, relative increase	%	20.70	IFN: 15.64	NI / p = 0.0194	Studies WA21092/3 pooled
RMS: MSFC	Adjusted mean change from baseline to week 96		0.248	IFN: 0.171	MMRM / p = 0.0038	Studies WA21092/3 pooled
RMS: NEDA	Pts with NEDA who had EDSS score ≥2.0 at baseline	%	45.7	IFN: 25.7	Imputation for missingness / p = <0.0001	Studies WA21092/3 pooled
RMS: SF-36 PCS	Mean change from baseline		0.152	IFN: -0.767	MMRM / p = 0.0217	Studies WA21092/3 pooled
PPMS: 12-week CDP	Pts at 120 weeks (KM estimate), primary endpoint	%	30.2	Placebo: 34.00	Clinical relevance / p = 0.0321	Study WA25046
PPMS: 24-week CDP	Pts at 120 weeks (KM estimate)	%	28.3	Placebo: 32.7	As above / p = 0.0365	Study WA25046
PPMS: Timed 25-foot Walk	Relative ratio to baseline at Week 120, adjusted geoemtric mean change (reduction)	%	38.933	Placebo: 55.097	MMRM / p = 0.0404,	Study WA25046
PPMS: SF-36 PCS	Change from baseline to Week 120, adjusted mean		-0.731	Placebo: -1.108	MMRM /p = 0.6034	Study WA25046
Unfavourable Effects						

Effect	Short Description	Unit	Ocrelizumab	Control	Uncertainties/ Strength of evidence	References
RMS IRRs	*Common symptoms:* pruritus, rash, throat irritation, and flushing	%	34.3	IFN: 9.7		Pool A
RMS Serious IRRs	Urticaria, angioedema, throat irritation, bronchospasm	%	0.1	IFN: 0.1		Pool A
RMS Infections	*Most common:* URT, UTIs, GTIs, skin infections, LRTs, herpes virus-associated infections	Rate/ 100PY (95% CI)	85.4 (80.7, 90.3)	IFN: 69.1 (64.8, 73.5)		Pool A
RMS Serious infection	*Most common:* UTI, appendicitis, cellulitis, pneumonia	Rate/ 100PY (95% CI)	0.83 (0.43, 1.45)	IFN: 1.79 (1.16, 2.64)		Pool A
RMS Malignancies		Rate/ 100PY (95% CI)	0.28 (0.08, 0.71)	IFN: 0.14 (0.02, 0.52)		Pool A
RMS Malignancies		Number of events (type of malignancy)	4 (breast cancer x 2, malignant melanoma, renal cancer)	IFN: 2 (mantle cell lymphoma, squamous cell carcinoma)		Pool A
PPMS IRRs	*Common symptoms:* pruritus, rash, throat irritation, and flushing	%	39.9	Placebo: 25.5		PPMS
PPMS Serious IRRs	tachycardia, pyrexia, chills, nausea, vomiting, pruritus, hypertension, hypotension muscle spasticity, ECG QT	%	1.0	Placebo: 0		PPMS
PPMS Infections	*Most common:* Nasopharyngitis, UTI, Influenza, URT	Rate/ 100PY (95% CI)	76.5 (72.0, 81.2)	Placebo: 76.1 (69.6, 83.0)		PPMS

Effect	Short Description	Unit	Ocrelizumab	Control	Uncertainties/ Strength of evidence	References
PPMS Serious infection	*Most common:* UTI and pneumonia	Rate/ 100PY (95% CI)	2.97 (2.14, 4.01)	Placebo: 2.88 (1.73, 4.50)		PPMS
PPMS Malignancies		Rate/ 100PY (95% CI)	0.92 (0.49, 1.57)	Placebo: 0.30 (0.04, 1.10)		PPMS
PPMS Malignancies		Number of events (type of malignancy)	13 (breast cancer x 4, basal cell carcinoma x 3, pancreatic cancer, malignant fibrous histiocytoma, endometrial cancer, anaplastic large-cell lymphoma)	Placebo: 2 (cervix adenocarcinoma, basal cell carcinoma)		PPMS

Abbreviations: 100PY=100 patient years, ARR= annualized relapse rate, CDI=confirmed disability improvement, CDP=confirmed disability progression, CI=confidence interval, EDSS=Expanded Disability Status Scale, GTIs= gastrointestinal tract infections, IFN: interferon beta-1a, IRRs=Infusion related reactions, KM=Kaplan-Meier, LRT= lower respiratory tract, MMRM=Mixed-Effect Model Repeated Measures, NEDA=no evidence of disease activity, NI=not identified, PCS=physical component summary, Pts=patients, SF-36= short-form-36 questionnaire, URT=upper respiratory tract infections, UTI=urinary tract infections

Notes:* Only primary and secondary efficacy clinical endpoints; not all results with p <0.05 were confirmatory due to broken hierarchical testing; pooling of data for RMS was only pre-specified endpoints for 12-week CDP, 24-week CDP and 12-week CDI; MSFC and SF-36 PCS had p-values 0.3261 and 0.2193, respectively, in Study 21092. 12-week CDI had p-value of 0.4019 in Study 21093.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

RMS

The population included in the RMS trial represents RMS patients with an active disease stage. Clinically relevant and consistent superior efficacy of ocrelizumab versus interferon beta-1a in the reduction of ARR and also clinically relevant effect on secondary endpoints in two pivotal phase III studies has been shown.

A clinically relevant effect has been shown across subgroups regardless of previous treatment or respond to other treatments. This is important as interferon beta-1a (IFN) is considered one of 4-5 medicines for first line treatment in RMS.

PPMS

There is a particularly high unmet medical need in patients with PPMS, as there are no disease modifying treatments approved.

The magnitude of the observed effect on the 12-week CDPis modest, but nevertheless.relevant in the context of a relentlessly progressive disease. There is no accepted definition of what would constitute a minimal clinical benefit and, as stressed by the patients, any delay in disease progression is important to them in this setting.

The identification of the PPMS patient population that may benefit from treatment with the drug was difficult.

The pathogenic mechanism in PPMS is one of extraordinary complexity. The co-existing processes of inflammation and neurodegeneration elicit themselves differently during the different stages of the disease, and mechanisms other than those involving B cells could be involved in the persistent inflammation, which ocrelizumab may act upon. Thus, the administration of a single monoclonal antibody and its very specific mechanism of action is unlikely to be able to fully counteract the whole pathological cascade in PPMS. One hypothesised manner in which the effects of ocrelizumab in this case could be mediated is the fact that by acting on the inflammatory component of the disease the drug could allow for an improved process of remyalination and repair to occur, thus indirectly influencing the neurodegeneration. This hypothesis has still to be confirmed, as at present there are not enough data to substantiate it.

The identification of the PPMS patient population that may benefit from treatment with the drug was difficult, as it had to rely on subgroup analyses, for which the study was not powered. After a number of discussions with the applicant and among experts, it was agreed that based on the available data presented in the analyses, it was reasonable to believe that patients for whom disease duration and level of disability, as well as available imaging features characteristic of inflammatory activity (i.e. T1 Gd-enhancing lesions and/or active [new or enlarging T2 lesions]) suggested that they are in the early phase of PPMS, were most likely to experience the most benefit from ocrelizumab treatment

Additionally, some supportive reasoning about the identification of a sub-population of PPMS patients that can benefit more from ocrelizumab, can be derived from the exploratory subgroup analysis of the findings from a similar trial performed with another monoclonal antibody (Olympus).

Therefore, the CHMP limited the indication to “early” PPMS where sufficient evidence of efficacy is available.

RMS and PPMS

The main safety issues with ocrelizumab is the risk of infusion related reactions and infections. Infusion related reactions, although frequent, were for the majority of patients manageable, which is also reflected in the low frequency of discontinuations due to IRRs. Infections occurred more frequently in the ocrelizumab groups. Even if serious infection or infection requiring IV antiinfectives occurred less frequently in the ocrelizumab group than in the IFN group, serious infections had a worse outcome (including 2 deaths) in OCR-treated patients, both in RMS (Pool A) and in PPMS patients, suggesting that ocrelizumab does cause an increased risk of infections. A worse outcome of serious infections is a concern with a B cell depleting therapy, as in the real world setting a higher frequency of serious infection is expected, potentially leading to higher mortality rates. On the other end, it is also true that the frequency of grade 4 (life-threatening) and grade 5 (fatal) infections was low in all treatment groups, and that in the placebo arm was about 0%, which is possibly an underestimation of the risk associated with the natural course of the disease. In any case, it is of some degree of reassurance that all life-threatening infections resolved without discontinuing ocrelizumab.

Further, it is still unknown if opportunistic infections and a higher frequency of infections is likely to occur if additional immunosuppressants are administered. Unlike IFN, ocrelizumab does not have an adverse effect in the liver. Furthermore, both in RMS (Pool A) and in PPMS, in the subgroup of subjects with lymphocytes confirmed to be <LLN, higher rates of serious infections were observed in OCR treated patients compared to IFN/ PBO treated patients. Increased rates of serious infection were observed in RMS patients and in Pool B over time (beginning at Dose 5).

The safety profile of ocrelizumab shows an increased frequency of malignancies compared to control groups, which seem to be driven by a cluster of breast cancer. However, the incidence was not higher as compared to epidemiological data and available data do not allow to definitely establish - nor rule out - a clear causality to ocrelizumab treatment. Uncertainties exist as regards the occurrence of rare opportunistic infections, like PML. However, due to the uncertainties regarding the imbalance of

malignancies, the currently proposed indication is a restriction of the indication to be used in patients with active RMS.

Balance of benefits and risks

RMS

Clinically relevant and superior efficacy versus IFN has been demonstrated regardless of previous treatment or response to prior treatment in a population with active disease. Due to the uncertainties regarding the imbalance in malignancies it is considered appropriate to restrict the indication to active RMS. The benefit/risk of ocrelizumab for the use in patients with active RMS was considered positive.

PPMS

The results of the pivotal study, supported by the additional evidence derived from the performed sub-group analyses, provided sufficient grounds to establish that a PPMS sub-population exists, in which the benefits outweigh the risks of treatment with ocrelizumab. The magnitude of the effect of ocrelizumab is considered modest, but sufficient as no other approved treatments are currently available. The safety profile in this population, including the uncertainties regarding the imbalance in malignancies, was considered in the context of the present unmet clinical need in a relentless, seriously debilitating disease. The apparent worse outcome of serious infections with ocrelizumab was based on very low numbers; and it is of some reassurance that all life-threatening infections resolved without discontinuing ocrelizumab.

The indication is limited to early PPMS patients as these are expected to benefit the most from ocrelizumab and for whom the potential risks will be more acceptable.

The benefit of ocrelizumab in the sought early PPMS indication is thus considered to outweigh the risks.

3.8. Conclusions

The overall B/R of Ocrevus is positive in the pursued indication including RMS and early PPMS.

Divergent position(s) are appended to this report.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Ocrevus is favourable in the following indication:

Ocrevus is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features (see section 5.1).

Ocrevus 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 (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product

Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Not applicable

Obligation to conduct post-authorisation measures

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that ocrelizumab is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

APPENDIX 1

DIVERGENT POSITION DATED 9 NOVEMBER 2017

DIVERGENT POSITION DATED 9 NOVEMBER 2017

Ocrevus EMEA/H/C/004043

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation for Ocrevus indicated for the treatment of adult patients with:

- relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features
- early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.

The reasons for divergent opinion were the following:

Efficacy in the PPMS population has not been sufficiently established. A single confirmatory trial has been conducted in this population. In the event of a submission with only one pivotal study, this has to be particularly compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality, and internal consistency.

The primary endpoint and most secondary endpoints were met; however, the demonstrated efficacy is not compelling from a statistical and clinical point of view.
The pre-specified subgroup analyses as well as post hoc analyses suggest that a subgroup of patients with early PPMS and signs of acute inflammation may be the patient population most likely to benefit. However, these exploratory subgroup analyses are hypotheses generating and do not identify a patient population where efficacy has been sufficiently established.

In view of the above considerations the undersigned delegates consider the benefit risk of this product to be negative:

Hanne Lomholt Larsen

Alar Irs

Robert James Hemmings

Greg Markey

Johann Lodewijk Hillege

Svein Rune Andersen