CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761053Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	761053
Priority or Standard	Priority
Submit Date(s)	4/28/16
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PDUFA Goal Date	December 28, 2016
Division/Office	Division of Neurology Products
Reviewer Name(s)	Lawrence Rodichok MD
Review Completion Date	9/12/16
Established Name	ocrelizumab
(Proposed) Trade Name	Ocrevus
Applicant	Genentech, Inc
Formulation(s)	Solution 30mg/mL
Dosing Regimen	600 mg IV every 24 weeks
Applicant Proposed Indication(s)/Population(s)	OCREVUS is indicated for the treatment of patients with relapsing forms of multiple sclerosis (RMS). OCREVUS is indicated for the treatment of patients with primary progressive multiple sclerosis (PPMS).
Recommendation on Regulatory Action	Approval: OCREVUS is indicated for the treatment of patients with relapsing forms of multiple sclerosis (RMS). Approval: OCREVUS is indicated for the treatment of patients with primary progressive multiple sclerosis (PPMS).
Recommended Indication(s)/Population(s) (if applicable)	Patients with Relapsing Forms of Multiple Sclerosis (RMS) Patients with Primary Progressive Multiple Sclerosis (PPMS)

Table of Contents

Table of Tables

Table of Figures

Glossary

AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CCOD	clinical cut-off date
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CRO	Contract Research Organization
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DAE	discontinuation due to an adverse event
DBL	Database lock
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
EDSS	Expanded Disability Status Scale
ETASU	elements to assure safe use
FACS	fluorescence-activated cell sorter
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization

IEC	institutional ethics committee
IND	Investigational New Drug
IRB	institutional review board
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
mL	milliliter
mM	millimolar
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NSAID	non-steroidal anti-inflammatory drug
OCR	ocrelizumab
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	post-marketing commitment
PMR	post-marketing requirement
PP	per protocol
(b) (4)	(b) (4)
PPI	patient package insert
PPMS	Primary Progressive Multiple Sclerosis
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
RMS	Relapsing Multiple Sclerosis
OUS	Rest of the World (i.e. outside the United States)
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	System Organ Class
SOP	standard operating procedure
SSRI	selective serotonin reuptake inhibitor

TEAE	treatment emergent adverse event
US	United States

1 Executive Summary

1.1. Product Introduction

Ocrelizumab (PRO70769; RO4964913) is a recombinant humanized glycosylated monoclonal antibody based on the human immunoglobulin G1 (IgG1) framework that contains subgroup-III variable heavy chain (V_HIII) and kappa subgroup-I variable light chain (VκI) sequences. The antibody consist of two identical light chains (213 amino acid residues each) and two identical heavy chains (452 amino acid residues each). Ocrelizumab also contains an N-linked glycosylation site at Asn302 on each of the two heavy chains. Ocrelizumab is produced in [redacted] (b) (4) cells and is directed against the CD20 antigen present on select normal as well as malignant B cells. Ocrelizumab was constructed using recombinant deoxyribonucleic acid (DNA) techniques from sequence information provided by the murine monoclonal antibody 2H7. CD20 is a B-cell surface molecule that is restricted in expression to pre−B cells and mature B cells but is not expressed earlier in the development of B cells. While ocrelizumab selectively depletes CD20-expressing B cells, the capacity for B-cell reconstitution and pre-existing humoral immunity are preserved. In addition, innate immunity and total T-cell numbers are not affected. The polypeptide structure consists of 2 light chains and 2 heavy chains held together by disulfide bonds.

Ocrelizumab Drug Product is supplied in 15 mL Type I glass vials as a sterile, single-use solution for IV infusion and contains no preservatives. Each vial contains [redacted] (b) (4) 300 mg of ocrelizumab, at a nominal fill volume of 10 mL. The drug product is formulated as 30 mg/mL ocrelizumab in [redacted] (b) (4) milliMolar (mM) sodium acetate at pH 5.3, with [redacted] (b) (4) mM trehalose dihydrate and 0.02% polysorbate 20. [redacted] (b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

Relapsing/Remitting Multiple Sclerosis (RMS)

Relapses

Two adequate and well controlled trials provide substantial evidence that treatment with ocrelizumab (OCR) 600 mg (OCR 600) given intravenously every 12 weeks reduces the frequency of relapses in comparison to treatment with Rebif in patients with relapsing forms of multiple sclerosis (MS).

Progression of disability

The same two adequate and well controlled trials also provide substantial evidence that treatment with OCR 600 reduces the number of periods of disability progression lasting 12 and 24 weeks measured by the Expanded Disability Status Scale score (EDSS)[1] in patients with relapsing forms of MS.

Evidence of disease activity on Magnetic Resonance Imaging

The same two adequate and well controlled trials provide substantial evidence that treatment with OCR 600 mg reduces evidence of disease activity on MRI scans using a variety of imaging methods in patients with relapsing forms of MS.

Primary Progressive Multiple Sclerosis

Progression of disability

In a single adequate and well controlled trial (study WA25046) there is evidence that treatment with ocrelizumab 600 mg given intravenously every 12 weeks as two doses of 300 mg separated by 14 days reduces the occurrence of periods of disability. The pre-specified primary endpoint was met, i.e. a statistically significant reduction in the proportion of patients with 12 week confirmed progression of disability as estimated by the Kaplan-Meier method and Cox proportion hazard estimate of the hazard ratio. However the result is not statistically persuasive and is sensitive to the methods of handling missing endpoint data. Analysis without imputation of missing endpoint data does not yield a statistically significant difference in efficacy compared to placebo for either 12 or 24 week confirmed progression of disability. The apparent absolute reduction in the proportion of patients who met these endpoints is less than 5% and over 30% still meet the criteria for confirmed progression of disability after two years of treatment with OCR 600. The reduction in 12 and 24 week confirmed progression of disability in the two trials in RMS patients does not provide convincing support for the reduction in disability seen in the single trial in PPMS patients because these populations differ significantly in their demographic and baseline disease characteristics. More importantly, the frequency and

duration of the periods of disability in the PPMS population differ substantially from those in the RMS population. These data do not adequately support that RMS is sufficiently related to PPMS to allow the use of data from the RMS studies to support the results of the study in patients with PPMS. Therefore there remains significant uncertainty as to whether treatment with OCR is effective for the treatment of PPMS. Although pharmacokinetic and pharmacodynamics results suggest that the single dose of 600 mg given after the first split dose in the RMS studies may not differ significantly from the split dose as given for all doses in the PPMS study, the relationship of the PK/PD measurements to efficacy, especially for PPMS, is not established. Therefore the use of single doses of 600mg after the first dose for treatment of PPMS, as in the studies of RMS, adds additional uncertainty.

1.3. Benefit-Risk Assessment

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Benefit-Risk Summary and Assessment

Relapsing forms of MS

Two adequate and well controlled trials in patients with RMS have provided substantial evidence that treatment with OCR 600 reduces the annualized relapse rate, reduces periods of disability lasting 12 and 24 weeks and reduces evidence of disease activity on magnetic resonance imaging in comparison to Rebif. There is evidence of a benefit on the acute loss of function due to a relapse (defined in part by an increase in disability) as well as for the longer 3 and 6 month periods of disability that are generally not related to relapses. These are all clinically relevant benefits that would justify a low to moderate safety risk. Based on the review of safety by Dr. Boehm the risk does appear to be relatively modest and manageable. The benefit to risk comparison justifies a recommendation of approval for this indication.

Primary progressive MS

A single adequate and well-controlled trial has provided evidence that treatment with OCR 600 may reduce periods of disability lasting 12 and 24 weeks. However the result is not persuasive. Analyses based on observed outcome, i.e. no imputation of missing outcome results, lead to a statistically non-significant result. The absolute reduction in the proportion of patients with 12 or 24 week confirmed disability is less than 5%; over 30% of patients meet the criteria for confirmed disability progression after 2 years of treatment with OCR 600. There is no indication that treatment with OCR 600 has a clinically meaningful benefit on longer term disability as measured by the EDSS or the Timed 25 foot walk test after 2 years of treatment. Therefore in the absence of scientifically valid data confirming the result, there is significant uncertainty as to whether treatment with OCR 600 leads to a clinically relevant reduction in intermediate periods of disability in the PPMS population. The characteristics of the periods of disability seen in the RMS population are significantly different from those in the PPMS population. For this key measure of effectiveness these two disorders are not sufficiently related to each other to justify using the benefit seen in the RMS population to support the less than persuasive evidence of a benefit seen in the PPMS population. There is also a concern that the pathophysiology of long term irreversible disability may differ from that responsible for shorter term disability seen with relapses and for periods lasting up to 6 months. Therefore there remains significant uncertainty as to the benefit of treatment with OCR 600 for PPMS. The safety risk in PPMS is no different from that in the RMS population, i.e. a modest and manageable risk. There is an unmet need for patients with PPMS since there is no approved therapy and progressive and irreversible disability is likely without effective treatment. Therefore despite the uncertainty as to benefit, the unmet need in the PPMS population and the relatively modest risk justifies approval for this indication.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• RMS is a condition associated periods of short term neurologic signs and symptoms due to relapses. It is also associated with periods of disability due in part to incomplete recovery from relapses. These periods of disability typically last about 3 to 6 months but commonly resolve after that. These features of RMS are generally thought to be due to acute inflammatory events that are disseminated over time and occur in most myelinated areas of the CNS and to a lesser extent within neuronal aggregates and even within the meninges. However longer term and irreversible disability may also develop due to neurodegenerative changes that are largely independent of the occurrence of relapses. These may not be due to acute inflammation but rather to a different but perhaps related type of pathophysiology. Two adequate and well-controlled trials provide substantial evidence that treatment with OCR 600 will reduce the occurrence of disabling relapses in a statistically significant and clinically relevant proportion of the RMS population. The two pivotal trials also demonstrate a statistically significant reduction in the relatively small proportion (~10%) of patients with RMS who experience periods of short term disability. There is minimal uncertainty regarding these benefits.	• Treatment with OCR 600 results in a statistically significant and clinically meaningful reduction in relapses and in the occurrence of short term periods of disability largely unrelated to relapses. Two adequate and well-controlled studies have demonstrated a reduction in the annualized relapse rate and the proportion of patients experiencing 12 and 24 week confirmed progression of disability, endpoints considered valid measures of function in MS patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• PPMS is generally considered a distinct "phenotype" of MS characterized by steady progression of disability, perhaps especially secondary to involvement of the spinal cord. Relapses are either absent or very infrequent. Treatments that have a robust benefit in RMS have been ineffective in trials of patients with PPMS. There may be a different underlying pathophysiology that causes the progressive and generally irreversible disability in PPMS patients. There are clear differences in the demographics and baseline disease characteristics of patients with PPMS compared to those with RMS. Study WA25046 provides evidence of a reduction in the progression of disability lasting 12 and 24 weeks in PPMS patients. However there is considerable uncertainty regarding this benefit since the result is not persuasive and is not confirmed in an independent adequate and well controlled study in PPMS patients. This uncertainty remains despite the reduction in 12 and 24 week confirmed progression of disability demonstrated in the 2 adequate and well controlled studies in RMS patients because, in addition to significant differences in the demographic and baseline disease characteristics of the PPMS compared to the RMS populations, the characteristics of the periods of disability that occur in the PPMS population in study WA25046 are significantly different from those characteristics in the RMS population as shown in studies WA21092 and WA21093.	• OCR 600 has been shown to reduce short term periods of disability in PPMS patients in a single adequate and well controlled trial. However the result is not statistically strong and there are no data that provide adequate confirmation of the result.
Current Treatment Options	• There is reasonable certainty that current approved therapies for RMS are effective in reducing the frequency of relapses. There is uncertainty as to whether the currently approved therapies reduce	• Currently approved therapies for MS are effective for the reduction of relapses. Most recently approved therapies appear to be

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	short term disability, i.e. 12 and 24 week confirmed disability, since this has been demonstrated in a single trial only for some of these therapies.	more effective than the early interferons but the safety of these therapies is variable and some carry serious risks. Therefore there is a need for a therapy that is either as effective in reducing relapses but carries less risk or that is more effective but comparable or lower risk compared to available therapies. The benefit of currently approved therapies on short term disability has been inconsistent. There is a need for a therapy with robust evidence of a reduction in these measures of disability. The evidence of benefit in the RMS population justifies the modest and manageable risk (see the review of safety by Dr. Boehm).
	• There are no therapies approved for the treatment of PPMS. Trials of therapies that have been approved for RMS have not shown a benefit in the PPMS population.	• The absence of an approved therapy for PPMS in this progressively disabling population would justify approval of a therapy even if there is some uncertainty regarding efficacy, assuming a modest and manageable risk, as appears to be the case for OCR 600.
Benefit	• In patients with RMS, treatment with OCR 600 reduces the frequency of relapses and reduces the frequency but not the duration of short term periods of disability. The results supporting these benefits in two adequate	• RMS: The benefit of treatment with OCR 600 on relapses and short term disability is persuasive and will justifies the modest and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	and well controlled trials are robust. • In a single adequate and well controlled trial, treatment with OCR 600 reduced the frequency of periods of disability lasting 12 and 24 weeks. However the result is not persuasive and therefore there is uncertainty as to whether treatment with OCR 600 reduces short term disability in PPMS patients. The reduction of short term disability in the two trials in RMS patients does not support a benefit in PPMS since the populations differ in disease characteristics and in the characteristics of the periods of disability. There are no data to support that treatment with OCR has a clinically meaningful effect on long term irreversible disability.	manageable risk (see review of safety by Dr. Boehm). • PPMS: The benefit of treatment with OCR 600 on short term disability for patients with PPMS is not persuasive and not confirmed by data in a comparable population in an adequate and well controlled trial. However the risk of treatment with OCR 600 is modest and manageable. Therefore, despite significant uncertainty as to the benefit in the PPMS population, the unmet need for these patients and the favorable benefit to risk comparison would justify approval.
Risk	• See the review of Safety by Dr. Boehm	
Risk Management	• See the review of Safety by Dr. Boehm	

2 Therapeutic Context

2.1. Analysis of Condition

Multiple Sclerosis is a chronic disorder of the CNS characterized by recurrent episodes (relapses) of neurologic deficits that are due to one or more areas of acute injury to myelin, oligodendrocytes and to a lesser extent axons and neurons. Areas of acute inflammatory injury may involve subcortical white matter, brainstem, optic nerve and /or spinal cord. The diagnostic criteria for MS essentially require clinical and/or imaging evidence of a dissemination of these events "in space and time"[2]. Although early relapses may be followed by complete recovery, over time the recurrent relapses are associated with an accumulation of residual deficits and increasing disability[3]. Over time a slow progression of disability independent of the occurrence of relapses is seen in most patients with MS[3,4]. This "relapsing and remitting" pattern with or without the slow progression of disability, occurs in approximately 85% of patients with MS. Of those with a typical relapsing onset, approximately one-third will enter a slowly progressive phase with or without superimposed relapses[5]. Although disability can result from residual deficits following relapses[6], relapses are probably not the dominant factor resulting in severe and permanent disability[7]. Therefore a reduction in the relapse rate does not necessarily correlate with a significant reduction in long term disability. However the early frequency and severity of relapses and incomplete recovery from early relapses all tend to predict a more rapid progression of irreversible disability[8,9]. Relapses are associated with a mean increase of 0.75 on the EDSS scale[6]. Most of the time the disability incurred at a relapse improves significantly within 2 to three months[6]. Increases on the EDSS that meet generally accepted criteria for confirmed progression of disability for 3 or 6 months are usually not sustained to one or two years[10].

Approximately 15% of patients with MS have a slowly progressive course from onset (PPMS). Current accepted clinical criteria for a diagnosis of PPMS require at least one year of steady progression (not otherwise defined), clinical and/or MRI evidence of in space and time which may be supported by the presence of oligoclonal bands in the cerebrospinal fluid[2]. The pathophysiologic and clinical relationship of PPMS to RMS is unclear. There are clear demographic differences in patients with PPMS compared to those with RMS[11]. The sexes are equally represented in PPMS whereas females predominate 2:1 in RMS. The mean age at onset is about 10 years later and the baseline EDSS score significantly higher. The disability in patients with PPMS typically reflects involvement of the spinal cord whereas that in RMS patients is more multifactorial. Whereas acute inflammation is prominent in RMS, it is not as prominent in PPMS which appears to have a significant neurodegenerative component. This is reflected in differences in the MRI findings where there may be more evidence of inflammation and

disruption of the blood brain barrier in RMS and more prominent evidence of spinal pathology in PPMS. These differences correlate with the experience to date that drugs that show clear benefit in the RMS population have not shown a statistically significant benefit in the PPMS population.

2.2. Analysis of Current Treatment Options

Relapsing forms of MS

The currently approved therapies for RMS are shown in Table 1 below. Available therapies reduce the relapse rate by 30 to 50%. While a reduction in the number of relapses is desirable it is unclear that this will result in a significant reduction in long term disability. Differences in methodology and the populations studied limit interpretation of the effect of these therapies on long-term disability. Several have shown a numeric reduction in some measure of disability that was confirmed 12 and/or 24 weeks after an initial significant increase in EDSS score. However, if a statistically significant reduction was seen in one trial, the result was usually not replicated in a second trial. Although most therapies approved for the treatment of RMS show a reduction in various MRI findings in RMS, there is no evidence at this time to support the use of any of these MRI measures as the primary criterion for the choice of therapy.

Because they were the earliest approved therapies and because there have been few major safety concerns, either a β -interferon or glatiramer acetate are often the initial choice for treatment for new onset typical RMS. Because the interferons share the same presumed mechanism of action and have similar efficacy, if the response is not adequate to one interferon then the choice of next therapy is usually not a different interferon and usually not glatiramer acetate. There are now several approved alternative therapies with efficacy at least comparable to the interferons and glatiramer acetate. The data available are not sufficient to conclude that the efficacy of any of the alternative therapies is superior to the older “first line” therapies.

Each has somewhat unique benefits and risks. Unless there is strong evidence of superior efficacy and/or a notable lack of safety concerns, any new approved therapy will most likely be used for those who have not responded adequately to the interferons, glatiramer acetate and possibly one of the approved oral therapies.

Primary Progressive MS

There are no therapies approved for the treatment of PPMS.

Table 1: FDA-approved treatments for Relapsing Forms of Multiple Sclerosis

Approved Drug	Name	Sponsor	Approved	Dose	Frequency	Major Safety Concerns
Beta interferon 1b	Betaseron (Betaferon in the EU)	Bayer	1993	0.25 mg –(initial dose 0.0625 mg - gradually increase over 6 weeks)	SC qod	None
Beta interferon 1a	Avonex	Biogen Idec	1996	30 µg (may start at 7.5µg & increase by 7.5 µg weekly for 3 weeks)	IM q week	None
Glatiramer acetate	Copaxone	Teva	1996	20 mg/day	SQ qd	None
Mitoxanthrone	Novantrone	EMD Serono	2000	12mg/m^2 IV over 5 to 15 min	IV q 3 mo	Cardiotoxicity
Beta interferon 1a	Rebif	EMD Serono Pfizer Inc.	2002	22µg or 44µg (start at 20% of target; increase over 4 weeks)	SQ tiw	None
Natalizumab	Tysabri	Elan	2004	300mg IV over 1 hour	every 4 weeks	PML
Beta interferon 1b	Extavia	Novartis	2009 (1993)	0.25 mg –(initial dose 0.0625 mg - gradually increase over 6 weeks)	SQ qod	None
Fingolimod	Gilenya	Novartis	2010	0.5 mg	orally once daily	First dose bradycardia CI for recent MI, unstable angina, TIA,CHF Macular edema Impaired PFTs Fetal risk
Teriflunomide	Aubagio	Sanofi	2012	7 mg or 14 mg	orally once daily	Black box warning for hepatotoxicity and teratogenicity; additional concerns for WBC decrease, renal failure, skin reactions; peripheral neuropathy

Approved Drug	Name	Sponsor	Approved	Dose	Frequency	Major Safety Concerns
Dimethyl fumarate	Tecfidera	Biogen-Idec	2013	120 mg for 7 days, then 240 mg	twice daily	Lymphopenia
PEGylated interferon β	Plegridy	Biogen	2014	125 µg (63 µg on day 1, 94 µg on day 15, the full dose starting on day 29)	Q2 weeks	None
Alemtuzumab	Lemtrada	Genzyme	2015	1st course: 12 mg/dy X5 2nd course: 12 mg/dy X3	2 courses 12 months apart	Black box warning for serious/fatal autoimmune conditions including thrombocytopenia and anti-glomerular basement membrane disease; serious and life-threatening infusion reactions; special facilities required for infusion; increased risk of malignancies; REMS
Daclizumab	Zinbryta	Biogen	2016	150 mg subcutaneously	monthly	Black box warning for hepatic injury including autoimmune hepatitis, other immune-mediated disorders.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Ocrelizumab is considered a new molecular entity. Ocrelizumab is not currently marketed in the US for any indication.

3.2. Summary of Presubmission/Submission Regulatory Activity

Pre-IND (IND 100593) meeting: June 14, 2007
Original IND: 1/9/2008
The initial protocol was for a trial of two doses of OCR, 600 and 1000 mg, with placebo and Avonex comparator groups.
Full Clinical HOLD: 2/11/2008
HOLD issues were related in part to justification of the placebo group.
Remove Clinical HOLD: 5/21/08
Ethical issues related to the placebo group were addressed.
SPA No Agreement: April 25, 2011
End of Phase 2 meeting: December 5, 2008
Fast Track Designation: March 6, 2013
Pre-BLA meeting – RMS indication: December 8, 2015
Breakthrough Therapy Designation: February 1, 2016
Pre-BLA meeting – PPMS indication: February 4, 2016
Priority review: June 24, 2016

3.3. Foreign Regulatory Actions and Marketing History

Ocrelizumab is not approved for any indication in any country.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

See the review by OSI. Inspections have not been completed at the time of this review.

4.2. Product Quality

See the review by the Chemistry, Manufacturing and Control reviewers which are not completed at the time of this review.

4.3. Clinical Microbiology

See the review by the CMC/microbiology reviewers.

4.4. Nonclinical Pharmacology/Toxicology

See the reviews by Drs. Freed and Wilcox.

4.5. Clinical Pharmacology

See the reviews by Drs. Parepally and Men.

4.5.1. Mechanism of Action

See the reviews by Drs. Parepally and Men.

4.5.2. Pharmacodynamics

See the reviews by Drs. Parepally and Men.

4.5.3. Pharmacokinetics

See the reviews by Drs. Parepally and Men.

4.6. Devices and Companion Diagnostic Issues

N/A

4.7. Consumer Study Reviews

N/A

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2: Clinical Trials Relevant to RMS and PPMS indications

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
WA21092	RCT; Comparator Rebif	600mg IV q24W	ARR; CDP12; CDP 24	96 weeks	821	RMS	141 sites in 32 countries
WA21093	RCT; Comparator Rebif	600mg IV q24W	ARR; CDP12; CDP 24	96 weeks	835	RMS	166 sites in 24 countries
WA25046	RCT; Comparator placebo	600mg IV q24W	CDP12; CDP 24	120 weeks	732	PPMS	182 sites in 29 countries
Studies to Support Safety							
See Review of Safety by Dr. Boehm							
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
WA21493	RCT; placebo and Avonex comparators	600 and 1000 mg IV q24W	Total Gd-enhancing lesions	24 week double-blind period	220	RMS	79 sites in the EU and North America

5.2. Review Strategy

RMS indication: The review for the indication for the treatment of RMS is limited to the two pivotal trials, WA 21092 and WA21093. These two trials are essentially identical in design and execution. The comparator was Rebif in both trials. The treatment duration of 96 weeks is considered adequate to support an indication for both reduction in relapse rate and reduction in 12 and 24 week confirmed progression of disability.

PPMS indication: The review is focused primarily on the one RCT in the PPMS population, WA25046. The applicant asserts that the data on progression of disability in the two trials in RMS patients can provide support for the result in the PPMS population (Summary of Clinical Efficacy Section 3.2 and following). Therefore the review is also focused on whether these two forms of MS are sufficiently related, especially in terms of the characteristics of the progression of disability that occurs in RMS compared to PPMS, as well as on whether the data in RMS provide confirmation of the result in study WA25046.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. WA21092: A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon β-1a (Rebif®) in patients with relapsing multiple sclerosis

6.1.1. Study Design

Overview and Objective

Study WA21092 ("OPERA I") was one of two RCT's whose objective was to assess the efficacy of ocrelizumab compared to Rebif as treatment for relapsing forms of multiple sclerosis as measured by a reduction in the annualized relapse rate after two years of treatment.

Trial Design

Study WA21092 was a randomized, 96-week, double-blind, double-dummy, parallel-group, active controlled Phase III study, designed to evaluate the efficacy and safety of ocrelizumab (OCR) in comparison to Rebif in patients with RMS who experienced at least either two documented clinical attacks within 2 years or one clinical attack within 1 year prior to screening (but not within 30 days prior to screening). The primary endpoint was evaluated at 96 weeks. The study design is summarized in **Figure 1.**

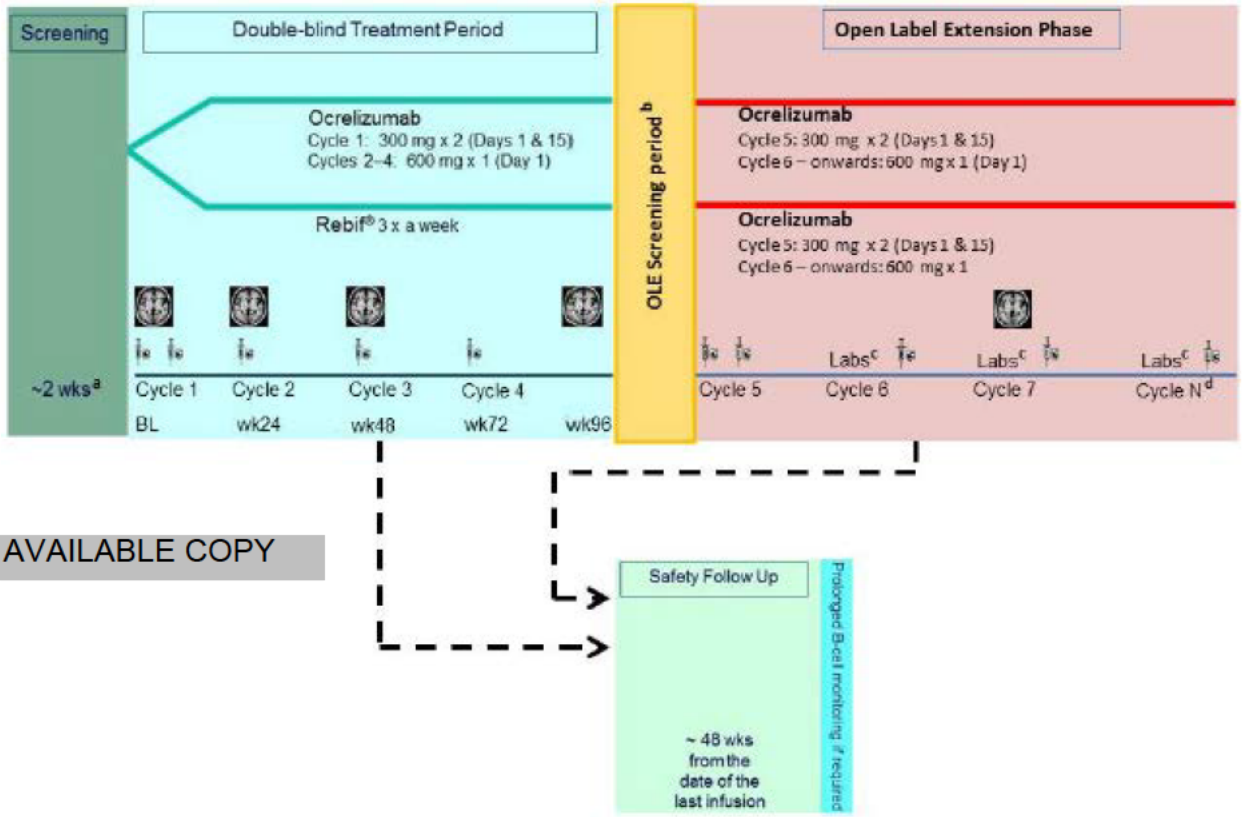
> ***Reviewer Comment: Interferon β 1a given as 44 µg subcutaneously three times per week (Rebif) has been shown to be superior to placebo in reducing the number of relapses per subject after two years of treatment (32% relative reduction) and has been shown to prolong the time to the first relapse (median 9 months vs 6 months). In a single study Rebif was shown to reduce the proportion of patients with 12-week confirmed progression of disability (37% vs 26%). Interpretation of any effect on relapses or progression of disability in comparison to other treatments for MS is limited by the lack of a concurrent placebo group in this trial to confirm any benefit from treatment with Rebif in disability endpoints.***

Patients who completed the 96-week double-blind treatment had the option to enter a single group, active treatment Open Label Extension (OLE) period provided that they fulfilled the eligibility criteria for the OLE.

The study consisted of the following study periods:

- Screening (up to 8 weeks prior to randomization)
- 96-week double-blind, double-dummy comparative treatment
- Safety Follow-Up (SFU) followed by B-cell monitoring. This included all patients who withdrew prematurely from study treatment during the 96 week, double-blind, double-dummy comparative treatment period, or during the OLE, as well as patients who did not enter the OLE. Patients did not receive study treatment during SFU.
- OLE screening
- OLE

Figure 1: WA21092 and WA21093: Overview of Study Design and Dosing Regimen



a. A Screening period of up to 8 weeks was allowed for relevant clinical, administrative, or operational reasons.
b. The OLE Phase Screening Period started after all assessments at the Week 96 Visit had been done. It could last up to 4 weeks. Note that during the OLE Phase Screening Period, patients received Rebif®/Rebif® placebo until the first infusion of Cycle 5.
c. In order to verify that patients met re-treatment criteria, patients in the Open-Label Extension Phase of the study came to the clinic approximately 2 weeks prior to infusions of Cycle 6, 7, etc.
d. The OLE Phase of the study could be terminated at any time. Cycle N represents a typical cycle that occurred every 24 weeks.

Randomization was 1:1.

Blinding

This study had a double-blind, double-dummy design. 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:

- There was a dedicated examining investigator / Expanded Disability Status Scale (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 (KPS).
- There was blinding of selected laboratory parameters that could reveal patient's allocation to study treatment. 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

Laboratory parameters that could lead to unblinding to treatment assignment, such as fluorescence-activated cell sorting (FACS) cell counts including CD19+ cells, lymphocyte count, IgM and IgG levels, and type 1 interferon neutralizing antibody levels were to remain blinded in all patients, except those meeting unblinding criteria for safety reasons. These laboratory parameters remained blinded during the double-blind, double-dummy treatment period, Safety Follow-Up Period, OLE Phase Screening Period, and during the first cycle of the OLE Phase (Cycle 5).

> ***Reviewer Comment: The treating investigator had access to previous assessments recorded in the medical record but should not have had access to EDSS scores recorded by the examining neurologist. If a query was needed to clarify an inconsistent EDSS then the query should have been sent to the examining neurologist who then would then have been able to see the previous EDSS scores when using*** (b) (4) ***to address the query. In principle, if there was no query at any time for a given subject then the examining neurologist should have never seen the previous EDSS scores.***

Key eligibility criteria

Key inclusion criteria

- Ages 18-55 years at screening, inclusive.
- Diagnosis of MS, in accordance with the revised McDonald criteria (2010)[2].
- At least 2 documented clinical attacks within the last 2 years prior to screening, or one clinical attack in the year prior to screening (but not within 30 days prior to screening).
- Neurological stability for ≥ 30 days prior to both screening and baseline.
- EDSS, at screening, from 0 to 5.5 inclusive.
- Documented MRI of the brain with abnormalities consistent with MS prior to screening.

Key exclusion criteria

- Diagnosis of primary progressive MS.
- Disease duration of more than 10 years in patients with an EDSS ≤ 2.0 at screening, i.e. a "benign" course of MS over 10 years
- Previous treatment with B-cell targeted therapies (i.e., rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab).
- Systemic corticosteroid therapy within 4 weeks prior to screening.
- Any previous treatment with alemtuzumab, anti-CD4 therapy, cladribine, mitoxantrone, daclizumab, teriflunomide, laquinimod, total body irradiation, or bone marrow transplantation.
- Treatment with cyclophosphamide, azathioprine, mycophenolate mofetil (MMF), cyclosporine, methotrexate, or natalizumab within 24 months prior to screening. (Patients previously treated with natalizumab were eligible for this study if the duration of treatment with natalizumab was < 1 year).
- Treatment with fingolimod or other S1P receptor modulator within 24 weeks prior to screening. Only patients with T lymphocyte count ≥ LLN were eligible for the study
- Treatment with IV immunoglobulin within 12 weeks prior to baseline.

Treatment – Ocrelizumab

Rationale for dose selection

The sponsor concluded that a dose of 600 mg every 12 weeks was the lowest, maximally effective dose. This was based on the results from study WA21493 in RMS patients. Two doses of ocrelizumab were studied, 2000 mg (administered as dual 1000 mg infusions on Days 1 and 15 of the first, 24-week treatment cycle) and 600 mg (administered as dual 300 mg infusions on

Days 1 and 15 of the first treatment cycle). Results of this study indicated that OCR 300 mg × 2 was effective in suppressing MRI lesion activity and reducing the risk of clinical relapses in RMS patients over 24 weeks. No difference in efficacy was seen between the OCR 1000 mg × 2 and 300 mg × 2 doses, on either MRI or clinical endpoints, in the intent-to-treat (ITT) study population. However, exploratory analyses, stratifying groups according to baseline MRI activity, suggest superior efficacy with 1000 mg × 2 versus 300 mg × 2, at 24 weeks, in patients with MRI activity at baseline (≥ 4 enhancing lesions). Similarly, in these patients, the 1000 mg × 2 dose was more effective than the 300 mg × 2 dose at Week 24 and (to a lesser extent) at Week 48, in reducing the absolute number of clinical relapses. Neither the MRI nor the clinical efficacy differences were statistically significant; however, the results suggested a reduction of clinical efficacy at lower doses, in active MS patients. This apparent dose effect was seen despite the fact that linear kinetics (so that complete receptor occupancy can reasonably be assumed) and near complete peripheral CD19 suppression were observed for both doses.

> *Reviewer Comment: The only dose studied in RMS was 600 mg every 6 months. At the 600 mg dose there is no indication of a decrease in efficacy for relapses with increasing numbers of gadolinium-enhancing lesions at baseline – see* **Table 150** *for a reviewer analysis of the unadjusted ARR for the pooled population from studies WA21092 and WA21093.*

Table 3: Overview of Dosing Regimen in the Double-Blind, Double-Dummy Treatment Period, studies WA21092 and WA21093

Study Medication	Double-blind, Double-dummy Treatment Period				
	1st Cycle Weeks 1-24		2nd Cycle Weeks 24-48	3rd Cycle Weeks 48-72	4th Cycle Weeks 72-96
Infusion	**Day 1**	**Day 15**	**Week 24**	**Week 48**	**Weeks 72**
OCR	300 mg IV	300 mg IV	600 mg IV	600 mg IV	600 mg IV
Rebif	S.C. 3 times per week	S.C. 3 times per week	S.C. 3 times per week	S.C. 3 times per week	S.C. 3 times per week

A minimum 20 week interval was required between the last infusion of a cycle and the first infusion of the next cycle.

The dose of Rebif was gradually increased from 8.8 µg three times per week (tiw) for the first 2 weeks, 22 µg tiw for the next two weeks and then 44 µg tiw thereafter. If necessary the dose could be reduced to 22 µg tiw.

100 mg of methylprednisolone was to be administered as a slow IV infusion about 30 minutes prior to each IV infusion of ocrelizumab/ocrelizumab placebo during the double-blind, double-dummy treatment period and prior to each IV infusion of ocrelizumab during the OLE Phase.

It was recommended (but not required) that the infusion be accompanied by prophylactic treatment with an analgesic/antipyretic and an IV or oral antihistamine 30 to 60 minutes prior to the start of an infusion. Patients who experienced a life threatening infusion-related event (CTCAE Grade 4) during an infusion should were to have the infusion stopped immediately. These patients were to be withdrawn from treatment and were to enter the Safety Follow-up Period.

Handling of IRRs

In the event of an IRR it was permissible to slow or the infusion rate or interrupt the infusion according to the following guide:

- IRR (CTCAE) Grade 1 or 2: the infusion rate was reduced to half the rate that was being given at the time of onset of the event, and, if tolerated, increased again 30 minutes after the event had resolved.
- IRR (CTCAE) Grade 3, or flushing, fever and throat pain cluster: infusion was interrupted immediately and the patient received aggressive symptomatic treatment; the infusion was re-started only after all the symptoms disappeared, with a rate at restart of half of the rate being given at the time of onset of the event.
- A life threatening IRR (CTCAE) Grade 4: infusion was stopped immediately and the patient received appropriate treatment; these patients were withdrawn from treatment and started the SFU.

Table 4: Overview of Dosing Regimen in the OLE Phase Screening Period and the OLE Phase, WA21092 and WA21093

Study Medication	OLE Screening	OLE Phase				
		5th Cycle		6th Cycle	7th Cycle	Nth Cycle
		Day 1	Day 15			
OCR	None	300 mg IV	300 mg IV	600 mg i.v	600 mg i.v	600 mg i.v
Rebif	Rebif/Rebif placebo 3 times/wk	None	None	None	None	None

Criteria for Re-Treatment with Ocrelizumab

Prior to the next cycle of study drug, patients were evaluated for the following pre-specified conditions and laboratory abnormalities that had to be met to allow for re-treatment. If any of these were present prior to re-dosing, further administration of ocrelizumab was to be suspended until resolved or held indefinitely:

- Life threatening (CTCAE Grade 4) infusion-related event that occurred during a previous ocrelizumab infusion
- Any significant or uncontrolled medical condition or treatment-emergent, clinically significant laboratory abnormality
- Active infection
- Absolute neutrophil count < $1.5 \times 10^3/\mu L$
- CD4 cell count < 250/µL
- Hypogammaglobulinemia, IgG < 3.3 g/L
- Ongoing pregnancy (for female patients)

Treatment – Rebif

The first subcutaneous injection of Rebif®/placebo was administered on Study Day 1. Patients were be instructed by a nurse or investigator how to self-administer the injections; the first dose of Rebif®/placebo was self-administered under the supervision of a nurse or physician. Thereafter, patients self-administered their Rebif®/placebo treatment three times weekly. Patients were instructed to administer Rebif®/placebo at the same time (preferably in the late afternoon or evening) on the same 3 days (e.g., Monday, Wednesday, and Friday) at least 48 hours apart.

Non-steroid anti-inflammatory drugs (ibuprofen) or acetaminophen were recommended in case of injection site reaction but were not routinely administered by protocol at any time during the study.

The protocol included rules for permanent or temporary discontinuation of Rebif for elevation of liver function studies

- ALT ≥ 10 × ULN or jaundice or other clinical symptoms of liver dysfunction – permanent discontinuation.
- ALT ≥ 5 × ULN – temporary discontinuation and frequent LFTs. In case of recurrence of toxicity (ALT > 3 x ULN, or other clinical symptoms of liver dysfunction) the injections of Rebif®/Rebif® placebo were discontinued permanently and these patients entered the

Safety Follow-Up Period (SFU). Re-initiation of therapy with Rebif® following elevation of liver function tests could only be considered once.

- ALT > 3 × ULN – no discontinuation and frequent LFTs.

Concomitant medications

See page **37** for the use of medications prior to administration of OCR 600. Treatments for MS symptoms such as dalfampridine for walking difficulty were allowed but were to be kept at the same dose throughout the study.

Treatment of relapses

The following standardized treatment regimen was allowed for the treatment of a relapse: 1000 mg methylprednisolone IV per day for a maximum of 5 consecutive days. In addition, at the discretion of the Investigator, corticosteroids could be either stopped abruptly or tapered over a maximum of 10 days. Patients were not required to discontinue the treatment period solely based on the occurrence of a relapse, unless the patient or Investigator determined that he or she had met the criteria for withdrawal.

Assessments

The schedule of assessments is summarized in **Table 5**.

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Table 5: Schedule of assessments for studies WA21092 and WA21093

	Screen	Double blind Double dummy Treatment Period										Delayed Dsoing Visit	Unscheduled Visit	Withdrawal from treatment visit
Cycle		1			2		3		4					
Visit	1	2/BL	3	4	5	6	7	8	9	10	11			
Week	-2	-	2	12	24	36	48	60	72	84	96			
Study Day	-14	1	15±2	85±4	169±2	253±4	337±2	421±4	505±2	589±4	673±2			
OCR admin		✓	✓		✓		✓		✓					
Rebif admin 3 times/wk		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
EDSS	X	X		X	X	X	X	X	X	X	X		X	X
Karnofsky		X												
MRI		X			X		X				X			X
Potential Relapses recorded	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Telephone interview every 4 weeks				→	→	→	→	→	→	→	→			
Adverse Events	SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X
Routine safety labs	X													
ECG pre- and post-dose	X	X							X					X
C-SSRS		X		X	X	X	X	X	X	X	X		X	X

Unscheduled visits

Patients who developed new or worsening neurological symptoms were seen at the investigational site as soon as possible regardless of the dates of their scheduled study visits, and regardless of the study period. Patients with new neurological symptoms suggestive of relapse had an EDSS performed by the Examining Investigator, whenever possible within 7 days of the onset of the relapse.

> ***Reviewer Comment: The frequency that potential relapses were evaluated within 7 days of onset is assessed in the following tables: (Table 25, Table 26, and Table 27).***

Assessment of relapses

All new or worsening neurological events consistent with a clinical relapse were reported on the dedicated page of eCRF. Patients with clinical relapses were referred to the Examining Investigator who was to assess the FSS/EDSS independently in order to allow confirmation as to whether or not the potential clinical relapse met the criteria for protocol-defined relapse.
A protocol-defined relapse was defined as the occurrence of new or worsening neurological symptoms attributable to MS that persisted for more than 24 hours and were not attributable to other causes such as a clinical fever, infection, injury or adverse reactions to medications.
The new or worsening neurological symptoms must have met the following:

- The symptoms should have been preceded by neurological stability for at least 30 days
- Symptoms should have been accompanied by objective neurological worsening meeting the following:
    - ≥0.5 points on EDSS scale
    - or ≥2 points on one of the following FSS scales: pyramidal, ambulation, cerebellar, brainstem, sensory, or visual
    - or ≥1 point on two or more FSS scales (pyramidal, ambulation, cerebellar, brainstem, sensory, or visual)

Any patient complaining of a neurological symptom, identified at a visit or over the phone, should have been referred to the Examining Investigator unless the Treating Investigator determined that the new symptoms were due to mitigating circumstances (such as an intensification of neurological symptoms from a transient systemic infection). Clinical relapses, regardless of whether they met criteria for a protocol-defined relapse were to be recorded on the pre-specified eCRF “MS relapse” eform.

MS relapses were not to be reported on the Adverse Event eform of the eCRF unless they met the criteria for a serious adverse event.

The procedure for the determination of a Protocol-Defined Relapse (PDR)

Since criteria to define a relapse were predetermined, no external or internal relapse adjudication committee was used.

A clinical relapse was confirmed as a PDR if the following conditions were met:

1. Clinical relapse was reported on eCRF.
2. On the MS relapse eCRF page the question "Did symptoms persist for >24 hours and were not being attributable…" was checked 'Yes'.
3. The EDSS at the first EDSS assessment at a visit (unscheduled or scheduled) on or after the onset date of the relapse was increased by ≥ 0.5 steps from the previous EDSS; OR FSS domains relevant to the relapse event (pyramidal, ambulation, cerebellar, brainstem, sensory, or converted visual) were increased by ≥ 2 points on one domain or ≥ 1 point on two or more domains.

   For each relapse that satisfied the 3 criteria above, it was then determined whether the potential relapse was within 30 days (i.e., the onset dates are ≤ 30 days apart) of a previous PDR. If a potential relapse was within 30 days, then the potential relapse was not a protocol-defined relapse.

This pre-specified algorithm was run by the Sponsor's statistical programming and analysis team before unblinding of primary analyses for the studies.

Disability

Disability progression was defined as an increase of ≥ 1.0 point from the baseline EDSS score that was not attributable to another etiology (e.g., fever, concurrent illness, or concomitant medication) when the baseline score is 5.5 or less, or an increase of ≥ 0.5 when the baseline score was above 5.5. 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 confirmation process was the same as that used for disability progression in Study WA25046 and is detailed in Appendix **13.4**.

Brain Imaging

MRI scans of the brain were obtained in all patients at baseline, Week 24, 48 and 96. In addition, brain MRI scans were obtained in patients withdrawn from the double-blind double-dummy period of treatment (at the withdrawal visit) if not performed during the previous 4 weeks.

Telephone interviews

The purpose of this "semi-structured" interview was to identify new or worsening neurological symptoms that warrant an unscheduled visit. The telephone interview was be conducted every 4 weeks (± 3 days) between the study visits during the double-blind, double-dummy treatment period, OLE Phase Screening Period, OLE Phase, and Safety Follow-Up Period starting from Week 8, until 48 weeks after the last infusion. Thereafter, for those patients who required prolonged B-cell monitoring, telephone interviews continued every 12 weeks (±7 days) between regular visits. The site only recorded in the eCRF the telephone interview as "Done" or "Not Done".

Study Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint was the annualized protocol-defined relapse rate at two years (96 weeks).

Secondary Endpoints

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

  Definition of confirmed disability progression (protocol section 5.3.2.2)
  Disability progression was defined as an increase of ≥ 1.0 point from the baseline EDSS score that was not attributable to another etiology (e.g., fever, concurrent illness, or concomitant medication) when the baseline score is 5.5 or less, or an increase of ≥ 0.5 when the baseline score is above 5.5. 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. Any non-confirmatory EDSS assessments between the initial and confirmation of disability progression were required be at least as high as the minimum change required for progression. All initial disability progression events up to Week 96 with corresponding confirmation visits at the next scheduled visit were taken into account for the statistical analysis irrespective of whether or not the confirmation visit occurred during the treatment phase or after study drug discontinuation, or during the OLE phase.

- The total number of T1 Gadolinium (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 confirmed disability improvement for at least 12 weeks
- The time to onset of confirmed disability progression for at least 24 weeks
- The total number of T1-hypo-intense lesions (chronic black holes) at Weeks 24, 48, and 96
- The change in MSFCS 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 No Evidence of Disease Activity (NEDA) by Week 96 OLE

Statistical Analysis Plan

Analysis population

All efficacy analyses were performed using the intent-to-treat (ITT) population. The ITT was defined as all randomized patients. Patients who prematurely withdrew from the study for any reason and for whom an assessment was not performed for whatever reason are included in the ITT analysis. Patients who received an incorrect therapy from that which was intended are included in the efficacy analyses according to their randomized treatment.

Relapses

The primary efficacy analysis for this trial compares the annualized protocol-defined relapse rate at 96 weeks between the OCR 600 group and the Rebif® group. The annualized relapse rates by 96 weeks are analyzed using a negative binomial model. Since all eligible patients were randomized to treatment stratified by region (United States versus OUS) and baseline EDSS (<4.0 versus ≥4.0), all analyses are stratified by these two variables.

Sample size estimation

The assumptions made to determine the sample size for the two RMS studies are summarized in **Table 6**.

Table 6: Number of clinical and protocol-defined relapses (PDR), per study, per arm, RMS studies

	WA21092		WA21093	
	Rebif	OCR 600	Rebif	OCR 600
Clinical relapses	208	131	209	133
PDR	166	96	168	98
Conversion rate	79.80%	73.30%	80.40%	73.70%

The sample size was estimated based on data from previous RMS trials, with the use of two-sided tests with an experiment-wise alpha of 0.05. The annualized rate of relapse among patients receiving ocrelizumab at 96 weeks was predicted to be 0.165 (standard deviation of approximately 0.60), as compared with 0.33 (standard deviation of approximately 0.80) among patients receiving the control treatment, Rebif® (this represented a relative reduction of 50% for ocrelizumab compared to the active comparator). For the annualized relapse rate, a t-test was used to determine the sample size between ocrelizumab and the control arm. The sample size of 400 patients per arm provided 84 percent power, maintaining the type I error rate of 0.05, and assuming a drop-out rate of approximately 20 percent (assuming that the relative reduction among patients who drop out is 25%).

For confirmed disability progression, a two group test of equal exponential survival with exponential dropout was used to determine the sample size. Assuming the 2-year confirmed disability progression rate is 18% for the Rebif® arm and 12.6% for the ocrelizumab arm (this represents a relative reduction of 30% on ocrelizumab compared to the active comparator), and assuming a drop-out rate of 20 percent over 2 years, the sample size of 400 per arm would provide 80 percent power, maintaining the type I error rate of 0.05 based on the pooled analysis of two RMS trials (800 patients treated with ocrelizumab 600 mg and 800 patients treated with Rebif®).

Secondary efficacy endpoints have been tested in hierarchal order, all at alpha = 0.05 level. The first secondary efficacy endpoint was to be tested if the primary endpoint reached the significance level at 0.05. With the exception of the three secondary efficacy endpoints which are analyzed at the pooled level, all secondary efficacy endpoints are tested if the secondary endpoint listed ahead of it reached the significance level at 0.05.

<u>The Time to Onset of Confirmed Disability Progression for At Least 12 Weeks During the 96 Week Comparative Treatment Period</u>

The time to onset of confirmed disability progression for at least 12 weeks during the 96-week comparative treatment period, the proportion of patients who had confirmed disability improvement for at least 12 weeks with the initial event of neurological improvement occurring during the 96-week double-blind, double-dummy treatment period, and the time to onset of confirmed disability progression for at least 24 weeks during the 96-week comparative

treatment period are analyzed using pooled data across the two identical studies running as a part of the Phase III program, with respect to ocrelizumab group versus Rebif® group. Patients who did not have confirmed disability progression by Week 96 visit, time of early discontinuation of treatment, or loss to follow up were to be censored at the date of their last EDSS assessment. Time to confirmed disability progression for ocrelizumab group and Rebif® group are compared using a two-sided log-rank test stratifying by region (United States versus OUS), baseline EDSS (<4.0 versus ≥4.0). 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.

Total Number of T1 Gadolinium-Enhanced Lesions as Detected by Brain MRI at Weeks 24, 48, and 96

The total number of T1 gadolinium (Gd)-enhanced lesions has been calculated as the sum of the individual number of T1 Gd-enhanced lesions at Weeks 24, 48 and 96. Data from other unscheduled assessments are not included in this summary or analysis. A negative binomial model is used to compare the difference between ocrelizumab and Rebif groups.

The Total Number of New, and/or Enlarging T2 Hyperintense Lesions as Detected by Brain Magnetic Resonance Imaging at Week 24, Week 48 and Week 96

The same approach has been used for the statistical analysis of new and/or enlarging T2 hyperintense lesions as for the total number of T1 Gd-enhanced lesions.

Proportion of Patients who have Disability Improvement Confirmed for At Least 12 Weeks

This endpoint was analyzed only for the subgroup of patients with a baseline EDSS score ≥ 2.0. The same approach to data derivation is used for disability improvement as for disability progression. The endpoint is a binary improved/not improved variable. For patients with a baseline EDSS score ≥ 2 and ≤ 5.5, disability improvement is defined as a reduction in EDSS score ≥ 1.0 compared to baseline EDSS score. For patients with a baseline EDSS score > 5.5, disability improvement is defined as a reduction in EDSS score of 0.5. All patients without disability improvement will be counted as not improved, independent of follow-up time. Data from the two studies with respect to ocrelizumab group vs Rebif® group will be pooled for analysis of this endpoint. The proportions in treatment groups will be compared using the Cochran-Mantel-Haenszel (CMH) χ 2 test stratified by geographical region (United States vs OUS) and baseline EDSS score (< 4.0 vs ≥ 4.0).

The Time to Onset of Confirmed Disability Progression for At Least 24 Weeks During the 96-Week Comparative Treatment Period

Time to confirmed disability progression between ocrelizumab group and Rebif® group using a 24-week confirmation window for disability progression was compared using the same analysis method as for time to confirmed disability progression using a 12-week confirmation window. Time to confirmed disability progression (24-week confirmation) is defined as the time from Baseline (Day 1) to the first disability progression, which is confirmed at the next regularly scheduled visit ≥ 161 days after the initial disability progression. All initial disability progression events up to Week 96 with corresponding confirmation visits at the next scheduled visit are taken into account for the statistical analysis. Data from the two studies with respect to ocrelizumab group versus Rebif® group have been pooled for analysis of this endpoint.

Total Number of T1-Hypo-Intense Lesions (Chronic Black Holes) at Weeks 24, 48, and 96

The same approach has been used for the statistical analysis of T1 hypointense lesions as for the total number of T1 Gadolinium-enhanced lesions.

The Change in Multiple Sclerosis Functional Composite Scale (MSFCS) Score from Baseline to Weeks 96

The change in MSFCS from baseline to Week 96 is compared between ocrelizumab group and Rebif® group using a Mixed-Effect Model Repeated Measures (MMRM) analysis, adjusting for baseline MSFCS, region (United States versus OUS), and baseline EDSS (<4.0 versus ≥4.0). .

The Percentage Change in Brain Volume as Detected by Brain Magnetic Resonance Imaging Scan from Week 24 to Week 96

The change in brain volume as detected by brain MRI from week 24 to Week 96 is compared between ocrelizumab group and Rebif® group using an MMRM analysis. Baseline covariates here are: brain volume at Week 24, baseline Gd-enhanced lesion (present or not), region (United States versus OUS), and baseline EDSS score (< 4.0 vs ≥ 4.0).

Change in Quality of Life, as Measured by the Short Form 36 version 2 Physical Component Summary (PCS) Score from Baseline to Week 96

The change in quality of life, as measured by the SF-36 PCS score from baseline to week 96 is compared between ocrelizumab group and Rebif group using a MMRM analysis. Baseline covariates are as follows: baseline PCS score, region (United States versus OUS), and baseline EDSS (< 4.0 vs ≥ 4.0).

Proportion of Patients Who Have No Evidence of Disease Activity (NEDA) by Week 96

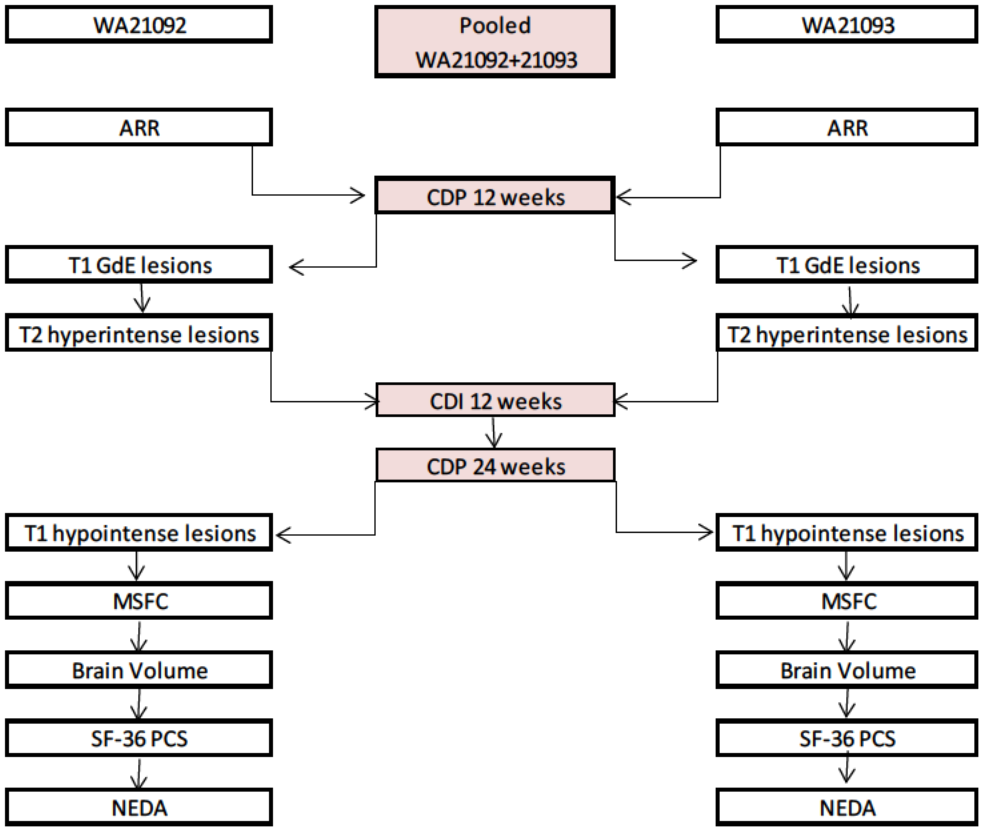
This endpoint is defined only for those patients with a baseline EDSS score ≥ 2.0.
All available data during the 96-week treatment period is used for the analysis.
Patients who completed the 96-week treatment period are considered as having evidence of disease activity if at least one of the following was reported during the 96-week treatment period

- protocol defined relapse,
- a CDP event
- having at least one MRI scan showing MRI activity (defined as Gd-enhancing T1 lesions, or new or enlarging T2 lesions).

Otherwise a patient is considered as having no evidence of disease activity (NEDA). Patients who discontinued treatment early with at least one event before early discontinuation were considered as having evidence of disease activity. Even if an event was not reported before early discontinuation, the patient was considered as having evidence of disease activity if the reason for early discontinuation is lack of efficacy or death; otherwise, it was considered a missing observation. The proportions within treatment groups are compared using the Cochran-Mantel-Haenszel (CMH) χ 2 test stratified by region (United States versus OUS) and baseline EDSS (<4.0 versus ≥4.0).

The hierarchy for analysis of secondary endpoints is shown in **Figure 2**.

Figure 2: Reviewer figure: Statistical Analysis hierarchy for Studies WA21092 and WA21093



ARR = annualized relapse rate; CDI = confirmed disability improvement; CDP = clinical disability progression; GdE = gadolinium enhancing; MSFC = multiple sclerosis functional composite; NEDA = no evidence of disease activity; SF-36 = short form health survey-36; PCS = physical component summary.

Protocol Amendments

There were four protocol amendments to the original Protocol WA21092 Version A released on 25 August 2010.

Table 7: Protocol Amendments, WA21092

Protocol version	Release Date	Changes	Number of subjects randomized
A	25 August 2010		0
B	1 June 2011		0
C	15 June 2012	1. Allow patients to continue previous MS therapies with β-interferons, glatiramer acetate and other permitted immunomodulatory therapies until randomization 2. Allow patients previously treated with dimethyl fumarate (Tecfidera)to enter the study following an adequate washout period (24 weeks)	286
D	14 March 2013	1. Addition of the following exploratory objectives: proportion of disease activity free patients, defined as absence of both relapses and sustained accumulation of disability, and absence of MRI activity by Week 96; evaluation of long term safety and efficacy of ocrelizumab in the OLE study phase 2. Clarification on how sustained disability progression is calculated	535 (Total =821)
E	4 September 2016	1. Update to the Statistical Considerations and Analytical Plan section of the protocol in line with the SAP amendment to implement European Medicines Agency (EMA) Scientific Advice and to increase statistical rigor. This included: a. Modifications to the secondary efficacy endpoints, their definitions and hierarchical order b. Modifications to the exploratory efficacy endpoints and their definitions c. Modifications to statistical methodology (replacement of analysis of covariance ANCOVA with Mixed-Effect Model Repeated Measures [MMRM] method) d. Clarifications to various aspects of the safety analysis, including change to the definition of safety population e. Change to the timing of database lock to allow for 12-week confirmation of all initial disability progression	

Protocol version	Release Date	Changes	Number of subjects randomized
		events during the 96-week comparative treatment period f. Clarification of the calculation of the baseline EDSS value, the timing of unblinding of the sites and EDSS examining investigators	

Data Quality and Integrity: Sponsor's Assurance

Monitoring visits for WA21092 and WA21093 were conducted by (b) (4) site monitors. Monitoring visits were conducted every 8-10 weeks during the treatment / double blind phase. All data points were source data verified. Sites were contacted by telephone at least every 2 weeks. Monitoring frequency did not change until all eligible patients at site had entered the Open Label Extension (OLE) phase of the study or discontinued treatment.

6.1.2. Study Results

Compliance with Good Clinical Practices

In Section 3.4 of the study report the sponsor provided a statement that the study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP). Study investigators were trained according to applicable Sponsor Standard Operating Procedures (SOPs). Approval from the IRB/EC was obtained before study start and was documented in a letter to the investigator specifying the date on which the committee met and granted the approval. Roche also obtained approval from the relevant Regulatory Authorities prior to starting the study. No modifications were made to the protocol after receipt of the IRB/EC approval. The Roche Clinical Quality Assurance group or designee conducted audits at five investigator sites. The Roche co-development partner (b) (4) performed two investigator audits and one internal audit. No critical audit findings were observed.

Financial Disclosure

The sponsor provided Form 3454 indicating that there were no financial arrangements with investigators whereby the value of compensation could be affected by the outcome of the study as defined in 21 CFR 54.2(b). A list of investigators with any financial interest is provided in Module 1, Section 1.3.4. All are "significant payments of other sorts". Investigators with

disclosable financial interests were recorded by 6 out of 1743 (0.3%) investigators. In Study WA21093, 48 of 166 sites participating were located in the United States. Of these 48 sites, 3 reported disclosable financial interest.

The number of patients in the MS studies treated at a site by an investigator with disclosable financial interests represents < 10% of the overall patients participating in the trials (20 and 81 patients in WA21092 and WA21093 respectively and 26 patients in WA25046). Any potential impact of disclosed financial interest on overall efficacy or safety outcomes is therefore expected to be limited.

In both RMS studies the ARR treatment effect at sites without disclosable financial interest remains significant and consistent (WA21092: ARR Ratio=0.533, p<0.0001; WA21093: ARR Ratio=0.557, p=0.0002) with the ITT analysis (WA21092: ARR Ratio=0.536, p< 0.0001; WA21093: ARR Ratio=0.532, p<0.0001; CSR WA21092 Table 17, CSR WA21093 Table 17). Investigators with disclosable financial interests did not unduly influence the primary outcome in the RMS studies.

The AE profiles from sites without disclosable financial interest are similar to the overall study results in Study WA21092 and Study WA21093. Investigators with disclosable financial interests did not unduly influence the safety outcome in the RMS studies.

> ***Reviewer Comment: There were relatively few investigators who reported a disclosable financial interest and there were relatively few patients enrolled at these sites.***

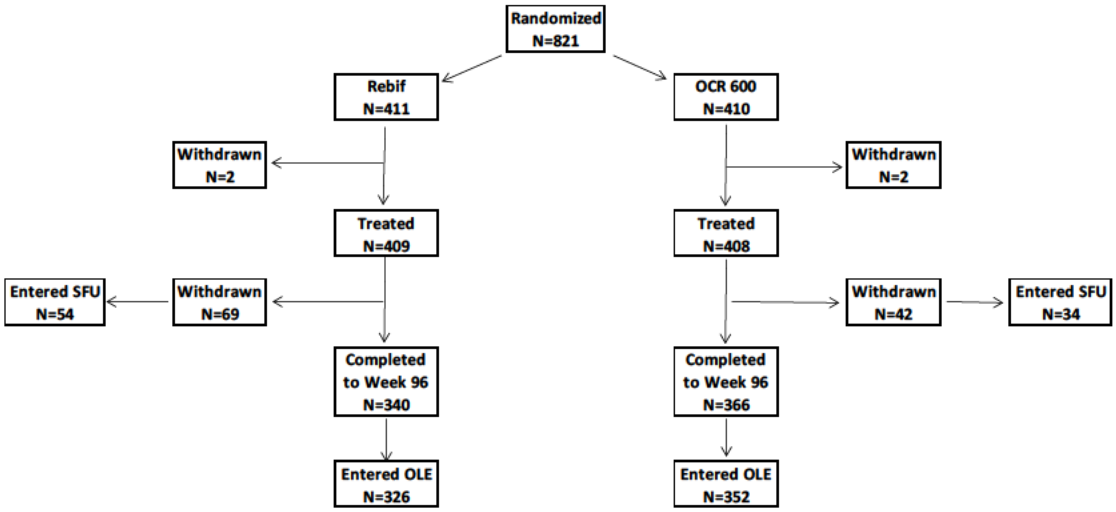
Patient Disposition

First patient randomized: 31 August 2011
Last patient randomized: 14 February 2013
Data cut-off date: 2 April 2015

1041 patients were screened and 821 were enrolled and randomized. The primary analysis population was the Intent to Treat (ITT) population which was defined as all randomized patients. Four subjects were randomized but not treated, 2 in each treatment group. Two of these were due to subject withdrawal of consent, one due to physician decision and one due to a protocol violation. The safety population therefore included the 817 subjects treated. Three patients received Rebif instead of OCR 600 at a single visit. These three patients were included in the OCR 600 group for the ITT and for safety since all but one dose of study medication was as randomized.

The disposition of patients is summarized in Figure 3.

Figure 3: Reviewer Figure: Disposition of patients in Study WA21092



A slightly higher proportion of patients in the OCR 600 group (89.3%) completed treatment compared to the group treated with Rebif (82.7%). The most common reason for premature discontinuation in both treatment groups was an adverse event (AE) although this was more common in the Rebif group (7%) compared to the OCR 600 group (3.9%).

Table 8: Reasons for premature discontinuation in study WA21092

Standardized Disposition Term	Rebif	OCR 600	Total Subjects
COMPLETED	340 (82.73%)	366 (89.27%)	706 (85.99%)
ADVERSE EVENT	29 (7.06%)	16 (3.90%)	45 (5.48%)
WITHDRAWAL BY SUBJECT	15 (3.65%)	15 (3.66%)	30 (3.65%)
OTHER	15 (3.65%)	10 (2.44%)	25 (3.05%)
LACK OF EFFICACY	13 (3.16%)	11 (2.68%)	24 (2.92%)
PREGNANCY	2 (0.49%)	4 (0.98%)	6 (0.73%)
NON-COMPLIANCE	3 (0.73%)	2 (0.49%)	5 (0.61%)
LOST TO FOLLOW-UP	1 (0.24%)	3 (0.73%)	4 (0.49%)
NON-COMPLIANCE WITH STUDY DRUG	3 (0.73%)	0 (0.00%)	3 (0.37%)
PROTOCOL VIOLATION	1 (0.24%)	2 (0.49%)	3 (0.37%)
PHYSICIAN DECISION	0 (0.00%)	1 (0.24%)	1 (0.12%)
DEATH	1 (0.24%)	0 (0.00%)	1 (0.12%)

Standardized Disposition Term	Rebif	OCR 600	Total Subjects
Total Subjects	411 (100.00%)	410 (100.00%)	821 (100.00%)
			(Denom=ColTot)

Source: JRevCTabDS DSDECODbyTRT01PfilterEPOCH_TRTpropOFTRTgrp.xls

Adverse events leading to withdrawal of treatment were infrequent in both treatment groups. In the OCR 600 group 14 patients (3.41% of the treatment group) withdrew from treatment due to an adverse event compared to 30 patients in the Rebif group (7.3% of the treatment group).The most common AE leading to withdrawal of treatment in the Rebif group was an AE of an influenza-like illness which occurred in 8 patients or about 2% of the treatment group. The most common in the OCR 600 group was an infusion related reaction which occurred in 6 patients or 1.5% of the treatment group. No other adverse event leading to discontinuation of treatment occurred in more than 2 patients in either treatment group.

The Screening period could last approximately 2 weeks but could be prolonged for up to 8 weeks for relevant clinical, administrative, or operational reasons. The mean screening time was approximately 25 days for both treatment groups. There were 17 patients whose Screening time was more than 56 days, 7 in the OCR 600 group (range 57 to 133 days) and 10 in the Rebif group (range 57 to 99 days).

Unblinding

A total of 8 patients were unblinded by the sponsor due to suspected unexpected serious adverse events. Twelve patients were unblinded at the request of the investigator.

Protocol Violations/Deviations

41 subjects did not meet all eligibility criteria, 17 treated with OCR 600 and 24 treated with Rebif. Four subjects in the OCR 600 group and 8 in the Rebif group did not meet the inclusion requirement for neurologic stability for 30 days or more prior to screening. Four subjects in the Rebif group did not meet the inclusion criterion for disease activity prior to screening. Four patients in the Rebif group met the exclusion criterion for disease duration of more than 10 years with a baseline EDSS of 2 or less ("benign MS") at screening. The most common eligibility criteria not met are shown in Table 9.

Table 9: Key eligibility criteria not met, WA21092

Category	InclusionExclusion Criterion	Rebif	OCR 600	Total

Category	InclusionExclusion Criterion	Rebif	OCR 600	Total
INCLUSION	Neurological stability for >= 30 days prior to both screening and baseline.	8 (0.97%)	4 (0.49%)	12 (1.46%)
EXCLUSION	Levels of serum IgM < 0.55 g/L.	2 (0.24%)	4 (0.49%)	6 (0.73%)
INCLUSION	At least 2 documented clinical attacks within the last 2 years prior to screening, or one clinical attack in the year prior to screening (but not within 30 days prior to screening).	4 (0.49%)	0 (0.00%)	4 (0.49%)
EXCLUSION	Disease duration of more than 10 years in patients with an EDSS <= 2.0 at screening.	4 (0.49%)	0 (0.00%)	4 (0.49%)

Source: JRevCtabIECatbyCritbyTRT01P.xls

Reviewer Comment: The inclusion of the above patients who did not meet all of the eligibility criteria is unlikely to have affected the efficacy results. Any bias would be in favor of Rebif.

Eligibility /Screening period

The duration of time to establish eligibility should have been 14 days or less for most patients and in exceptional cases it could take up to 8 weeks. The actual mean period between informed consent and randomization was over 3 weeks (Table 10). There were 17 patients whose screening period was more than 8 Weeks (56 days), 7 in the OCR 600 group (range 57 to 133 days) and 10 in the Rebif group (range 57 to 99 days). During this screening period the EDSS score did not change for 71% of the OCR 600 group and for 76% of the Rebif group. The EDSS score increased from screening to randomization for 14.7% of the OCR 600 group and for 17.7% of the Rebif group; it decreased for 14.3% of the OCR 600 group and for 10.2% of the Rebif group. Only 7 patients did not have an EDSS score at both screening and randomization, 3 in the OCR 600 group and 4 in the Rebif group.

Table 10: Duration of Screening Period, WA21092, ITT

TRT01P	Time from informed consent to randomization in days					
	N	Mean	Std Dev	Median	Min	Max
Rebif	411	24.94	14.07	20	6	99
OCR 600	410	25.07	14.02	21	4	133

Source: WA 21092 rev ADSL RANDDTminusINFCODT By (TRT01P).jmp

Table of Demographic Characteristics

The two treatment groups were balanced for key demographic characteristics at baseline. The population was approximately 65% female as expected for the RMS population. The baseline age was less than 40 years in 60%. Over 90% were of the white race. Approximately 25% were from the US (Table 11).

Table 11: Reviewer table: Baseline demographic characteristics, WA21092, ITT

	OCR 600	Rebif
SEX, n, %		
Female	270, 65.9%	272, 66.2%
Male	140, 34.1%	139, 33.8%
AGE		
Mean (SD), years	38.0 (9.3)	37.7 (9.4)
Median, years	38	38
Min, Max, years	18, 58	18, 57
<40, n, %	244, 59.5%	243, 59.1%
≥40, n, %	166, 40.5%	168, 40.9%
RACE, n, %		
White	375, 91.5%	375, 91.2%
Other	10, 2.4%	14, 3.4%
Multiple	5, 1.2%	9, 2.2%
Black or African American	19, 4.6%	12, 2.9%
Asian	0, 0.0%	1, 0.2%
American Indian or Alaska native	1, 0.2%	0, 0.0%
ETHNIC GROUP		
Not Hispanic or Latino	328, 80.0%	315, 76.6%
Hispanic or Latino	45, 11.0%	61, 14.8%
Not reported	37, 9.0%	35, 8.5%
Country group		
OUS	305, 74.4%	306, 74.5%
US	105, 25.6%	105, 25.5%
Region		
EU/Switzerland/Norway	211, 51.5%	204, 49.6%
USA/Canada/Australia	105, 25.6%	108, 26.3%
Non-EU/Israel/Africa	68, 16.6%	64, 15.6%
Latin America	26, 6.3%	35, 8.5%

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The two treatment groups were also comparable for the clinical status of RMS at baseline (Table 12). The mean and median EDSS score at baseline were not significantly different. Most patients had either one or two relapses in the past 2 years. More than half of the patients did not have a gadolinium-enhancing lesion at baseline. Three-fourths had not been treated previously for MS.

Table 12: Baseline characteristics of MS, WA21092, ITT

	OCR 600 N=410	Rebif N=411
Baseline EDSS		
Mean (SD)	2.82 (1.24)	2.71 (1.29)
Median	2.5	2.5

	OCR 600 N=410	Rebif N=411
Min, Max	0, 6	0, 6
<4	314, 76.6%	318, 77.4%
≥4	96, 23.4%	92, 22.4%
Duration since MS Symptom Onset category		
<= 3 Years	38.9%	38.0%
> 3 to <= 5 Years	14.6%	12.2%
> 5 to <= 10 Years	25.5%	25.4%
> 10 Years	20.9%	24.4%
Relapses in the previous 2 years		
1	170, 41.5%	195, 47.5%
2	180, 43.9%	157, 38.2%
3	42, 10.2%	35, 8.5%
≥4	23, 5.6%	23, 5.6%
Baseline Gadolinium-enhancing lesions*		
0	233, 56.8%	252, 61.3%
1	64, 15.6%	52, 12.7%
2	30, 7.3%	30, 7.3%
3	20, 4.9%	16, 3.9%
4	58, 14.2%	57, 13.9%
missing	5, 1.2%	4, 1.0%
Previous treatment for MS		
Yes	109, 26.6%	119, 29.0%

*: see **Table 35** for additional baseline MRI assessments

Exposure

The duration of exposure to study treatment was comparable for the two treatment groups and close to the maximum of 96 weeks for the double-blind treatment period (**Table 13**). The duration of exposure for the individual infusions for the OCR 600 and OCR 600 placebo groups were also comparable at 3.3±0.7 hours for both groups. The duration of an individual infusion was essentially the same for those actually receiving OCR 600 (mean = 3.34 hours) compared to those receiving OCR 600 placebo (3.30 hours). The actual number of OCR 600 or OCR 600 placebo doses was close to the expected number of 5 (**Table 14**) and the average total dose was approximately 2300 mg compared to an expected 3000mg if all patients received all 5 doses during the 96 week treatment period (**Table 15**).

Table 13: Duration of exposure to treatment by treatment group, WA21092, ITT

Treatment	Duration of Exposure during the double-blind treatment period (weeks) (EXP96WKS)					
	Total	Mean	Std Dev	Median	Min	Max
Rebif	411	90.22	18.49	96.14	2.29	101.00
OCR 600	410	92.55	15.29	96.14	0.14	107.71

Source: WA 21092 rev ASL EXP96WKS By (TRT01P).xlsx

Table 14: Actual number of doses of OCR or OCR placebo administered, WA21092, ITT

Treatment	Total doses (EXDOSNT)						
	N OUSs	Mean	Std Dev	Median	Min	Max	N Missing
Rebif/OCR 600 placebo	409	4.66	0.97	5	1	8	0
OCR 600	408	4.80	0.83	5	1	6	0

Source: EXTCATT_OCRorOCRPBO Subset of EXTCAT_PERIOD Subset of APERIODC_TRT Subset of WA 21092 rev AEX EXDOSNT By (TRT01P).jmp

Table 15: Total dose of OCR 600 administered, WA21092, ITT

Total	Total dose of OCR 600 administered (EXDOST)				
	Mean	Std Dev	Median	Min	Max
408	2285.50	484.44	2400	9	3000

Source: Summary of EXCATT_OCR Subset of EXTCATT_OCRorOCRPBO Subset of EXTCAT_PERIOD Subset of APERIODC_TRT Subset of WA 21092 rev AEX.jmp

The actual number of Rebif or Rebif placebo doses administered is close to the number expected for the 96 week trial, i.e. 288 doses (Table 16).

Table 16: Actual number of doses of Rebif or Rebif placebo administered, WA21092, ITT

Treatment	Number of doses administered (EXATOTSU)						
	N OUSs	Mean	Std Dev	Median	Min	Max	N Missing
Rebif	407	246.63	77.5	286	1	297	0
OCR 600/Rebif placebo	403	263.33	54.0	286	5	300	0

Source: EXTCATT_REBIForREBIFPBO Subset of EXTCAT_PERIOD Subset of APERIODC_TRT Subset of WA 21092 rev AEX EXATOTSU By (TRT01P).jmp

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance with Rebif or Rebif placebo dosing was monitored by counting the number of used vials returned. Overall percent compliance was essentially the same in the two groups (Table 17).

Table 17: Percent compliance for Rebif or Rebif placebo, WA21092, ITT

Treatment	Percent Compliance						
	N OUSs	Mean	Std Dev	Median	Min	Max	N Missing
Rebif	407	92.53	15.20	99.16	9.81	109.80	0
OCR 600/Rebif placebo	403	94.93	9.88	99.16	29.37	106.67	0

Source: EXTCATT_REBIForREBIFPBO Subset of EXTCAT_PERIOD Subset of APERIODC_TRT Subset of WA 21092 rev AEX PercentCompliance By (TRT01P).jmp

The most common concomitant medications used during the treatment phase of the trial were anti-inflammatory agents and antihistamines (Table 18). Approximately 9% of patients reported previous use of an interferon and 9% reported previous use of glatiramer acetate.

Table 18: Most common concomitant medications during the treatment phase, WA21092, ITT

Standardized Medication Name	Rebif (n, %TRT01P)	OCR 600 (n, %TRT01P)	Subjects
METHYLPREDNISOLONE	409 (99.51%)	407 (99.51%)	816 (99.39%)
PARACETAMOL	314 (76.40%)	311 (76.04%)	625 (76.13%)
IBUPROFEN	129 (31.39%)	107 (26.16%)	236 (28.75%)
DIPHENHYDRAMINE	94 (22.87%)	102 (24.94%)	196 (23.87%)
*ACRIVASTINE/*AMMONIUM CHLORIDE/ *CALAMINE/ *CAMPHOR/*CODEINE PHOSPHATE/ *DIPHENHYDRAMINE/ *MENTHOL/*SODIUM CITRATE /*ZINC...	77 (18.73%)	79 (19.32%)	156 (19.00%)
CETIRIZINE	68 (16.55%)	60 (14.67%)	128 (15.59%)
LORATADINE	51 (12.41%)	58 (14.18%)	109 (13.28%)
CHLOROPYRAMINE	32 (7.79%)	32 (7.82%)	64 (7.80%)
OMEPRAZOLE	32 (7.79%)	31 (7.58%)	63 (7.67%)
CIPROFLOXACIN	32 (7.79%)	31 (7.58%)	63 (7.67%)

Source: JRevCTab ACM STDNAMEbyTRT01PfilterPERIOD_TRT.xls

Rescue medication

During the treatment phase intravenous corticosteroids were given for an MS relapse 160 times for the Rebif group and 87 times for the OCR 600 group, indicating that IV corticosteroids were given for essentially all acute relapses. Intravenous corticosteroids were given 17 times to 15 patients for an infusion related reaction to OCR 600.

Efficacy Results – Primary Endpoint

Annualized Relapse Rate

New or worsening neurologic symptoms were reported as a "Multiple Sclerosis Relapse" if the

investigator determined that these symptoms met the initial criteria for a relapse but these symptoms were reported as an adverse event if they were not considered compatible with a potential protocol-defined relapse. All of these potential relapse events were recorded in the section of the eCRF that also included adverse events and infusion-related reactions and are all included in the AAE dataset. Using the AAE dataset, during the double-blind treatment period, 132 potential relapses were reported by the investigator for 90 subjects in the OCR 600 group (25.7% of the treatment group) and 208 potential relapses were reported for 134 subjects (36.6% of the treatment group) in the Rebif group.

> *Reviewer Comment: On review of all other adverse events in the Nervous System Disorders SOC, there do not appear to be any other events that could represent a relapse with the exception of 2 AEs of "optic neuritis", both in the OCR 600 group. The number of "Clinical Relapses" in the AAE dataset corresponds to the number of "Clinical Relapses" (CLINRLP) events reported in the ARLP dataset for the Rebif group but there is one less CLINRLP in the ARLP dataset for the OCR 600 group.*

Table 19: Reviewer table: number of potential relapses during the double-blind treatment phase, by treatment group, WA21092, ITT

Number of relapses	Number of patients	
	OCR 600	Rebif
1	61	84
2	19	30
3	8	17
4	1	2
5	1	1

Source: Rebif Subset of AEDECOD_MSRL Subset of AEBODSYS_NSD Subset of APERIODC_TRT Subset of WA 21092 rev AAE By (USUBJID) By (N OUSs).jmp and OCR Subset of AEDECOD_MSRL Subset of AEBODSYS_NSD Subset of APERIODC_TRT Subset of WA 21092 rev AAE.jmp

When the above events were assessed using the automated confirmation process (see Appendix 13.5), it was determined that there were 96 protocol-defined relapses (PDR) that occurred in 71 patients in the OCR 600 group compared to 166 in 120 patients in the Rebif group. The rate of confirmation was slightly higher for the Rebif group (79.8%) compared to the OCR 600 group (73.3%). Of those relapses that were confirmed, 137/166 (82.5%) in the Rebif group and 91/96 (94.8%) met the criterion of an increase in the EDSS of 0.5 or more; 145/166 and 78/96 met the FSS criteria in the Rebif and OCR 600 groups respectively. 126/166 and 73/96 met both criteria.

Table 20: Reviewer table: Confirmed relapses and confirmation rate by treatment group, WA21092, ITT

Confirmed Relapse	OCR 600			Rebif		
	CLINRLP, N	PDR, N	PDR3*, N	CLINRLP, N	PDR, N	PDR3, N
N	0	35	35	0	42	35
Y	131	96	96	208	166	96
% of CLINRLP		73.3%	73.3%		79.8%	80.8%

Source: APERIODC_TRT Subset of WA 21092 rev ARLP By (AVALC).jmp

*: PDR30FL not assessed, i.e. the event did not have to begin more than 30 days after a preceding relapse

The mean duration exposure to assigned therapy during the double-blind treatment phase is shown in Table 21.

Table 21: Mean duration of double blind treatment by treatment group, ITT

Treatment	96 Week Exposure Duration (years) (EXP96YRS)						
	N	Mean	Std Dev	Median	Min	Max	Sum (yrs)
Rebif	411	1.73	0.35	1.84	0.04	1.94	677.52
OCR 600	410	1.77	0.29	1.84	0.00	2.06	705.45

Source: WA 21092 rev ADSL EXP96YRS By (TRT01P).jmp

Based on the number of protocol-defined relapses and the sum of the total duration of time on double-blind treatment for each group, the unadjusted ARR by treatment group was:

Table 22: Reviewer table: Annualized Relapse Rate, reviewer calculation, unadjusted, WA21092, ITT

Treatment group	Unadjusted ARR
OCR 600	0.136
Rebif	0.245

The difference in ARR is statistically significant, p<0.0001 (ARR Rebif-ARR OCR / (ARR Rebif+ARR OCR)$^{1/2}$; Z=5.584). The relative reduction is 44.5%.

The sponsor's report of the unadjusted and adjusted ARR is shown in Table 23.

Table 23: Sponsor table: Annualized Protocol-Defined Relapse Rate by Week 96 (Negative Binomial Model) Primary Analysis (ITT Population)

Efficacy Variable	Rebif	OCR 600mg
	(N=411)	(N=410)

Efficacy Variable	Rebif (N=411)	OCR 600mg (N=410)
Total number of relapses	166	96
Total patient-years followed	678.1	706.3
Unadjusted annualized relapse rate *	0.245	0.136
Adjusted annualized relapse rate **	0.292	0.156
95% CI of adjusted annualized relapse rate	(0.235, 0.361)	(0.122, 0.200)
Adjusted annualized relapse rate ratio **		0.536
95% CI of adjusted annualized relapse rate ratio		(0.400, 0.719)
p-value		<.0001

* The total number of relapses for all patients in the treatment group divided by the total patient-years of exposure to that treatment.
** Adjusted by Baseline EDSS (<4.0 vs. >=4.0) and Geographical Region (US vs. OUS).
Log-transformed exposure time is included as an offset variable.
Source: CSR WA21092 Table 19, page 112/6491.

Reviewer Comment: The reviewer calculation of the unadjusted ARR and that by the sponsor adjusted for baseline EDSS and geographical region are essentially the same.

The proportion of patients with one or more relapses was 0.173 in the group treated with OCR 600 compared to 0.292 for the Rebif group. The corresponding rates of relapse-free patients were 0.827 and 0.708 for the OCR 600 and Rebif groups respectively. The difference in proportions of patients with and without a relapse is significant (nominal p-value <0.0001).

Primary endpoint by subgroups

The reduction in ARR was similar for most of the subgroups of interest. The largest difference was between those with and without gadolinium-enhancing lesions at baseline where the reduction in ARR was 67.2% for those with vs. 19.9% for those without gadolinium-enhancing lesions at baseline. There was no major difference between males and females. The benefit tended to be greater for those less than 40 years old and those with a baseline EDSS less than 4. Comparable analyses of the unadjusted ARR by subgroup for study WA 21093 are in Table 66.

Table 24: Reviewer table: Unadjusted Annualized Relapse rate in subgroups, WA21092, ITT

	Rebif N=411		OCR 600 N=410		
	PDRs, n	Unadjusted ARR	PDRs, n	Unadjusted ARR	% reduction
ITT	166	0.245	96	0.136	44.5%
Subgroup					
Sex					
Female	117	0.260	63	0.135	48.1%
Male	49	0.216	33	0.139	35.7%
Region					
OUS	122	0.239	76	0.144	39.8%

	Rebif N=411		OCR 600 N=410		
	PDRs, n	Unadjusted ARR	PDRs, n	Unadjusted ARR	% reduction
US	44	0.245	20	0.122	50.2%
Age category					
<40	99	0.253	48	0.116	54.2%
≥40	67	0.235	48	0.165	29.8%
Baseline EDSS category					
<4	111	0.211	56	0.103	51.2%
≥4	55	0.366	40	0.248	32.2%
Number of relapses in the last 2 years category					
1	70	0.224	31	0.106	52.7%
2	62	0.236	44	0.145	38.6%
3	13	0.212	7	0.093	56.1%
≥4	20	0.505	14	0.439	13.1%
Previous treatment for MS					
Yes	57	0.310	35	0.192	38.1%
No	109	0.221	61	0.117	47.1%
Baseline presence of gadolinium-enhancing lesions					
Yes	81	0.326	32	0.107	67.2%
No	85	0.201	64	0.161	19.9%
Body Weight Category					
<75kg	90	0.257	60	0.150	41.6%
≥75kg	75	0.230	34	0.112	51.3%

Reviewer Comment: Based on the results of study WA21493, the efficacy in patients with 4 or more gadolinium-enhancing lesions at baseline was of interest (see page 35). However there were only 33 PDRs in the Rebif group (ARR=0.372) and 9 PDRs in the OCR 600 group (ARR=0.091) for those with 4 or more Gd-enhancing lesions and therefore the results are somewhat uninformative on this issue. Nevertheless there was a 75.5% reduction in the ARR and thus no indication of a lack of efficacy in the group with 4 or more gadolinium-enhancing lesions at baseline.

Data Quality and Integrity – Reviewers' Assessment

Accurate identification and assessment of a relapse may depend on the interval between onset and clinical evaluation. A potential relapse (CLINRLP) was to be assessed whenever possible within 7 days of the onset of the event. The actual mean time is shown in Table 25. The mean time was slightly longer for the Rebif group but the median time was the same. The EDSS assessment occurred within 7 days in 68% of the Rebif group and in 71% of the OCR 600 group. For this group the rate of confirmation (PDR) was 85.8% and 82.8% for the Rebif and OCR 600 groups respectively (Table 26). For those whose EDSS assessment was more than 7 days after

the start of the potential relapse, the confirmation rates were 67.2% and 50% for the Rebif and OCR 600 groups respectively (Table 27).

Table 25: Time from relapse onset to EDSS assessment of the relapse (days), Clinical Relapses, WA21092, ITT

Treatment	Time from RLP start to study day of POEDSS (days)						
	Total	Mean	Std Dev	Median	Min	Max	N Missing
Rebif	208	11.38	18.31	5	0	116	0
OCR 600	131	9.83	15.0	5	0	83	0

Source: PARAMCD_CLINRLP Subset of APERIODC_TRT Subset of WA 21092 rev FDARLP RLPstart to EDSS By (TRT01P).jmp

Table 26: Rates of confirmation of a CLINRLP as a PDR for those with EDSS assessment 7 days or less after relapse onset, WA21092

Treatment	CLINRLP	PDR			
	n	No, n	% of CLINRLP	Yes, n	% of CLINRLP
Rebif	141	20	14.2%	121	85.8%
OCR 600	93	16	17.2%	77	82.8%

Source: RLPonset toEDSS 7orless Subset of APERIODC_TRT Subset of WA 21092 rev FDARLP TRT01P By PARAMCD by AVALC.xlsx

Table 27: Rates of confirmation of a CLINRLP as a PDR for those with EDSS assessment more than 7 days or after relapse onset, WA21092

Treatment	CLINRLP	PDR			
	n	No, n	% of CLINRLP	Yes, n	% of CLINRLP
Rebif	67	22	32.8%	45	67.2%
OCR 600	38	19	50.0%	19	50.0%

Source: RLPonsettoEDSS more than 7 Subset of APERIODC_TRT Subset of WA 21092 rev FDARLP TRT01P by PARAMCD By AVALC.xlsx

Reviewer Comment: The time interval from the onset of the relapse to the clinical assessment is not ideal but this has not been unusual for this type of trial. The times and rates of confirmation are similar for the two treatment groups. The unadjusted ARR for all clinical relapses (CINRLP) (Table 28) also shows a statistically significant difference in favor of OCR 600 with a relative reduction of 38.6%. Therefore the confirmation process itself did not alter the treatment effect of OCR 600. It is unclear however what effect, if any, the delay in assessment of relapses may have had on the overall results of the trial.

Table 28: Unadjusted ARR for all clinical relapses, WA21092, ITT

Treatment group	Unadjusted ARR
OCR 600	0.180
Rebif	0.293*

*: p<0.0001

Efficacy Results – Secondary and other relevant endpoints

Confirmed Progression of Disability

The pre-specified population for the CDP12 and CDP24 endpoints following the ARR for both WA21092 and WA21093 is the pooled population from both RMS studies. The analysis of the pooled population is included in Section 6.3.2 . The following analyses are of study WA21092 alone.

During the 96 weeks of double-blinded treatment, an initial progression of disability occurred 110 times in 89 subjects in the OCR group and 175 times in 127 patients in the Rebif group. Approximately 30% of these events were confirmed as CDP12 events. If there was an initial progression but the patient discontinued before a valid confirmatory assessment could occur then the event was categorized as a CDPW12 event. These were not included in the calculation of the endpoint for the RMS trials ("no imputation") but these were included in the CDP rates for the PPMS trials ("with imputation"). Three such events occurred in one patient in each of the treatment groups. A higher proportion of patients with an IDP event in the Rebif group had a CDP12 event compared to the OCR 600 group, 39% vs. 35%. Table 29 summarizes the outcome of the IDPs for the two treatment groups.

Table 29: Disposition of IDP events to CDP12, CDPW12 or no CDP by treatment group, ITT

Progression category	OCR		Rebif	
	Subjects	Events	Subjects	Events
IDPs	89	110	127	175
CDP12 (% of IDPs)	31 (35%)	31 (28%)	50 (39%)	55 (31%)
CDPW12	1	1	3	3
Total CDP12 (% of IDPs)	32 (36%)	32 (29%)	53 (42%)	58 (33%)
Unconfirmed IDPs	57 (64%)	78 (71%)	74 (58%)	(%)

Reviewer Comment: Patients with an IDP may have met the criteria for a CDP12 or CDP24 multiple times throughout the trial. The total number of such "CDP events" is represented in Table 29 above. The number of times an individual subject met the criteria at least once is seen in Table 30 below.

The simple proportion of patients in the ITT with a 12 week confirmed progression of disability is shown in Table 30. For the RMS studies progression was not imputed for those who discontinued treatment following an initial progression (CDPW12). Since CDPW12 was included in the calculation of this endpoint in the PPMS trial (WA25046) both methods are included in the table. The difference in proportions shows a statistically significant reduction with OCR 600 treatment. The relative reduction is 33% without imputation for the CDPW12 patients and 38.5% when they are included.

Table 30: Reviewer table: Number and proportion of subjects with at least one IDP and CDP12 or CDPW12, ITT

	OCR 600 ITT		Rebif ITT	
PARAMCD	N	%	N	%
No CDP12	379	92%	361	88%
No CDP12 or CDPW12	378	92%	358	87%
CDP12	31	**8%***	50	**12%**
CDPW12	1		3	
CDP12 or CDPW12	32	**8%****	53	**13%**
Total	410	100.0%	411	100.0%

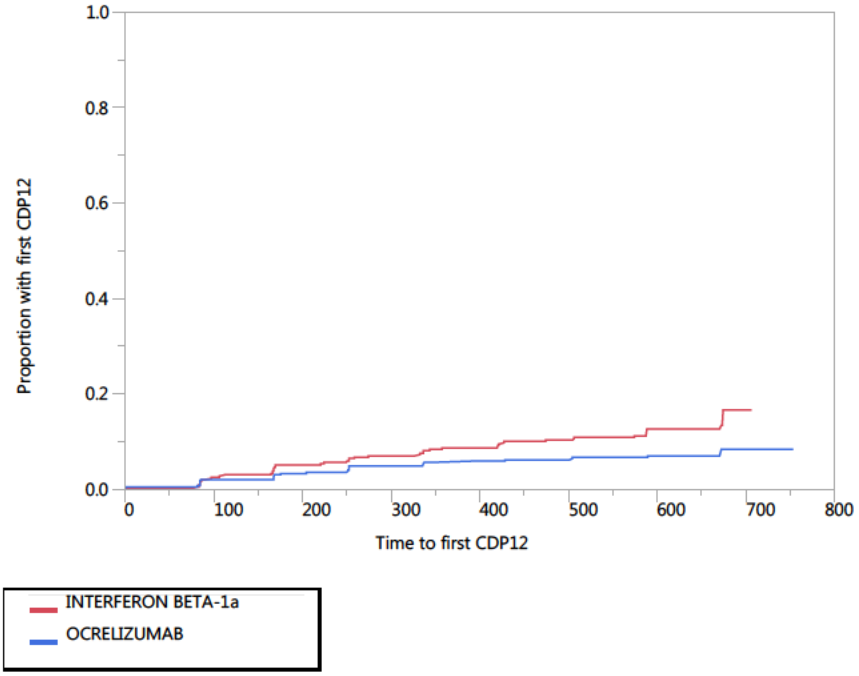
Source: ACDP dataset
CDP12: Confirmed Disability Progression 12 weeks; CDPW12: imputed CDP12 at withdrawal from treatment
*: p=0.0346 OCR vs Rebif, Fisher's exact test
**: p=0.0215 OCR vs Rebif, Fisher's exact test

> *Reviewer Comment: The overall proportion of patients with 12 week confirmed progression of disability is much lower in studies WA21092 and WA21093 compared to the proportion in study WA25046 in the PPMS population– see* Table 147.

The time to the first CDP12 alone, the pre-specified endpoint (Figure 4), or to the first CDP12 or CDPW12, comparable to the calculation in study WA25046 (Figure 5), both show a statistically significant benefit from OCR 600 treatment.

Figure 4: Time to first CDP12, ITT

Product-Limit Survival Fit
Failure Plot



Summary

Treatment group	CDP12	No CDP12
OCR 600	31	379
Rebif	50	360

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	5.7024	1	0.0169*
Wilcoxon	5.2044	1	0.0225*

Source: Join CDP12orCDPW12 with TRTorSCR EDSSatADYrevmax inclNM with ADSL.jmp

The influence of the two stratification factors and other baseline characteristics on the proportion with CDP12 is shown in Table 31. OCR 600 appears to be most efficacious in patients aged 45 years or less although interpretation of the difference from those over 45 years old is limited by the relatively small number of patients in the older age category. The same is true for the difference in efficacy in the OUS compared to the US.

> *Reviewer Comment: As for a reduction in relapses, OCR 600 may be most effective for progression of disability in those with active disease as evidenced by the presence of gadolinium-enhancing lesions.*

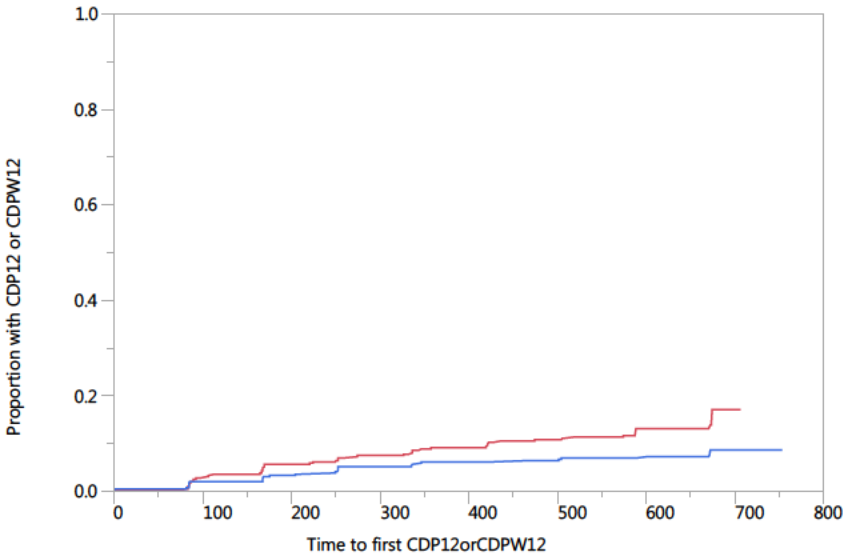
Table 31: Reviewer table: Time to first CDP12 by stratification and key baseline factors

	OCR		Rebif		
	CDP12	No CDP12	CDP12	No CDP12	Log Rank
Sex					
M, N= 541	18	252	29	242	0.0779
F, N=279	21	118	13	127	0.1113
IXRS Age					
≤45, N= 642	21	305	37	284	0.0160
>45, N= 173	10	74	13	76	0.5574
IXRS Region					
OUS, N= 611	17	288	35	271	0.0070
US, N= 209	14	91	15	89	0.6977
Relapse free during treatment (NPDRCAT)					
Yes, N=629	21	318	20	270	0.6253
No, N=191	10	61	30	90	0.0641
Baseline EDSS category					
<4, N=632	27	287	40	278	0.0728
≥4, N=188	4	92	10	82	0.0816
Race					
White	29	346	46	328	0.0254
Ethnic group					
Hispanic or Latino, N=106	4	41	10	51	0.2387
Not Hispanic or Latino, N=642	23	305	35	279	0.0462
Not Reported, N=72	4	33	5	30	0.7228
Baseline T1 Gd Enhanced Lesions Category					
0, N=484	17	216	26	225	0.2229
1, N=116	1	63	6	46	0.0219
2, N=60	0	30	4	26	0.0348
3, n=36	5	15	4	12	0.9077
≥4, N=115	8	50	10	47	0.4470
Baseline T1 Gd-enhancing Lesions Flag (BGDLESFL)					
Yes, n=327	14	158	24	131	0.0237
No=n=484	17	216	26	225	0.2229
Baseline Number of T2 Lesions category					
0-5, N=29	0	12	3	14	0.1753
6-9, N=28	2	14	1	11	0.8331
>9, N=758	29	351	46	332	0.0235
Baseline Weight category					
<75kg, N=445	11	222	26	186	0.0024
≥75kg, N=373	19	157	24	173	0.6194
Previous MS treatment					
Yes, N=227	10	99	14	104	0.4460
No, N=593	21	280	36	256	0.0202
Per Protocol Population Flag					
Yes, N=780	30	364	49	337	0.0126
No, N=40	1	15	1	23	0.7958

When the CDPW12 events are included, as was the case for the same analysis in the PPMS population, the difference remains statistically significant (Figure 5).

Figure 5: Reviewer figure: Time to first CDP12 or CDPW12, WA21092, ITT

Product-Limit Survival Fit
Failure Plot



Summary

Treatment group	CDP12/CDPW12	N0 CDP12/CDPW12
OCR 600	32	378
Rebif	52	358

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	6.0463	1	0.0139*
Wilcoxon	5.5856	1	0.0181*

Source: Join CDP12orCDPW12 with TRTorSCR EDSSatADYrevmax inclNM with ADSL.jmp

Reviewer Comment: The same Kaplan-Meier analyses for CDP12 and for CDP12/CDPW12 using the all treated population, i.e. excluding those who were randomized but not treated, yield essentially the same statistically significant difference.

24 Week Confirmed Disability Progression (CDP24)

Approximately 23% of IDP events were confirmed 24 weeks later. Of subjects with an IDP, 27% of those treated with OCR 600 had a confirmed progression 24 weeks later compared to 31% of those treated with Rebif (Table 32).

Table 32: Disposition of IDP events to CDP24, CDPW24 or no CDP by treatment group, WA21092, ITT

Progression category	OCR		Rebif	
	Subjects	Events	Subjects	Events
IDPs	89	110	127	175
CDP24 (% of IDPs)	24 (27%)	24 (22%)	39 (31%)	40 (23%)
CDPW24	1	1	3	3
CDP24 or CDPW24 (% of IDPs)	25(28%)	25 (23%)	42 (33%)	43 (25%)
Unconfirmed IDPs	64 (72%)	85 (77%)	85 (67%)	132 (75%)

The simple proportion of patients in the ITT with a 24 week confirmed progression of disability is shown in Table 33. For the RMS studies progression was not imputed for those who discontinued treatment following an initial progression (CDPW24). Since CDPW24 was included in the calculation of this endpoint in the PPMS trial (WA25046) both methods are included in the table. The difference in proportions with a CDP24 event shows a reduction with OCR 600 treatment that is not quite statistically significant. The relative reduction is 40% without or with imputation of the CDPW24 events.

Table 33: Reviewer table: Number and proportion of subjects with at least one IDP and CDP24 or CDPW24, WA21092, ITT

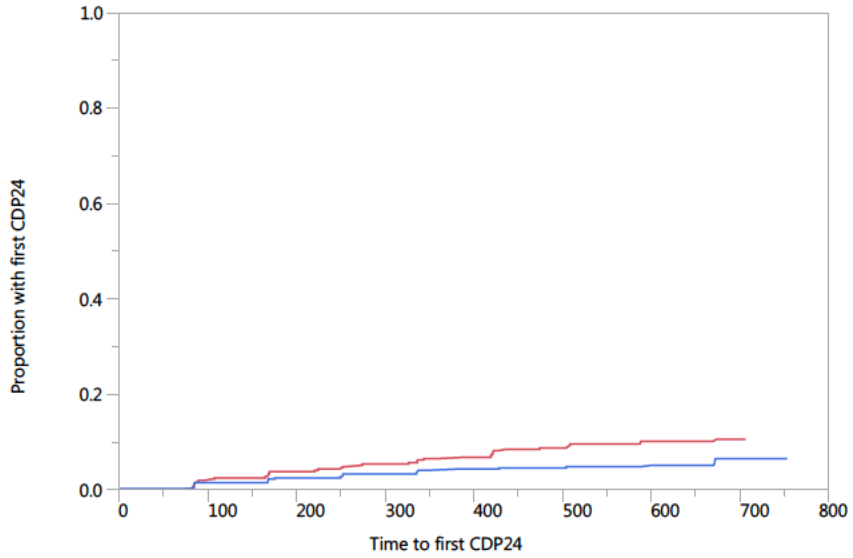
	OCR 600 ITT		Rebif ITT	
PARAMCD	N	%	N	%
No CDP24	386	94 %	372	91 %
No CDP24 or CDPW24	385	94 %	369	90 %
CDP24	**24**	**6 %***	**39**	**10 %**
CDPW24	1		3	
CDP24 or CDPW24	**25**	**6 %****	**42**	**10 %**
Total	410	100.0%	411	100.0%

Source: ACDP dataset
CDP12: Confirmed Disability Progression 12 weeks; CDPW12: imputed CDP12 at withdrawal from treatment
*: p=0.0657 OCR vs Rebif, Fisher's exact test
**: p=0.0407 OCR vs Rebif, Fisher's exact test

The time to the first CDP24 alone, the pre-specified endpoint (Figure 6) or to the first CDP24 or CDPW24 (Figure 7), comparable to the calculation in study WA25046, both show a statistically significant benefit from OCR 600 treatment.

Figure 6: Reviewer figure: Time to the first CDP24, WA21092, ITT

Product-Limit Survival Fit
Failure Plot



Summary

Group	CDP24	N0 CDP24
Rebif	39	371
OCR 600	24	386
Combined	63	757

Tests Between Groups

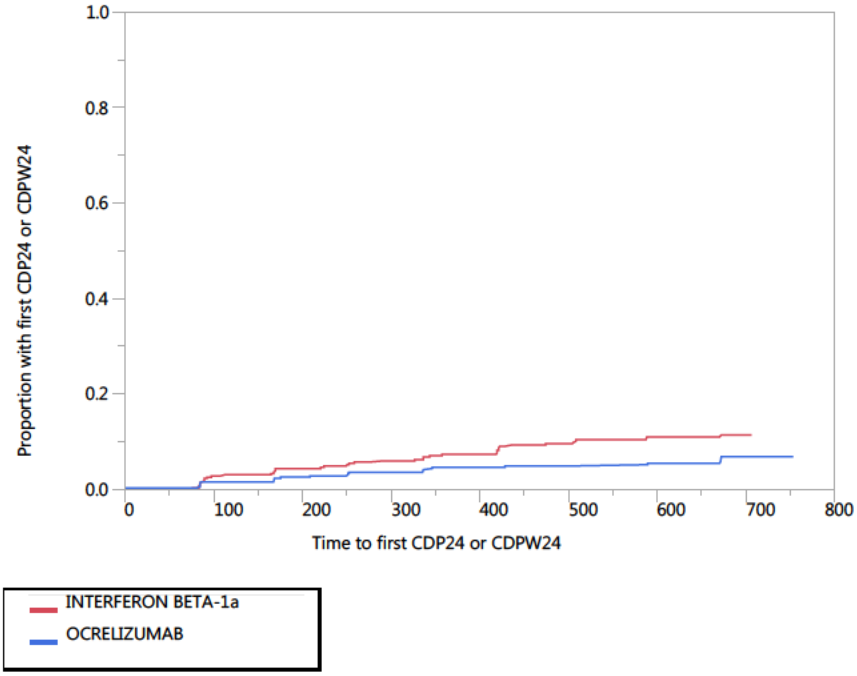
Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	4.4590	1	0.0347*
Wilcoxon	4.7777	1	0.0288*

Source: Join CDP24orCDPW24 with TRTorSCR EDSSatADYrevmax inclNM with ADSL.jmp

CDP24 or CDPW24

Figure 7: Reviewer figure: Time to first CDP24 or CDPW24, WA21092, ITT

Product-Limit Survival Fit
Failure Plot



Summary

Group	CDP24/CDPW24	No CDP24/CDPW24
Rebif	42	368
OCR 600	25	385
Combined	67	753

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	5.3010	1	0.0213*
Wilcoxon	5.6639	1	0.0173*

Source: Join CDP24orCDPW24 with TRTorSCR EDSSatADYrevmax inclNM with ADSL.jmp

The sponsor assessed the proportion of subjects whose initial progression of disability was sustained for all EDSS assessments from the initial progression to the last EDSS. Of the 31 subjects in the OCR group with a CDP12, 14 (45% or 3.4% of the ITT treatment group) had sustained progression to the last EDSS and of the 50 subjects in the Rebif group 29 (58% or 7.1% of the ITT treatment group) had sustained progression to the last EDSS.

The duration of any given progression meeting the criteria for an IDP is shown in Table 34. There is no difference between the treatment groups for this measure of periods of disability although there are more such periods in the Rebif group compared to the group treated with OCR 600.

Table 34: Reviewer table: Duration from the time IDP criteria met to the time not met or last EDSS, WA21092, ITT

Treatment	Duration in Days (AVAL)					
	Total IDPs	Mean	Std Dev	Median	Min	Max
Rebif	175	122.12	135.48	85	1	597
OCR 600	110	121.06	134.06	85	1	671

Source: CDPDUR Subset of WA21092 ACDP AVAL By (TRT01P).jmp

Reviewer Comment: In these exploratory analyses it appears that treatment with OCR 600 may not affect the duration of a period of disability. Rather, treatment with OCR 600 reduces the number of such episodes.

MRI Endpoints

At baseline the two treatment arms did not differ significantly in any of the assessments of disease activity (Table 35).

Table 35: Reviewer table: Baseline MRI results, WA21092

Treatment	Total	Mean	Std Dev	Median	Min	Max
Number gadolinium enhancing lesions (AVAL)						
Rebif	405	1.88	5.19	0	0	50
OCR 600	401	1.70	4.17	0	0	48
Normalized Brain Volume, cm^3						
Rebif	403	1498.2	86.7	1503.0	1251.8	1718.0
OCR 600	402	1500.6	84.1	1498.4	1271.7	1736.5
T1 hypointense lesions						
Rebif	405	33.02	37.24	21	0	247
OCR 600	401	33.26	35.42	21	0	226
Non-enhancing T1 lesion volume, cm^3						
Rebif	406	3.31	5.09	1.33	0	34.13
OCR 600	402	3.48	6.00	1.26	0	46.94
T2 Lesion Count						
Rebif	406	51.11	40.0	41	1	226
OCR 600	404	51.17	39.11	40.5	1	218
T2 Lesion Volume						
Rebif	407	9.74	11.30	6.19	0.029	63.46
OCR 600	405	10.83	13.93	5.65	0.026	83.17

Source: ZTESTCD_Subset of APERIODC_SCR Subset of ZDCAT_MRISCAN Subset of WA 21092 rev AMRI

Total Number of T1 Gadolinium–Enhanced Lesions as Detected by Brain Magnetic Resonance Imaging at Weeks 24, 48, and 96

Not all patients had an MRI assessment of gadolinium-enhancing lesions (CONSGD) at week 24, week 48 and week 96. An assessment of gadolinium-enhancing lesions was available for 753, 734 and 512 patients at weeks 24, 48 and 96 weeks respectively. To assess this endpoint the sponsor used a negative binomial model with the log transform of the number of MRI scans done as the offset variable.

> *Reviewer Comment: To assess this endpoint this reviewer analyzed the population that did have an assessment of gadolinium-enhancing lesions at all three visits. Since this method does not include the full ITT the mean value is lower than that in Table 37 in which the sponsor used modeling to include all available data. See the review by Dr. Yan for a review of the results based on modeling. The reviewer method nevertheless shows a similar large reduction in the number of new gadolinium-enhancing lesions over the double blind treatment phase of the trial (Table 36). This also suggests that the sponsor's imputation of missing MRI values does not alter the result.*

Table 36: Reviewer table: Sum of T1 gadolinium-enhancing lesions, WA21092, population with assessment at weeks 24, 48 and 96.

TRT01P	Mean (AVAL weeks 24 48 and 96)						
	Total patients with all 3 assessments	Mean	Std Dev	Median	Min	Max	N Missing
Rebif	242	0.299	1.10	0	0	14	0
OCR 600	263	0.023	0.16	0	0	2	0

Source: Join AVISIT Weeks 24 48 96 Subset of ZDTEST_CONSGD Subset of APERIODC_TRT Subset of ZDCAT_MRISCAN Subset of WA 21092 rev AMRI Mean AVAL weeks 24 48 and 96 By (TRT01P).jmp
*: p<0.0001, t-test, 2-tailed

The result for the population with an assessment at all three visits is comparable to that of the sponsor using modelling (Table 37). The relative reduction was 92.3% using the reviewer method and 94.2% using the sponsor's method.

Table 37: Sponsor Table 28: Total Number of T1 Gadolinium–Enhancing Lesions as Detected by Brain MRI at Scheduled Visits during the Double-Blind Treatment Period (ITT Population)

MRI variable	Rebif	OCR 600
n	377	388
Total number T1 Gadolinium-Enhancing Lesions	337	21
Total number of Brain MRI Scans	1064	1118
Unadjusted rate *	0.317	0.016
Adjusted rate **	0.286	0.016
95% CI of adjusted rate	0.200, 0.409	0.009, 0.030
Adjusted rate ratio **		0.058

95% CI of Adjusted rate ratio		0.032, 0.104
p-value		<0.0001

* The total number of T1 gadolinium-enhancing lesions for all patients in the treatment group divided by the total number of brain MRI scans. The total number of lesions is calculated as the sum of the individual number of lesions at Weeks 24, 48, and 96.
** Adjusted by Baseline T1 Gd Lesion (present or not), Baseline EDSS (<4.0 vs. >=4.0) and Geographical Region (US vs. OUS). Log-transformed number of brain MRI scans is included as an offset variable.
Source: CSR WA21092 Table 28, page 135/6491

New and/or enlarging T2 hyperintense lesions

Not all patients had an assessment of new and/or newly enlarging T2 hyperintense lesions at weeks 24, 48 and 96. A result was available for 757, 735 and 514 patients at weeks 24, 48 and 96 respectively. The sponsor used the same methods to assess this endpoint as for gadolinium-enhancing lesions. An analysis limited to the population of patients that did have all three assessments is seen in Table 38. This result is comparable to that of the sponsor using modeling (Table 39). The relative reduction was 85.2% using the reviewer method and 77.1% using the sponsor's method.

Table 38: Reviewer table: New or newly enlarging T2 lesions, WA21092, population with assessment at weeks 24, 48 and 96

Treatment	Mean of Weeks 24, 48 and 96					
	N	Mean	Std Dev	Median	Min	Max
Rebif	243	1.82	3.64	0.33	0	25.3
OCR 600	265	0.27	0.72	0	0	5.7

Source: Join AVISIT Weeks 24 48 96 Subset of ZDTEST_NEWT2 Subset of APERIODC_TRT Subset of ZDCAT_MRISCAN Subset of WA 21092 rev AMRI Mean of Weeks 24 48 96 By (TRT01P).jmp
*: p<0.0001, unpaired t-test, 2-tailed

Table 39: Sponsor Table 30: Total Number of New and/or Enlarging T2 Hyperintense Lesions as Detected by Brain MRI at Scheduled Visits (WA21092, ITT Population)

MRI variable	Rebif	OCR 600
n	378	390
Total number of new and enlarging T2 hyperintense lesions	1916	430
Total number of Brain MRI Scans	1066	1123
Unadjusted rate *	1.797	0.383
Adjusted rate **	1.413	0.323
95% CI of adjusted rate	1.123, 1.777	0.256, 0.407
Adjusted rate ratio **		0.229
95% CI of Adjusted rate ratio		0.174, 0.300
p-value		<0.0001

* The total number of new and/or enlarging T2 lesions for all patients in the treatment group divided by the total number of brain MRI scans. The total number of lesions is calculated as the sum of the individual number of lesions at Weeks 24, 48, and 96.

** Adjusted by Baseline T2 Lesion Count, Baseline EDSS (<4.0 vs. >=4.0) and Geographical Region (US vs. OUS). Log-transformed number of brain MRI scans is included as an offset variable.
Source: CSR WA21092 Table 30, page 137/6491

Total number of T1-hypointense lesions (Chronic Black Holes) at Weeks 24, 48 and 96.

The number of T1-hypointense lesions was assessed in 752, 734 and 512 patients at weeks 24, 48 and 96 respectively. An analysis of this endpoint based on the population that had all three assessments is shown in Table 40. The results are comparable to those of the sponsor using a negative binomial model with an offset variable of the log transform of the number of MRI scans (Table 41). The relative reduction was 64.3% using the reviewer method and 57.2% using the sponsor's method.

Table 40: Reviewer table: Number of new T1-hypointense lesions at weeks 24, 48 and 96, WA21092, population with an assessment at all three visits

Treatment	Mean of Weeks 24 48 and 96					
	N	Mean	Std Dev	Median	Min	Max
Rebif	242	1.12	2.18	0.33	0	14.7
OCR 600	263	0.40	1.02	0	0	11

Source: Join AVISIT Weeks 24 48 96 Subset of ZDTEST_ NT1LESC Subset of APERIODC_TRT Subset of ZDCAT_MRISCAN Subset of WA 21092 rev AMRI Mean of Weeks 24 48 96 By (TRT01P).jmp
P<0.0001, unpaired t-test, 2-tailed

Table 41: Sponsor Table 32: Total Number of New T1 Hypointense Lesions as Detected by Brain MRI at scheduled visits during the Double-Blind treatment Period: (ITT Population)

MRI variable	Rebif	OCR 600
n	377	388
Total number of T1 hypointense lesions	1307	564
Total number of Brain MRI Scans	1064	1116
Unadjusted rate *	1.228	0.505
Adjusted rate **	0.982	0.420
95% CI of adjusted rate	1.123, 1.777	0.256, 0.407
Adjusted rate ratio **		0.428
95% CI of Adjusted rate ratio		0.328, 0.557
p-value		<0.0001

* The total number of T1-Hypo-Intense Lesions (Chronic Black Holes) for all patients in the treatment group divided by the total number of brain MRI scans. The total number of lesions is calculated as the sum of the individual number of lesions at Weeks 24, 48, and 96.
** Adjusted by Baseline T1-Hypo-Intense Lesion Count, Baseline EDSS (<4.0 vs. >=4.0) and Geographical Region (US vs. OUS). Log-transformed number of brain MRI scans is included as an offset variable.

Percentage Change in Brain Volume as Detected by Brain Magnetic Resonance Imaging from Baseline to Week 96

There was a small but gradual decline in brain volume in both treatment arms over the 96 week double blind treatment period.

Table 42: Reviewer table: Percent change in brain volume from baseline to weeks 24, 48 and 96, WA21092, population with all three assessments

	Percent change (AVAL)						
		Mean		Std Dev		Median	
AVISIT	Total	Rebif	OCR 600	Rebif	OCR 600	Rebif	OCR 600
WEEK 24	701	-0.51	-0.37	0.64	0.50	-0.44	-0.34
WEEK 48	648	-0.80	-0.63	0.78	0.66	-0.74	-0.50
WEEK 96	417	-1.23	-0.90*	1.00	0.85	-1.09	-0.78

Source: PARAMCD_PBVC Subset of ZTEST_PBVC Subset of APERIODC_TRT Subset of ZDCAT_MRISCAN Subset of WA 21092 rev AMRI AVAL By (AVISIT).xlsx
*: p=0.0003, unpaired t-test, 2-tailed

Reviewer Comment: The sponsor's results for the percent change in brain volume using the baseline value as the reference are comparable to those in the table above. The sponsor assessed the same endpoint using Week 24 as the "baseline". The rationale for this analysis was that there may be "pseudo-atrophy" in the first 6 months due to reduction in inflammation with treatment. Both treatment groups had a smaller reduction in brain volume at weeks 48 and 96 compared to using the actual baseline as the reference. The reduction in volume was less than 1% in both groups but there was less of a percent reduction in volume in the OCR 600mg group (-0.57±0.61) compared to the Rebif group (-0.75±0.79).

Dose/Dose Response

Dose vs. response was not assessed in this trial.

Durability of Response

Durability of response was not assessed in this trial.

Persistence of Effect

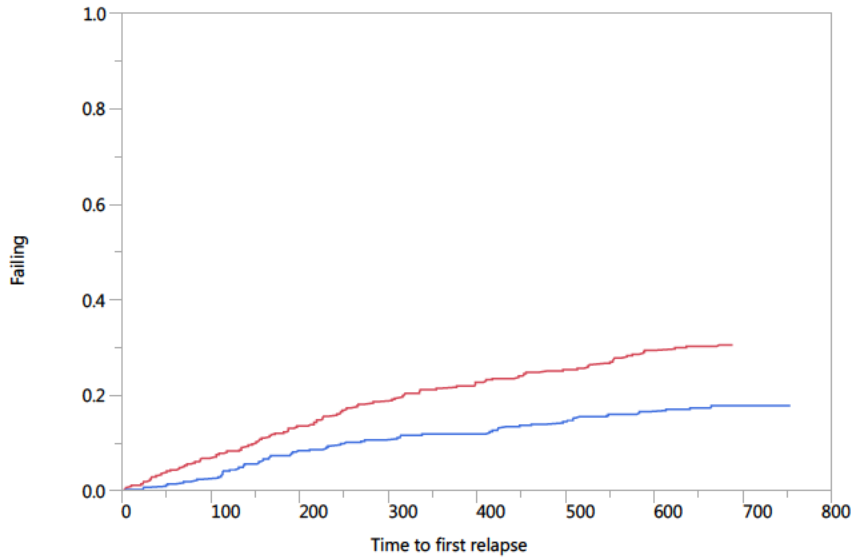
Efficacy following withdrawal of treatment was not assessed.

Additional Analyses Conducted on the Individual Trial

For those treated with OCR 600, 71 patients (17.3%) had a least one relapse and 120 patients treated with Rebif (29.2%) had a least one relapse. The time to the first relapse using the Kaplan-Meier model is shown in **Figure 8.**

Figure 8: Time to first protocol-defined relapse, WA21092, ITT

Product-Limit Survival Fit
Failure Plot



Summary

Treatment	First Relapse	No relapse
Rebif	120	291
OCR 600	71	339
Combined	191	630

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	17.5237	1	<.0001*
Wilcoxon	17.4468	1	<.0001*

Source: Join revADSL with AVALC_Y PDR by ASTDYmin incl NM.jmp

Additional MRI endpoints

Percentage Change in Total T2 Lesion Volume as Detected by Brain Magnetic Resonance Imaging from baseline to Week 96

Six hundred ninety six (696) patients had an assessment of total T2 lesion volume at baseline and at week 96. The change from baseline to week 96 is shown in **Table 43.** The sponsor

reports nearly identical results (CSR WA21092 page 1008/6491).

Table 43: Reviewer table: T2 lesion volume, percent change from baseline to week 96, WA21092, population with both assessments

Treatment	Percent change from SCRBL to Week 96					
	N	Mean	Std Dev	Median	Min	Max
Rebif	336	1.38	49.1	-3.01	-55.3	759.3
OCR 600	360	-5.84	16.5	-4.25	-67.1	127.1

Source: PARAMCD_T2LESV Subset of AVISIT_SCRBL and Week 96 Subset of ZDCAT_MRISCAN Subset of WA 21092 rev AMRI Percent Change from SCRBL to Week 96 By (TRT01P).jmp

Karnofsky Performance Score

An alternate measure of functional status, the Karnofsky score, was assessed periodically throughout the trial. The baseline score was essentially the same for the two treatment groups (Table 44). The change at 96 weeks for those with both assessments showed a statistically significant change that may be too small to be clinically relevant (Table 45 and Table 46).

Table 44: Reviewer table: Baseline Karnofsky Score, WA21092, ITT

Treatment	Karnofsky Score (ZASTRESN)						
	Total	Mean	Std Dev	Median	Min	Max	N Missing
Rebif	391	84.78	11.48	90	40	100	0
OCR 600	397	84.41	10.47	90	60	100	0

Source: AVISIT_BL Subset of WA 21092 rev AKPS ZASTRESN By (TRT01P).jmp

Table 45: Reviewer table: Change in Karnofsky score from baseline to Week 96, WA21092, population with both assessments

Treatment	Karnofsky score, change from baseline to week 96						
	Total	Mean	Std Dev	Median	Min	Max	N Missing
Rebif	307	-0.79	8.5	0	-30	30	66
OCR 600	338	0.98*	8.2	0	-30	20	72

Source: APBLFL_Y Subset of AVISIT_WEEK 96 Subset of WA 21092 rev AKPS CHG By (TRT01P).jmp
*: p=0.0073, unpaired t-test, two tailed

Table 46: Distribution of change from baseline to week 96 Karnofsky Score, WA21092, ITT

Absolute Change from Baseline	INTERFERON BETA-1a	OCRELIZUMAB	Subjects
-30	4 (0.49%)	1 (0.12%)	5 (0.61%)
-20	10 (1.22%)	6 (0.73%)	16 (1.95%)
-10	38 (4.63%)	43 (5.24%)	81 (9.87%)

Absolute Change from Baseline	INTERFERON BETA-1a	OCRELIZUMAB	Subjects
0	154 (18.76%)	143 (17.42%)	297 (36.18%)
Missing	66 (8.04%)	73 (8.89%)	139 (16.93%)
10	38 (4.63%)	64 (7.80%)	102 (12.42%)
20	4 (0.49%)	10 (1.22%)	14 (1.71%)
30	1 (0.12%)	0 (0.00%)	1 (0.12%)
Subjects	406 (49.45%)	406 (49.45%)	821 (100.00%)
Denominator			(All patients)

Source: JRevCTab WA21092 AKPS CHGbyTRT01PfilterAVISIT_Week96.xls

6.2. WA21093: A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon β-1a (Rebif®) in patients with relapsing multiple sclerosis

6.2.1. Study Design

Overview and Objective

Study WA21093 is identical in design to that of study WA21092

Trial Design

Study WA21093 is identical in design to that of study WA21092

Study Endpoints

See Study WA21092

Statistical Analysis Plan

See Study WA21092

Protocol Amendments

The amendments made to study WA21092 are applicable to study WA21093

Data Quality and Integrity: Sponsor's Assurance

See page 51

6.2.2. Study Results

Compliance with Good Clinical Practices

See page **51**

Financial Disclosure

See page **51**

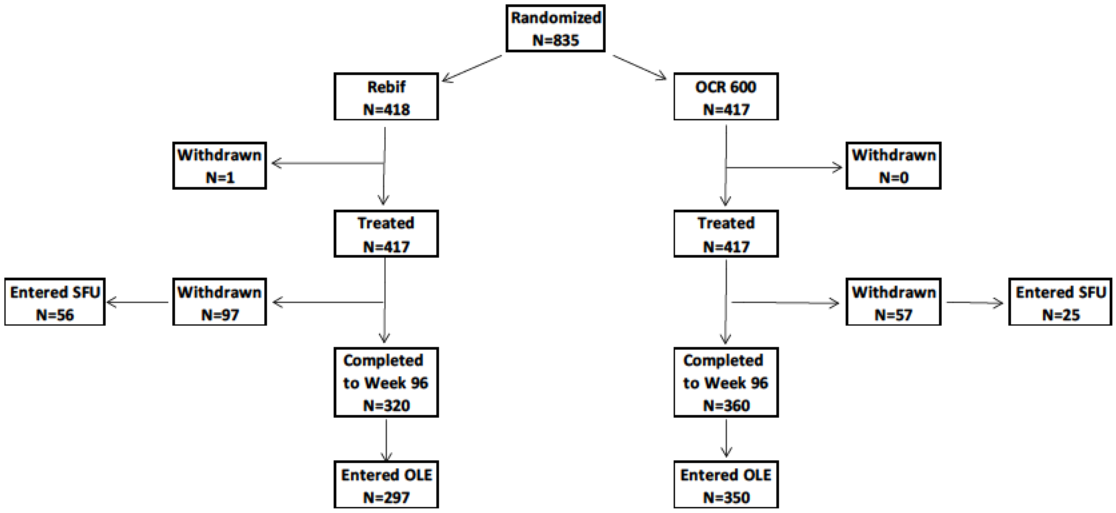
Patient Disposition

First patient randomized: 20 September 2011
Last patient randomized: 28 March 2013
Data cut-off date: 12 May 2015

835 patients were enrolled at 166 sites in 24 countries. The primary analysis population was the Intent to Treat (ITT) population which was defined as all randomized patients. One patient in the Rebif group was randomized but not treated. The safety population therefore consisted of 834 patients treated, 417 in each treatment group. One patient randomized to Rebif received a dose of OCR 600 at a single visit. This patient is included in the ITT for all efficacy analyses and in the safety population as randomized.

The disposition of patients in study WA21093 is summarized in **Figure 9**.

Figure 9: Reviewer Figure: Disposition of patients in Study WA21093



The completion rate was slightly higher in the group treated with OCR 600 (86.3%) compared to the group treated with Rebif (76.6%). The most common reason for premature discontinuation from treatment was an adverse event, 6.0% in the Rebif group compared to 3.8% in the OCR 600 group. Withdrawal for lack of efficacy was more common in the Rebif group (3.6%) compared to the OCR 600 group (1.4%) (Table 47).

Table 47: Disposition of patients in study WA21093

DSDECOD	Total		Rebif		OCR 600	
	N	%	N	%	N	%
Completed	680	81.4%	320	76.6%	360	86.3%
Did Not Complete	155	18.6%	98	23.4%	57	13.7%
Total	**835**	**100.0%**	**418**	**100.0%**	**417**	**100.0%**
Reason For Non-Completion						
Adverse Event	41	4.9%	25	6.0%	16	3.8%
Withdrawal By Subject	37	4.4%	25	6.0%	12	2.9%
Other	26	3.1%	16	3.8%	10	2.4%
Lack Of Efficacy	21	2.5%	15	3.6%	6	1.4%
Lost To Follow-Up	16	1.9%	10	2.4%	6	1.4%
Non-Compliance	4	0.5%	1	0.2%	3	0.7%
Pregnancy	3	0.4%	3	0.7%	0	0.0%
Death	2	0.2%	1	0.2%	1	0.2%
Non-Compliance With Study Drug	2	0.2%	1	0.2%	1	0.2%

DSDECOD	Total		Rebif		OCR 600	
	N	%	N	%	N	%
Protocol Violation	2	0.2%	1	0.2%	1	0.2%
Physician Decision	1	0.1%	0	0.0%	1	0.2%
	155		**98**		**57**	

Source: DSSCAT_TRTMNT Subset of Join DS with ADSL TRT01P By (DSDECOD).xlsx

Unblinding

There were 8 patients whose treatment assignment was unblinded by the sponsor to investigate a suspected unexpected serious adverse drug reaction and there were 19 patients whose treatment assignment was unblinded at the request of the investigator for treatment and/or safety reasons.

Protocol Violations/Deviations

35 subjects did not meet all eligibility criteria, 15 in the OCR 600 group and 20 in the Rebif group. Six patients in the Rebif group and 3 in the OCR 600 group did not meet the requirement for neurological stability for 30 days or more prior to screening. Two patients in the Rebif group and 3 in the OCR 600 group should have been excluded because of a disease duration greater than 10 years with a baseline EDSS of 2.0 or less (i.e. "benign MS"). Most of the remaining patients did not meet the criteria related to previous treatments. The most common eligibility criteria not met are shown in Table 48. There were 11 and 12 protocol violations in the OCR 600 and Rebif groups respectively, all related to administration of study drug.

Table 48: Key eligibility criteria not met, WA21093

Category	Inclusion/Exclusion criterion	Total	Rebif	OCR 600
INCLUSION	Neurological stability for >= 30 days prior to both screening and baseline.	9	6	3
INCLUSION	At least 2 documented clinical attacks within the last 2 years prior to screening, or one clinical attack in the year prior to screening (but not within 30 days prior to screening).	7	4	3
EXCLUSION	Disease duration of more than 10 years in patients with an EDSS <= 2.0 at screening.	5	2	3
EXCLUSION	Infection requiring hospitalization or treatment with IV antibiotics within 4 weeks prior to baseline visit or oral antibiotics within 2 weeks prior to baseline visit.	5	2	3

Source: Join IE with ADSL TRT01P IECAT by IETEST by TRT01P desc.jmp

Reviewer Comment: Inclusion of the subjects who did not meet all eligibility criteria is not ideal but it is unlikely that these subjects will have affected the key outcome measures.

Eligibility /Screening period

The duration of time to establish eligibility should have been 14 days or less for most patients and in exceptional cases a screening period of up to 8 weeks was allowed. The actual mean and median period between informed consent and randomization was over 3 weeks (Table 49). Sixteen (16) Rebif patients (3.8%) and 17 OCR (4.1%) patients had a screening period over 8 weeks (56 days) before randomization. There was no change in EDSS from screening to randomization for approximately 67% of the patients in both arms of the trial. Approximately 15% had an increase and 15% a decrease in EDSS score.

Table 49: Duration of Screening Period, WA21093, ITT

Treatment	Screening time (RANDDT minus INFCODT in days)					
	Total	Mean	Std Dev	Median	Min	Max
Rebif	418	26.86	14.88	22	7	123
OCR 600	417	27.21	15.05	22	7	100

Source: WA 21093 rev ADSL RANDDTminusINFCODT By (TRT01P).jmp

Reviewer Comment: A prolonged screening period is not ideal but not unusual for a small proportion of patients in an RMS trial. One concern is that the level of disability may have changed since enrollment. However in this trial the "baseline" EDSS is the average of the screening and the EDSS at randomization and the treatment arms are balanced for the proportion that remained the same, increased or decreased between screening and randomization. Therefore it is unlikely that the long screening period had a significant effect on the study results.

Table of Demographic Characteristics

The two treatment groups were balanced for key demographic characteristics at baseline. The population was approximately 65% female as expected for the RMS population. The baseline age was less than 40 years in 60%. Approximately 90% were of the white race. Just over 25% were from the US (Table 50).

Table 50: Baseline demographic characteristics, WA21093, ITT

	OCR 600	Rebif
SEX, n, %		
Female	271, 65.0%	280, 67.0%
Male	146, 35.0%	138, 33.0%
AGE		
Mean (SD)	37.1 (9.1)	37.74(9.0)
Median	37	37
Min, Max	18, 55	18, 55
<40	252, 60.4%	242, 57.7%
≥40	165, 39.6%	177, 42.3%
RACE, n, %		
White	368, 88.2%	382, 91.4%
Other	19, 4.6%	9, 2.2%
Multiple	4, 1.0%	1, 0.2%
Black or African American	21, 5.0%	20, 4.8%
Asian	2, 0.5%	2, 0.5%
American Indian or Alaska native	2, 0.5%	4, 1.0%
Native Hawaiian or other Pacific Islander	1, 0.2%	0, 0.0%
ETHNIC GROUP		
Not Hispanic or Latino	335, 80.3%	338, 80.8%
Hispanic or Latino	56, 13.4%	51, 12.2%
Not reported	26, 6.2%	29, 6.9%
Country group		
OUS	305, 73.1%	304, 72.7%
US	112, 26.9%	114, 27.3%
Region		
EU/Switzerland/Norway	187, 44.8%	182, 43.5%
USA/Canada/Australia	153, 36.7%	157, 37.6%
Non-EU/Israel/Africa	58, 13.9%	53, 12.7%
Latin America	19, 4.6%	26, 6.2%

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The characteristics of RMS at baseline were essentially the same for the two treatment groups (Table 51). The mean and median EDSS scores at baseline were not significantly different. Most patients had either one or two relapses in the past 2 years. More than half of the patients did not have a gadolinium-enhancing lesion at baseline. Three-fourths had not been treated previously for MS.

Table 51: Baseline disease characteristics, WA21093, ITT

	OCR 600 N=410	Rebif N=411
Baseline EDSS		
Mean (SD)	2.73 (1.29)	2.79 (1.38)
Median	2.5	2.5
Min, Max	0, 6	0, 6
<4	315, 75.5%	309, 73.9%
≥4	102, 24.5%	109, 26.1%
Duration since MS Symptom Onset category (ONSETCAT)		
<= 3 Years	35.7%	37.8%
> 3 to <= 5 Years	12.9%	11.2%
> 5 to <= 10 Years	28.1%	26.3%
> 10 Years	23.3%	24.6%
Relapses in the previous 2 years		
1	194, 46.5%	187, 44.7%
2	147, 35.3%	167, 40.0%
3	58, 13.9%	41, 9.8%
≥4	17, 4.1%	22, 5.3%
Baseline Gadolinium-enhancing lesions*		
0	252, 60.4%	243, 58.1%
1	58, 13.9%	62, 14.8%
2	33, 7.9%	38, 9.1%
3	15, 3.6%	14, 3.3%
≥4	55, 13.2%	58, 13.9%
missing	4, 1.0%	3, 0.7%
Previous treatment for MS		
Yes	114, 27.3%	105, 25.1%

*: for additional baseline MRI results see **Table 77**

Exposure

The duration of exposure to study treatment was comparable for the two treatment groups and close to the maximum of 96 weeks for the double-blind treatment period (**Table 52**). The duration of exposure for the individual infusions for the OCR 600 and OCR 600 placebo groups were also comparable at 3.3±0.7 hours for both groups. The duration of an individual infusion was essentially the same for those actually receiving OCR 600 (mean = 3.34 hours) compared to those receiving OCR 600 placebo (3.30 hours). The actual number of OCR 600 or OCR 600 placebo doses was close to the expected number of 5 (**Table 53**) and the average total dose was approximately 2300 mg compared to an expected 3000 mg if all patients received all 5 doses during the 96 week treatment period (**Table 54**). The actual number of Rebif/Rebif placebo

doses was close to the expected 288 doses if all patients had 3 doses per week for 96 weeks (Table 55).

Table 52: Duration of exposure to treatment during the double blind treatment period, WA21093, ITT

	96 Week Exposure Duration (weeks) (EXP96WKS)					
TRT01P	N OUSs	Mean	Std Dev	Median	Min	Max
Rebif	418	85.93	23.34	96.14	0.14	104.9
OCR 600	417	90.23	19.46	96.14	0.14	104

Source: WA 21093 rev ADSL By EXP96WKS (TRT01P).jmp

Table 53: Total number of doses of OCR or OCR placebo, WA21093, ITT

Treatment	Total doses (EXDOSNT)					
	N OUSs	Mean	Std Dev	Median	Min	Max
Rebif/OCR 600 placebo	416	4.52	1.07	5	1	8
OCR 600	417	4.76	0.96	5	1	8

Source: EXTCATT_OCRorOCRPBO Subset of EXTCAT_PERIOD Subset of APERIODC_TRT Subset of WA 21093 rev AEX EXDOSNT By (TRT01P).jmp

Table 54: Total dose of OCR 600 administered to those randomized to OCR 600, WA21093, ITT

Total	Total dose of OCR 600 administered (EXDOST)				
	Mean	Std Dev	Median	Min	Max
417	2262.80	547.75	2400	52.5	4200

Source: Summary of EXCATT_OCR Subset of EXTCATT_OCRorOCRPBO Subset of EXTCAT_PERIOD Subset of APERIODC_TRT Subset of WA 21093 rev AEX.jmp

The actual number of Rebif or Rebif placebo doses administered is close to the number expected for the 96 week trial, i.e. 288 doses

Table 55: Total number of Rebif/Rebif placebo doses administered during the double blind treatment period, WA21093, ITT

Treatment	Number of doses administered (EXATOTSU)					
	N OUSs	Mean	Std Dev	Median	Min	Max
Rebif	410	233.41	84.20	280	1	312
OCR 600/Rebif placebo	410	259.32	62.00	285	0	301

Source: EXTCATT_REBIForREBIFPBO Subset of EXTCAT_PERIOD Subset of APERIODC_TRT Subset of WA 21092 rev AEX EXATOTSU By (TRT01P).jmp

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance with Rebif/Rebif placebo was monitored by counting the number of vials used. The expected number of doses over 96 weeks was 288. The actual number of doses administered is shown in Table 56. Percent compliance is shown in Table 57. The total number of doses of OCR 600 or OCR 600 placebo was close to the expected number of 5 doses for the 96 week treatment period (Table 58). The total dose administered to those randomized to OCR 600 was close to the expected dose of 3000mg for the planned 5 cycles (Table 59).

Table 56: Actual number of doses of Rebif or Rebif placebo administered, WA21093, ITT

Treatment	Total number of Actual Syringe used (EXATOTSU)					
	Total	Mean	Std Dev	Median	Min	Max
Rebif	410	233.4	84.2	280	1	312
OCR 600/Rebif placebo	410	259.3	62.00	285	0	301

Source: EXTCATT_RebifORRebifPBO Subset of EXTCAT_PERIOD Subset of APERIODC_TRT Subset of WA 21093 rev AEX EXATOTSU By (TRT01P).jmp

Table 57: Percent compliance for Rebif or Rebif Placebo, WA21093, ITT

Treatment	Rebif compliance (EXATOTSU/EXPTOTSU)					
	Total	Mean	Std Dev	Median	Min	Max
Rebif	410	92.31	38.3	97.78	14.3	777.78
OCR 600/Rebif placebo	410	94.23	11.6	98.81	0	107.70

Source: EXTCATT_RebifORRebifPBO Subset of EXTCAT_PERIOD Subset of APERIODC_TRT Subset of WA 21093 rev AEX RebifCompliance By (TRT01P).jmp

Table 58: Total number of doses of OCR 600 or OCR placeb0, WA21093, ITT

Treatment	Total doses (EXDOSNT)					
	N Rows	Mean	Std Dev	Median	Min	Max
Rebif/OCR placebo	409	4.66	0.97	5	1	8
OCR 600	408	4.80	0.83	5	1	6

EXTCATT_OCRorOCRPBO Subset of EXTCAT_PERIOD Subset of APERIODC_TRT Subset of WA 21092 rev AEX EXDOSNT By (TRT01P).jmp

Table 59: Mean total dose of OCR 600 administered to the group randomized to OCR 600, WA21093, ITT

	Total dose of OCR 600 administered (EXDOST)				
N Rows	Mean	Std Dev	Median	Min	Max
408	2285.50	484.44	2400	9	3000

Summary of EXCATT_OCR Subset of EXTCATT_OCRorOCRPBO Subset of EXTCAT_PERIOD Subset of APERIODC_TRT Subset of WA 21092 rev AEX.jmp

Concomitant medications

The most common concomitant medications during the treatment phase were anti-inflammatory drugs and anti-histamines (Table 60). There were no differences between the treatment groups. Approximately 18% of patients reported previous use of an interferon and 10% reported previous use of glatiramer acetate.

Table 60: Most common concomitant medications during the treatment phase, WA21093, ITT

Standardized Medication Name	Rebif	OCR 600	All patients
METHYLPREDNISOLONE	417 (99.76%)	417 (100.00%)	834 (99.88%)
PARACETAMOL	363 (86.84%)	358 (85.85%)	721 (86.35%)
*ACRIVASTINE/*AMMONIUM CHLORIDE/ *CALAMINE/*CAMPHOR/*CODEINE PHOSPHATE/*DIPHENHYDRAMINE/*ME NTHOL/*SODIUM CITRATE/*ZINC...	128 (30.62%)	127 (30.46%)	255 (30.54%)
CETIRIZINE	100 (23.92%)	97 (23.26%)	197 (23.59%)
IBUPROFEN	105 (25.12%)	92 (22.06%)	197 (23.59%)
DIPHENHYDRAMINE	69 (16.51%)	61 (14.63%)	130 (15.57%)
AMOXICILLIN	34 (8.13%)	41 (9.83%)	75 (8.98%)
OMEPRAZOLE	48 (11.48%)	25 (6.00%)	73 (8.74%)
CHLOROPYRAMINE	31 (7.42%)	37 (8.87%)	68 (8.14%)
CIPROFLOXACIN	36 (8.61%)	26 (6.24%)	62 (7.43%)

Source: JRevCTab ACM STDNAMEbyTRT01PfilterPERIOD_TRT.xls

Rescue medication

During the treatment phase intravenous corticosteroids were given for an MS relapse 160 times for the Rebif group and 87 times for the OCR 600 group, indicating that IV corticosteroids were given for essentially all acute relapses. Intravenous corticosteroids were given 17 times to 15 patients for an infusion related reaction to OCR 600.

Efficacy Results - Primary Endpoint

Investigators reported 133 potential relapses in 94 patients treated with OCR 600 and 209 potential relapses in 143 patients treated with Rebif. A review of adverse events in the Nervous System disorders SOC revealed only one AE of optic neuritis in a Rebif patient and 2 AEs of transverse myelitis that could have represented a relapse rather than an adverse event. For the group treated with OCR 600, approximately 80% of relapses reported by the investigator (CLINRLP) were confirmed as protocol defined relapses (PDR). For the group treated with Rebif approximately 74% were confirmed (Table 61).

Table 61: Reviewer table: confirmation rate for reported clinical relapses and number of protocol-defined relapses, WA21093, ITT

AVALC*	Rebif			OCR 600		
	CLINRLP, N	PDR, N	PDR3, N	CLINRLP, N	PDR, N	PDR3, N
N	0	41	38	0	35	35
Y	209	168	171	133	98	98
% of CLINRLP		80.4 %	81.8 %	-	73.7 %	73.7 %

Source: APERIODC_TRT Subset of WA 21093 rev ARLP.jmp by PARAMCD and by AVALC
*: Clinical Relapse (CLINRLP) confirmed, Yes or No
CLINRLP = Investigator-reported relapse; PDR= Protocol-defined Relapse; PDR3 = PDR no criterion for 30 days after a relapse

During the 96 week double-blind treatment period, at least one relapse occurred in 74 patients treated with OCR 600 and in 119 patients treated with Rebif.

Table 62: Reviewer table: number of PDRs per subject, WA21093, ITT

Number of relapses	Treatment group	
	OCR 600, number of patients	Rebif number of patients
1	55	86
2	16	22
3	2	8
4	0	2
5	1	0
6	0	1

Source: OCR Subset of AVALC_Y Subset of PARAMCD_PDR Subset of APERIODC_TRT Subset of WA 21093 rev ARLP.jmp
Source: Rebif Subset of AVALC_Y Subset of PARAMCD_PDR Subset of APERIODC_TRT Subset of WA 21093 rev ARLP.jmp

Table 63: Reviewer table: Exposure time*, WA21093, ITT

Treatment	Exposure in years (EXP96YRS)						
	N OUSs	Mean	Std Dev	Median	Min	Max	Sum
Rebif	418	1.65	0.45	1.84	0.003	2.01	688.39
OCR 600	417	1.73	0.37	1.84	0.003	1.99	721.05

Source: WA 21093 rev ADSL EXP96YRS By (TRT01P).jmp
*: (Early treatment discontinuation date or date of week 96 visit for completers minus study day 1) +1

Based on the number of PDRs and exposure time during the blinded treatment phase (Table 63) the unadjusted ARR is seen in Table 64. The unadjusted rate is similar to the adjusted rate reported by the sponsor (Table 65).

Table 64: Reviewer table: Annualized Relapse Rate, WA21093, ITT

Treatment group	Number of relapses	Group exposure time (years)	Unadjusted ARR

OCR 600	98	721.05	0.136*
Rebif	168	688.39	0.244

*: Z=5.54, p<0.0001

Table 65: Sponsor table: Unadjusted and adjusted ARR, WA21093, ITT

Efficacy variable	OCR 600 N=417	Rebif N=418
Total relapses	98	168
Total patient-years followed	709.5	661.0
Unadjusted ARR*	0.138	0.254
Adjusted ARR**	0.155	0.290
95% CI of adjusted ARR	(0.121, 0.198)	(0.234, 0.361)
Adjusted ARR ratio**	0.532	
95% CI of adjusted ARR ratio	(0.397, 0.714)	
p-value	<0.0001	

* The total number of relapses for all patients in the treatment group divided by the total patient-years of exposure to that treatment.
** Adjusted by Baseline EDSS (<4.0 vs. >=4.0) and Geographical Region (US vs. OUS).
Log-transformed exposure time is included as an offset variable.
Source: CSR WA21093 Table 19, page 111/6798

Subgroups

The treatment effect attributable to OCR 600 was similar for most subgroups (Table 66). It was much smaller for the US compared to OUS sites but the smaller sample size for the US limits interpretation of the difference. The treatment effect was more prominent in those less than 40 years old, those not previously treated for MS and in those with gadolinium-enhancing lesions at baseline.

Table 66: Reviewer table: Unadjusted Annualized Relapse rate in subgroups, WA21093, ITT

	Rebif N=418		OCR 600 N=417		
	PDRs, n	Unadjusted ARR	PDRs, n	Unadjusted ARR	% reduction
ITT	168	0.244	98	0.136	44.3%
Subgroup					
Sex					
Female	116	0.253	67	0.145	42.7%
Male	52	0.225	31	0.119	47.1%
Region					
OUS	132	0.255	67	0.125	51.0%
US	36	0.211	31	0.170	19.4%
Age category					
<40	113	0.426	55	0.167	60.8%
≥40	55	0.195	43	0.136	30.3%

	Rebif N=418		OCR 600 N=417		
	PDRs, n	Unadjusted ARR	PDRs, n	Unadjusted ARR	% reduction
Baseline EDSS category					
<4	115	0.223	62	0.114	48.9%
≥4	53	0.307	35	0.201	34.5%
Number of relapses in the last 2 years category					
1	50	0.161	29	0.087	46.0%
2	78	0.286	36	0.140	51.1%
3	22	0.340	24	0.239	29.7%
≥4	18	0.463	9	0.300	35.2%
Previous treatment for MS					
Yes	51	0.303	22	0.110	63.7%
No	117	0.225	76	0.146	35.1%
Baseline presence of gadolinium-enhancing lesions					
Yes	86	0.305	38	0.137	55.1%
No	79	0.196	60	0.137	30.1%
Body Weight Category					
<75kg	92	0.249	46	0.098	60.7%
≥75kg	74	0.242	52	0.153	36.8%

Data Quality and Integrity - Reviewers' Assessment

Accurate identification and assessment of a relapse may depend on the interval between onset and clinical evaluation. A potential relapse (CLINRLP) was to be assessed whenever possible within 7 days of the onset of the event. The actual mean time is shown in Table 67 . The mean and the median times were slightly longer for the Rebif group. The EDSS assessment occurred within 7 days in 54.1% of the Rebif group and in 57.9% of the OCR 600 group. For this group the rate of confirmation (PDR) was 84.1% and 76.6% for the Rebif and OCR 600 groups respectively (Table 68).For those whose EDSS assessment was more than 7 days after the start of the potential relapse, the confirmation rates were just slightly lower at 76.0% and 69.6% for the Rebif and OCR 600 groups respectively (Table 69).

Table 67: Time from relapse onset to EDSS assessment of the relapse (days), Clinical Relapses, WA21093, ITT

Treatment	Time from RLP start to study day of post-RLP EDSS (POEDSS) (days)						
	Total	Mean	Std Dev	Median	Min	Max	N Missing
Rebif	209	13.15	16.45	7	0	88	0
OCR 600	133	11.57	15.27	6	0	83	0

Source: PARAMCD_CLINRLP Subset of APERIODC_TRT Subset of WA 21093 rev FDARLP RLPstart to EDSS By (TRT01P).jmp

Table 68: Rates of confirmation of a CLINRLP as a PDR for those with EDSS assessment 7 days or less after relapse onset, WA21093, ITT

Treatment	CLINRLP	PDR			
	n	No, n	% of CLINRLP	Yes, n	% of CLINRLP
Rebif	113	18	15.9%	95	84.1%
OCR 600	77	18	23.4%	59	76.6%

Source: RLPonset toEDSS 7orless Subset of APERIODC_TRT Subset of WA 21093 rev FDARLP TRT01P By PARAMCD by AVALC.xlsx

Table 69: Rates of confirmation of a CLINRLP as a PDR for those with EDSS assessment more than 7 days or less after relapse onset, WA31093, ITT

Treatment	CLINRLP	PDR			
	n	No, n	% of CLINRLP	Yes, n	% of CLINRLP
Rebif	96	23	24.0%	73	76.0%
OCR 600	56	17	30.4%	39	69.6%

Source: RLPonsettoEDSS more than 7 Subset of APERIODC_TRT Subset of WA 21093 rev FDARLP TRT01P by PARAMCD By AVALC.xlsx

Reviewer Comment: The time interval from the onset of the relapse to the clinical assessment is not ideal but this had not been unusual for this type of trial. The intervals are about 2 days later than those in WA21092. The confirmation rates are lower compared to those in WA21092. The times and rates of confirmation are similar for the two treatment groups. The unadjusted ARR for all clinical relapses (Table 70) also shows a statistically significant difference in favor of OCR 600 with a relative reduction of 39.2%. Therefore the confirmation process itself did not appear to alter the treatment effect of OCR 600. It is unclear however what effect, if any, the delay in assessment of many relapses may have had on the overall results of the trial.

Table 70: Unadjusted ARR for all clinical relapses, WA21093, ITT

Treatment group	Unadjusted ARR
OCR 600	0.185
Rebif	0.304*

*: p<0.0001

Efficacy Results - Secondary and other relevant endpoints

Confirmed Progression of Disability

Reviewer Comment: The pre-specified population for analysis of confirmed disability progression at 12 or 24 weeks is the pooled population from both RMS studies, WA21092 and WA21093 – see Figure 2 for the hierarchy of the closed sequential analysis of endpoints for both RMS studies. See Section 6.3.2 for the analysis of confirmed progression of disability (CDP12 and CDP24) for the primary analysis pooled population.

CDP12

During the 96 weeks of double-blinded treatment, an initial progression of disability occurred 156 times in 105 subjects in the OCR group and 192 times in 137 patients in the Rebif group. Approximately 35% of these events were confirmed as CDP12 events. A higher proportion of patients in the Rebif group had a CDP12 event compared to the OCR 600 group, 42% vs. 35%. Table 71 summarizes the outcome of the confirmation process for the IDPs for the two treatment groups.

Table 71: Disposition of IDP events to CDP12, CDPW12 or no CDP by treatment group, WA21093, ITT

Progression category	OCR		Rebif	
	Subjects	Events	Subjects	Events
IDPs	105	156	137	192
CDP12 (% of IDPs)	44 (42%)	53 (34%)	63 (46%)	67 (35%)
CDPW12	7	6	8	8
Total CDP12 (% of IDPs)	51 (49%)	59 (38%)	71 (52%)	75 (39%)
Unconfirmed IDPs	54 (51%)	97 (62%)	66(48%)	117(61%)

The simple proportion of patients in the ITT with a 12 week confirmed progression of disability is shown in Table 72. For the RMS studies progression was not imputed for those who discontinued treatment following an initial progression (CDPW12). Since CDPW12 was included in the calculation of this endpoint in the PPMS trial (WA25046) both methods are included in the table. The difference in proportions shows a reduction with OCR 600 treatment that is not quite statistically significant. The relative reduction is 27% without imputation for the CDPW12 patients and 29.4% when they are included.

Table 72: Reviewer table: Number and proportion of subjects with at least one IDP and CDP12 or CDPW12, WA21093, ITT

PARAMCD	OCR 600 ITT	Rebif ITT

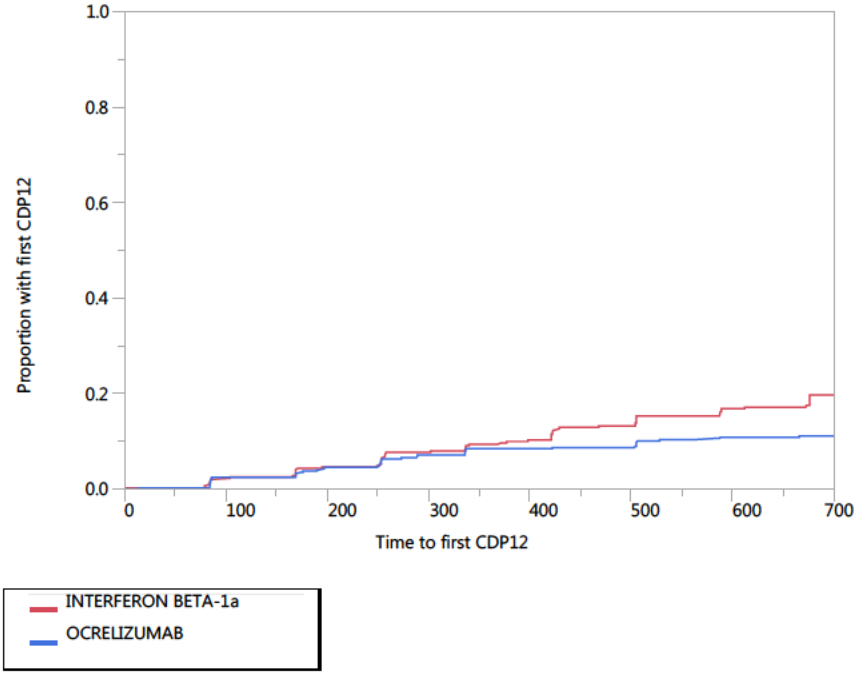
	N	%	N	%
No CDP12	373	90 %	355	85 %
No CDP12 or CDPW12	366	88 %	347	83 %
CDP12	**44**	**11%***	**63**	**15%**
CDPW12	7		8	
CDP12 or CDPW12	**51**	**12****	**71**	**17%**
Total	417	100.0%	418	100.0%

Source: ACDP dataset
CDP12: Confirmed Disability Progression 12 weeks; CDPW12: imputed CDP12 at withdrawal from treatment
*: p=0.0620 OCR vs Rebif, Fisher's exact test
**: p=0.0624 OCR vs Rebif, Fisher's exact test

The time to the first CDP12 alone, the pre-specified endpoint (Figure 10) or to the first CDP12 or CDPW12, comparable to the calculation in study WA25046 (Figure 11) both show a statistically significant benefit from treatment with OCR 600.

Figure 10: Time to first CDP12, WA21093, ITT

Product-Limit Survival Fit
Failure Plot



Summary

Group	CDP 12	No CDP 12
Rebif	63	355
OCR 600	44	373

Combined	107	728

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	5.7769	1	0.0162*
Wilcoxon	4.5560	1	0.0328*

Source: Join CDP12orCDPW12 with TRTorSCR EDSSatADYrevmax inclNM with ADSL.jmp

The influence of the stratification and other key baseline factors on the time to first CDP12 analysis is shown in **Table 73**.

Reviewer Comment: For most of the factors in the table the numbers of patients in any given category is too small to draw firm conclusions regarding the influence of these demographic and baseline disease characteristics. The analyses using the pooled population from both WA21092 and WA21093 provide more interpretable estimates.

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Table 73: Influence of stratification and key baseline factors on the analysis of time to first CDP12, WA21093, ITT

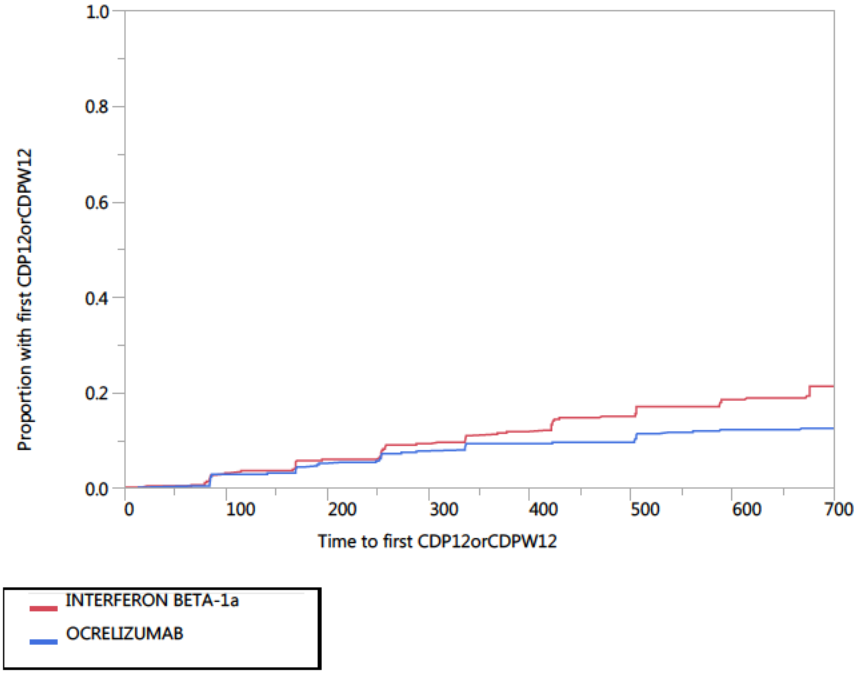
	OCR		Rebif		
	Failed	Censored	Failed	Censored	Log Rank
Sex					
M, N= 284	14	132	22	116	0.0628
F, N=551	30	241	41	239	0.1067
IXRS Age					
≤45, N= 657	31	293	45	288	0.0652
>45, N=178	13	80	18	67	0.0877
IXRS Region					
OUS, N= 609	28	277	44	260	0.0188
US, N=226	16	96	19	95	0.3875
Relapse free during treatment (NPDRCAT)					
Yes, N=642	26	317	30	269	0.1695
No, N=193	18	56	33	86	0.3211
Baseline EDSS category					
<4, N=624	37	278	47	262	0.1070
≥4, N=211	7	95	16	93	0.0346
Race					
White, N=750	39	329	54	328	0.0732
Ethnic group					
Hispanic or Latino, N=107	5	51	14	37	0.0079
Not Hispanic or Latino, N=673	36	299	46	292	0.1196
Not Reported, N=55	3	23	3	26	0.9945
Baseline T1 Gd Enhanced Lesions Category					
0, N=495	26	226	39	204	0.0245
1, N=120	8	50	12	50	0.3796
2, N=71	5	28	5	33	0.7513
3, n=29	2	13	1	13	0.6864
≥4, N=113	3	52	5	53	0.3917
Baseline Number of T2 Lesions category					
0-5, N=28	2	13	1	12	0.5452
6-9, N=42	0	20	1	21	0.2758
>9, N=760	42	337	61	320	0.0170
Baseline Weight category					
<75kg, N=440	17	200	35	188	0.0037
≥75kg, N=383	27	167	28	161	0.5391
Previous MS treatment					
Yes, N=219	12	102	17	88	0.1196
No, N=616	32	271	46	267	0.0588
Per Protocol Population Flag					
Yes, N=798	42	360	60	336	0.0192

	OCR		Rebif		
	Failed	Censored	Failed	Censored	Log Rank
No, N=37	2	13	3	19	0.5714

The analysis of time to first CDP12 when those who discontinued prematurely without a confirmatory visit (CDPW12) are included does not differ from the analysis of CDP12 alone (**Figure 11**).

Figure 11: Time to first CDP12 or CDPW12, WA21093, ITT

Product-Limit Survival Fit
Failure Plot



Summary

Group	CDP12/CDPW12	No CDP12/CDPW12
Rebif	71	347
OCR 600	50	367
Combined	121	714

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	6.1225	1	0.0133*
Wilcoxon	5.0228	1	0.0250*

Source: Join CDP12orCDPW12 with TRTorSCR EDSSatADYrevmax inclNM with ADSL.jmp

CDP24

During the 96 weeks of double-blinded treatment, an initial progression of disability occurred 156 times in 105 subjects in the OCR group and 192 times in 137 patients in the Rebif group. In the OCR 600 group 22% of these events were confirmed as CDP12 events compared to 26% in the Rebif group. A higher proportion of patients in the Rebif group had a CDP12 event compared to the OCR 600 group, 35% vs. 31%.

Table 74 summarizes the outcome of the IDPs for the two treatment groups.

Table 74: Disposition of IDP events to CDP24, CDPW24 or no CDP by treatment group, WA21093, ITT

Progression category	OCR		Rebif	
	Subjects	Events	Subjects	Events
IDPs	105	156	137	192
CDP24 (% of IDPs)	33 (31%)	35 (22%)	48 (35%)	49 (26%)
CDPW24	6	6	12	12
Total CDP24 (% of IDPs)	39 (37%)	41 (26%)	60 (44%)	61 (32%)
Unconfirmed IDPs	66 (63%)	115 (74%)	77 (56%)	131 (68%)

The simple proportion of patients in the ITT with a 24 week confirmed progression of disability is shown in Table 75. For the RMS studies progression was not imputed for those who discontinued treatment following an initial progression (CDPW24). Since CDPW24 was included in the calculation of this endpoint in the PPMS trial (WA25046) both methods are included in the table. The difference in proportions shows a reduction with OCR 600 treatment that is not quite statistically significant. The relative reduction is 33% without imputation for the CDPW24 patients and 36% when they are included.

Table 75: Reviewer table: Number and proportion of subjects with at least one IDP and CDP24 or CDPW24, WA21093, ITT

	OCR 600 ITT		Rebif ITT	
PARAMCD	N	%	N	%
No CDP24	384	92%	370	89%
No CDP24 or CDPW12	378	91%	358	86%
CDP24	**33**	**8%***	**48**	**12%**
CDPW24	6		12	
CDP24 or CDPW24	**39**	**9%****	**60**	**14%**
Total	417	100.0%	418	100.0%

Source: ACDP dataset
CDP12: Confirmed Disability Progression 12 weeks; CDPW12: imputed CDP12 at withdrawal from treatment
*: p=0.1012 OCR vs Rebif, Fisher's exact test
**: p=0.0319 OCR vs Rebif, Fisher's exact test

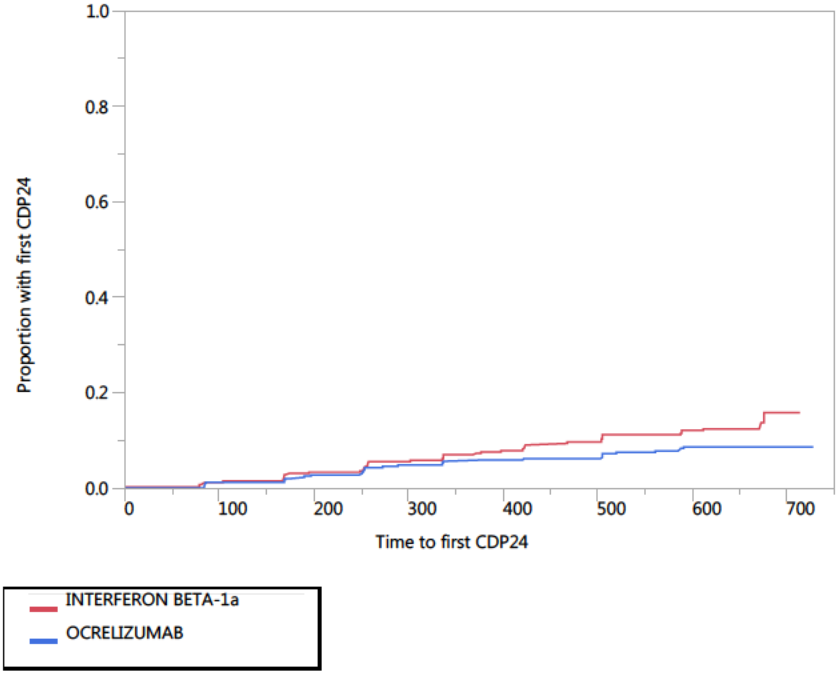
Time to event

An analysis of the time to the first CDP 24 showed a significant benefit from OCR 600 treatment without (Figure 12) or with (Figure 13) inclusion of the CDPW24 events.

CDP24 event only

Figure 12: Time to first CDP24, WA21093, ITT

Product-Limit Survival Fit
Failure Plot



Summary

Group	CDP24	No CDP24
Rebif	48	370
OCR 600	33	384
Combined	81	754

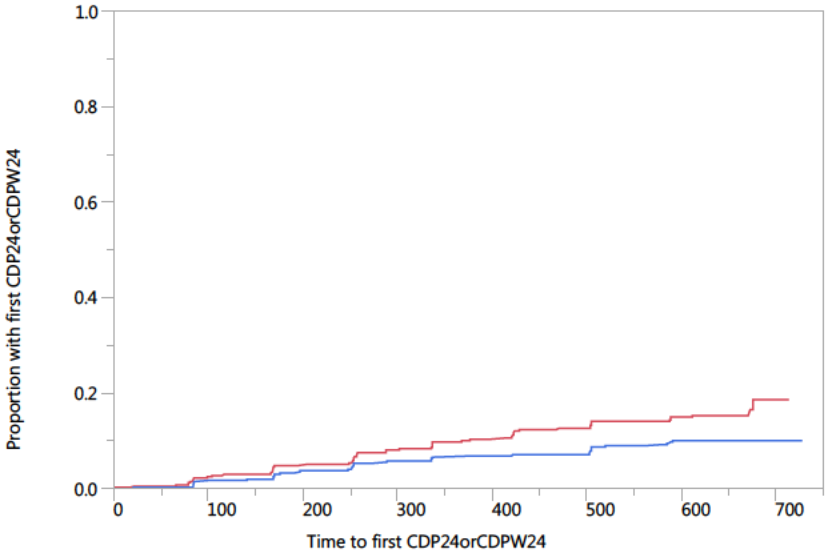
Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	4.3986	1	0.0360*
Wilcoxon	3.4202	1	0.0644

Source: Join CDP24orCDPW24 with TRTorSCR EDSSatADYrevmax inclNM with ADSL.jmp

Figure 13: Reviewer figure: Time to first CDP24 or CDPW24, WA21093, ITT

Product-Limit Survival Fit
Failure Plot



Summary

Treatment Group	CDP24/CDPW24	No CDP24/CDPW24
Rebif	60	358
OCR 600	39	378
Combined	99	736

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	6.5685	1	0.0104*
Wilcoxon	5.5817	1	0.0181*

Source: Join CDP24orCDPW24 with TRTorSCR EDSSatADYrevmax inclNM with ADSL.jmp

CDP duration

The duration of any period of disability was not different between the two treatment groups (Table 76).

Table 76 : Reviewer table: Duration from the time IDP criteria met to the time not met or last EDSS, WA21093, ITT

Treatment	Number of Days (AVAL)

	N	Mean	Std Dev	Median	Min	Max
INTERFERON BETA-1a	192	117.40	116.99	85	1	592
OCRELIZUMAB	156	118.87	107.98	85	1	589

Source: PARAMCD_CDPDUR Subset of WA21093 ACDP AVAL By (TRT01P).jmp

CDP last

For the group treated with Rebif, 11.5% had an initial progression of disability that lasted to the last EDSS score; for the OCR 600 group the comparable rate was 6.5%.

MRI Endpoints

At baseline the two treatment arms did not differ significantly in any of the assessments of disease activity (Table 77).

Table 77: Reviewer table: Baseline MRI results, WA21093

Treatment	Total	Mean	Std Dev	Median	Min	Max
Number gadolinium enhancing lesions (AVAL)						
Rebif	413	1.94	4.86	0	0	54
OCR 600	411	1.83	4.97	0	0	56
Normalized Brain Volume, cm^3						
Rebif	412	1500.9	91.12	1506.1	1245.9	1751.9
OCR 600	412	1504.5	92.85	1510.7	1202.7	1761.3
T1 hypointense lesions						
Rebif	413	32.89	33.12	21	0	184
OCR 600	410	31.66	35.18	20	0	200
Non-enhancing T1 lesion volume, cm^3						
Rebif	413	3.39	5.16	1.25	0	32.81
OCR 600	411	3.52	6.21	1.16	0	42.83
T2 Lesion Count						
Rebif	414	50.97	35.75	45	0	218
OCR 600	411	49.30	38.70	39	1	233
T2 Lesion Volume						
Rebif	414	10.63	12.32	6.15	0	76.06
OCR 600	412	10.72	14.31	5.25	0.03	96.00

Source: ZTESTCD_Subset of APERIODC_SCR Subset of ZDCAT_MRISCAN Subset of WA 21093 rev AMRI

Total Number of T1 Gadolinium–Enhanced Lesions as Detected by Brain Magnetic Resonance Imaging at Weeks 24, 48, and 96

Not all patients had an MRI assessment of new T1 gadolinium-enhancing lesions (CONSGD) at week 24 (N=757), week 48 (N=707) and week 96 (N=510). To assess this endpoint the reviewer analysis was limited to those patients who had all three assessments. Using this method, the sum of new T1 gadolinium-enhancing lesions for weeks 24, 48 and 96 was significantly lower in the group treated with OCR 600 compared to the group treated with Rebif (Table 78). The result is comparable to that of the sponsor in which all data was included in a negative binomial model with the log transform of the number of MRI scans done as the offset variable (Table 79).

Table 78: Reviewer table: Sum of T1 gadolinium-enhancing lesions at the 24, 48 and 96 week visits, population with all three assessments, WA21093

Treatment	Mean AVAL weeks 24 48 and 96					
	Total patients with all 3 assessments	Mean	Std Dev	Median	Min	Max
Rebif	228	0.4094	0.9800	0	0	6.67
OCR 600	272	0.0221*	0.1499	0	0	2

Source: Join AVISIT Weeks 24 48 96 Subset of ZDTEST_CONSGD Subset of APERIODC_TRT Subset of ZDCAT_MRISCAN Subset of WA 21093 rev AMRI Mean AVAL weeks 24 48 and 96 By (TRT01P).jmp
*: p<0.0001, unpaired t-test, 2-tailed

Table 79: Sponsor Table 28: Total Number of T1 Gadolinium–Enhancing Lesions as Detected by Brain MRI at Scheduled Visits during the Double-Blind Treatment Period (ITT Population)

MRI variable	Rebif	OCR 600
n	375	389
Total number T1 Gadolinium-Enhancing Lesions	465	21
Total number of Brain MRI Scans	1017	1117
Unadjusted rate *	0.457	0.019
Adjusted rate **	0.416	0.021
95% CI of adjusted rate	0.309, 0.561	0.012, 0.036
Adjusted rate ratio **		0.051
95% CI of Adjusted rate ratio		0.029, 0.089
p-value		<0.0001

* The total number of T1 gadolinium-enhancing lesions for all patients in the treatment group divided by the total number of brain MRI scans. The total number of lesions is calculated as the sum of the individual number of lesions at Weeks 24, 48, and 96.
** Adjusted by Baseline T1 Gd Lesion (present or not), Baseline EDSS (<4.0 vs. >=4.0) and Geographical Region (US vs. OUS). Log-transformed number of brain MRI scans is included as an offset variable.
Source: CSR WA21093 Table 28, page 135/6798

Total Number of New and/or Enlarging T2 Hyperintense Lesions as Detected by Brain Magnetic Resonance Imaging at Weeks 24, 48, and 96

As for the assessment of gadolinium-enhancing lesions, not all patients had an MRI assessment of new and/or enlarging T2 hyperintense lesions week 24 (N=761), week 48 (N=713) and week 96 (N=512). To assess this endpoint for those patients the reviewer analysis was limited to those patients who had all three assessments. Using this method, the sum of new and/or enlarging T2 hyperintense lesions for weeks 24, 48 and 96 was significantly lower in the group treated with OCR 600 compared to the group treated with Rebif (Table 80). The result is comparable to that of the sponsor which included all data using a negative binomial model with the log transform of the number of MRI scans done as the offset variable (Table 81).

Table 80: Reviewer table: Total New and/or Enlarging T2 hyperintense lesions for Weeks 24, 48 and 96, population with all 3 assessments, WA21093

Treatment	Mean of Weeks 24, 48 and 96					
	N	Mean	Std Dev	Median	Min	Max
Rebif	231	1.94	4.38	0.33	0	44
OCR 600	276	0.33	0.82	0	0	7.67

Source: Join AVISIT Weeks 24 48 96 Subset of ZDTEST_NEWT2 Subset of APERIODC_TRT Subset of ZDCAT_MRISCAN Subset of WA 21093 rev AMRI Mean of Weeks 24 48 96 By (TRT01P).jmp
*: p<0.0001, unpaired t-test, 2-tailed

Table 81: Sponsor Table 30: Total Number of New and/or Enlarging T2 Hyperintense Lesions as Detected by Brain MRI at Scheduled Visits (ITT Population)

MRI variable	Rebif	OCR 600
n	376	390
Total number of new and enlarging T2 hyperintense lesions	2103	380
Total number of Brain MRI Scans	1025	1123
Unadjusted rate *	2.052	0.338
Adjusted rate **	1.904	0.325
95% CI of adjusted rate	1.123, 1.777	0.256, 0.407
Adjusted rate ratio **		0.171
95% CI of Adjusted rate ratio		0.130, 0.225
p-value		<0.0001

* The total number of new and/or enlarging T2 lesions for all patients in the treatment group divided by the total number of brain MRI scans. The total number of lesions is calculated as the sum of the individual number of lesions at Weeks 24, 48, and 96.
** Adjusted by Baseline T2 Lesion Count, Baseline EDSS (<4.0 vs. >=4.0) and Geographical Region (US vs. OUS). Log-transformed number of brain MRI scans is included as an offset variable.
Source: CSR WA21093 Table 30, page 137/6798

Total Number of T1-Hypo-Intense Lesions (Chronic Black Holes) at Weeks 24, 48, and 96

Not all patients had an MRI assessment of T1-Hypo-Intense Lesions at week 24 (N=757), week 48 (N=707) and week 96 (N=507). To assess this endpoint the reviewer analysis was limited to those patients who had all three assessments. Using this method, the sum of T1-hypointense lesions for weeks 24, 48 and 96 was significantly lower in the group treated with OCR 600 compared to the group treated with Rebif (Table 82). The result is comparable to that of the sponsor using a negative binomial model with the log transform of the number of MRI scans done as the offset variable (Table 83).

Table 82: Reviewer table: Number of new T1-hypointense lesions at weeks 24, 48 and 96, population with an assessment at all three visits

Treatment	Mean of Weeks 24 48 and 96					
	N	Mean	Std Dev	Median	Min	Max
Rebif	228	1.30	2.98	0.33	0	32
OCR 600	271	0.458*	1.07	0	0	7

Source: Join AVISIT Weeks 24 48 96 Subset of ZDTEST_ NT1LESC Subset of APERIODC_TRT Subset of ZDCAT_MRISCAN Subset of WA 21093 rev AMRI Mean of Weeks 24 48 96 By (TRT01P).jmp

*: p<0.0001

Table 83: Sponsor Table 32 Total Number of New T1 Hypointense Lesions as Detected by Brain MRI at scheduled visits during the Double-Blind treatment Period: (ITT Population)

MRI variable	Rebif	OCR 600
n	375	389
Total number of T1 hypointense lesions	1484	567
Total number of Brain MRI Scans	1016	1115
Unadjusted rate *	1.461	0.509
Adjusted rate **	1.255	0.449
95% CI of adjusted rate	1.123, 1.777	0.256, 0.407
Adjusted rate ratio **		0.357
95% CI of Adjusted rate ratio		0.272, 0.470
p-value		<0.0001

* The total number of T1-Hypo-Intense Lesions (Chronic Black Holes) for all patients in the treatment group divided by the total number of brain MRI scans. The total number of lesions is calculated as the sum of the individual number of lesions at Weeks 24, 48, and 96.
** Adjusted by Baseline T1-Hypo-Intense Lesion Count, Baseline EDSS (<4.0 vs. >=4.0) and Geographical Region (US vs. OUS). Log-transformed number of brain MRI scans is included as an offset variable.
Source: CSR WA21093 Table 32, page 139/6798

Percentage Change in Brain Volume as Detected by Brain Magnetic Resonance Imaging Scan from Week 24 to Week 96

Both treatment groups had small decrease in brain volume as measured by the SIENA software (Structural Image Evaluation, using Normalization, of Atrophy). The decrease was smaller in the group treated with OCR 600 (Table 84).

Table 84: Percent change in brain volume at weeks 24, 48 and 96, population with an assessment at each time point, WA21093

	Percent change (AVAL)						
		Mean		Std Dev		Median	
AVISIT	Total	Rebif	OCR 600	Rebif	OCR 600	Rebif	OCR 600
WEEK 24	696	-0.55	-0.38	0.67	0.58	-0.47	-0.33
WEEK 48	646	-0.86	-0.63	0.80	0.72	-0.74	-0.55
WEEK 96	445	-1.25	-0.95*	1.03	1.03	-1.13	-0.78

Source: PARAMCD_PBVC Subset of ZTEST_PBVC Subset of APERIODC_TRT Subset of ZDCAT_MRISCAN Subset of WA 21093 rev AMRI AVAL By (AVISIT).xlsx
*:p=0.0023, unpaired t-test, 2-tailed

Dose/Dose Response

Only one dose was studied in this trial

Durability of Response

The durability of the response reported in the double blind treatment phase was not assessed.

Persistence of Effect

The persistence of the treatment effect was not assessed.

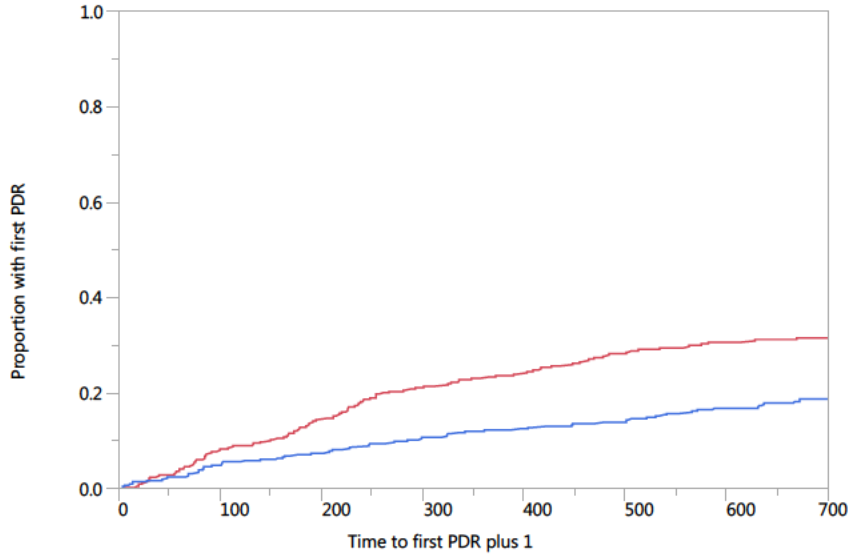
Additional Analyses Conducted on the Individual Trial

Time to first protocol-defined relapse

For those treated with OCR 600, 74 patients (17.8%) had a least one relapse and 119 patients treated with Rebif (28.5%) had a least one relapse. The time to the first relapse using the Kaplan-Meier model is shown in **Figure 14**.

Figure 14: Time to first protocol-defined relapse, WA21093, ITT

Product-Limit Survival Fit
Failure Plot



Summary

Group	PDR	No PDR
Rebif	119	299
OCR 600	74	343
Combined	193	642

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	17.0631	1	<.0001*
Wilcoxon	17.9519	1	<.0001*

Source: Join revADSL with AVALC_Y PDR by ASTDYmin incl NM.jmp

Additional MRI endpoints

Percentage Change in Total T2 Lesion Volume as Detected by Brain Magnetic Resonance Imaging from baseline to Week 96

Table 85: Reviewer table: T2 lesion volume, percent change from baseline to week 96, WA21093, population with both assessments

Treatment	Percent change from SCRBL to Week 96

	N OUSs	Mean	Std Dev	Median	Min	Max
Rebif	314	-2.15	27.02	-3.71	-72.22	307.72
OCR 600	359	-7.63	17.06	-5.53	-89.76	110.40

Source: PARAMCD_T2LESV Subset of AVISIT_SCRBL and Week 96 Subset of ZDCAT_MRISCAN Subset of WA 21093 rev AMRI Percent Change from baseline to Week 96 By (TRT01P).jmp

Reviewer Comment: The sponsor's result for the above endpoint is essentially identical to the reviewer result (CSR WA21093 page 1034/6798).

Karnofsky Performance Score (see Appendix 13.6)

The Karnofsky Performance Score (KPS) is an alternate assessment of function. It was measured periodically throughout the trial. The change from baseline to week 96 was not statistically significant.

Table 86: Baseline Karnofsky Performance Score, WA21093, ITT

Treatment	Karnofsky Performance Score (ZASTRESN)						
	Total	Mean	Std Dev	Median	Min	Max	N Missing
Rebif	390	84.13	11.5	90	30	100	0
OCR 600	407	84.5	11.6	90	20	100	0

Source: AVISIT_BL Subset of WA 21093 rev AKPS ZASTRESN By (TRT01P).jmp

Table 87: Karnofsky Score change from baseline to Week 96, WA21093, population with both assessments, ITT

	Change from Baseline to Week 96, Karnofsky score					
N Rows	Mean	Std Dev	Median	Min	Max	N Missing
276	-0.4	10.2	0	-40	50	76
314	1.07*	10.1	0	-30	70	72

Source: APBLFL_Y Subset of AVISIT_WEEK 96 Subset of WA 21093 rev AKPS CHG By (TRT01P).jmp
*: p=0.0796, unpaired t-test, two tailed.

Table 88: Distribution of the Absolute Change in Karnofsky Performance Score from Baseline to Week 96, WA21093 population with both assessments

Absolute Change from Baseline	Rebif	OCR 600	Patients
-40	1 (0.12%)	0 (0.00%)	1 (0.12%)
-30	3 (0.36%)	3 (0.36%)	6 (0.72%)
-20	5 (0.60%)	6 (0.72%)	11 (1.32%)
-10	48 (5.75%)	40 (4.79%)	88 (10.54%)
Missing	78 (9.34%)	74 (8.86%)	152 (18.20%)
0	90 (10.78%)	128 (15.33%)	218 (26.11%)
10	47 (5.63%)	54 (6.47%)	101 (12.10%)
20	6 (0.72%)	11 (1.32%)	17 (2.04%)
30	0 (0.00%)	1 (0.12%)	1 (0.12%)
50	1 (0.12%)	0 (0.00%)	1 (0.12%)
70	0 (0.00%)	1 (0.12%)	1 (0.12%)
Subjects	414 (49.58%)	417 (49.94%)	835 (100.00%)
Denominator			(All patients)

Source: JRevCTab WA21093 AKPS CHGbyTRT01PfilterAVISIT_WEEK 96.xls

6.3. WA 21092 and WA21093 Pooled

6.3.1. Study Design

For selected secondary endpoints the analysis population was the combined ITT population pooled from studies WA21092 and WA21093 – see **Figure 2**. The key pooled analyses of efficacy were of the CDP 12 week and CDP 24 week endpoints.

6.3.2. Results of Pooled Analyses of Efficacy

Disposition

For the pooled population of studies WA21092 and WA21093, a total of 1656 patients were randomized 1:1 to Rebif (N = 829) or OCR (N = 827). Three patients from the Rebif treatment group and two from the OCR treatment group withdrew from the study before receiving any treatment; these patients remained in the ITT population as randomized. The overall disposition of patients for this pooled population is shown in **Figure 15**.

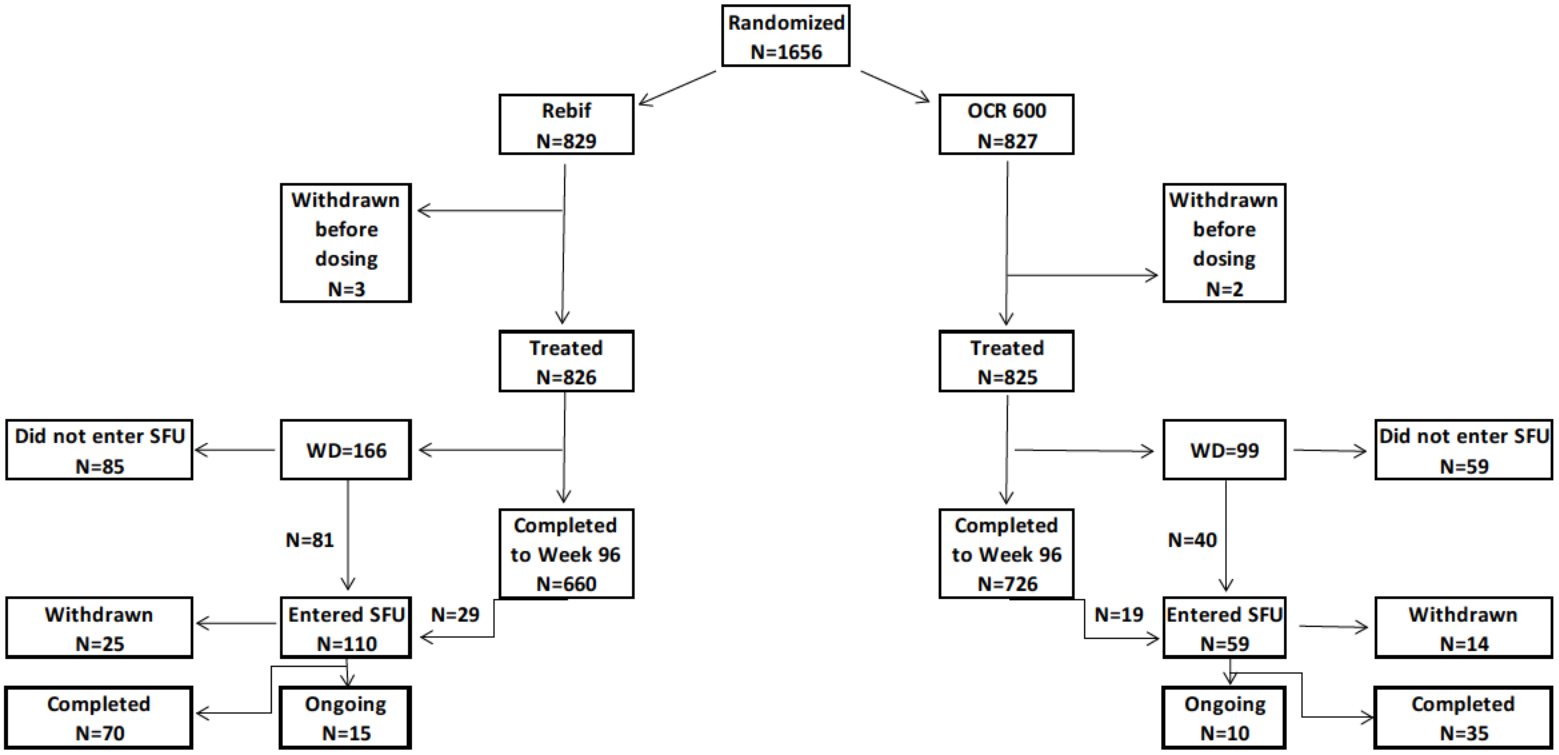
Demographics and Baseline disease characteristics

The demographics and baseline disease characteristics of the pooled population did not differ significantly from the individual RMS studies (**Table 89**).

Table 89: Reviewer Table: Demographics and Baseline disease characteristics of RMS pooled population compared to WA21092 and WA21093

	Pooled		WA21092		WA21093	
	OCR N=827	Rebif N=829	OCR	Rebif	OCR	Rebif
Age						
Mean	37.5 (0.2)	37.5 (9.2)	38.0 (9.3)	37.7 (9.4)	37.1 (9.1)	37.74(9.0)
Median	38	38	38	38	37	37
Sex						
M	552 (66.8%)	541 (65.3%)	270, 65.9%	272, 66.2%	271, 65.0%	280, 67.0%
F	277 (33.5%)	286 (34.5%)	140, 34.1%	139, 33.8%	146, 35.0%	138, 33.0%
Race						
White	743 (89.9%)	757 (91.3%)	375, 91.5%	375, 91.2%	368, 88.2%	382, 91.4%
All others	84 (10.2%)	72 (8.7%)	35, 8.5%	36, 8.8%	49, 11.8%	36, 8.6%
Region						
OUS	610 (73.8%)	610 (73.6%)	305, 74.4%	306, 74.5%	305, 73.1%	304, 72.7%
USA	217 (26.2%)	219 (26.4%)	105, 25.6%	105, 25.5%	112, 26.9%	114, 27.3%
Duration since onset (yrs)						
Mean	6.47±6.2	6.47±6.1	6.74 (6.37)	6.25 (5.98)	6.72, (6.10)	6.68 (6.13)
Median	5.1	4.8	4.88	4.62	5.16	5.07
Baseline EDSS						
Mean	2.77±1.26	2.75±1.33	2.82 (1.24)	2.71 (1.29)	2.73 (1.29)	2.79 (1.38)
Median	2.5	2.5	2.5	2.5	2.5	2.5
Baseline Gadolinium enhancing lesions						
Mean	1.76±4.6	1.91±5.0	1.69 (4.16)	1.88 (5.18)	1.81 (4.96)	1.95 (4.86)
Median	0	0	0	0	0	0
Number of relapses in the past year						
Mean	1.32±0.67	1.34±0.69	1.31 (0.65)	1.33 (0.64)	1.33 (0.69)	1.34 (0.73)
Median	1	1	1	1	1	1
Previous Treatment for MS						
No	604, 73.0%	605, 73.0%	301, 73.4%	292, 71.1%	303, 72.7%	313, 74.9%
Yes	223, 27.0%	224, 27.0%	109, 26.6%	119, 29.0%	114, 27.3%	105, 25.1%

Figure 15: Reviewer Figure: Disposition of patients for the pooled population for studies WA21092 and WA21093



CCOD = Clinical Cut-off Date
*: Figure 2 CSR page 82

Confirmed Progression of Disability – 12 Weeks

During the 96 weeks of double-blinded treatment an initial progression of disability (IDP) occurred 367 times (0.44 per patient) in 264 (31.9% of 829) patients being treated with Rebif and 266 times (0.32 per patient) in 194 patients (23.5% of 827) being treated with OCR 600. Progression of disability was confirmed at 12 weeks in 113 patients in the Rebif group and in 75 patients in the OCR group. In addition there were 11 IDPs in the Rebif group and 7 in the OCR group that were imputed as confirmed because a confirmatory assessment was not available due to patient withdrawal from the study (CDPW12). The total number of patients with a CDP12 or CDPW12 was 123 in the Rebif group (14.8% of the ITT) and 82 in the OCR group (9.9% of the ITT). Table 90 summarizes the outcome of the IDPs for the two treatment groups.

Table 90: Reviewer table: Summary of progressions at subject and event level

	OCR 600		Rebif	
	Patients	Events	Patients	Events
IDPs	194	266	264	367
CDP12 (% of IDPs)	75 (38.7%)	84 (31.6%)	113 (42.8%)	123 (33.5%)
CDPW12	7	7	11	11
Total CDP12 (% of IDPs)	82 (42.3%)	91 (34.2%)	124 (47%)	133 (36.2%)
Unconfirmed IDPs	112 (57.7%)	175 (65.8%)	140 (53%)	234 (68.8%)

Source: Pooled ACDP

The simple proportion of patients in the ITT with a 12 week confirmed progression of disability is shown in Table 91. For the individual and pooled RMS studies progression was not imputed for those who discontinued treatment following an initial progression (CDPW12). Since CDPW12 was included in the calculation of this endpoint in the PPMS trial (WA25046) both methods are included in the table. The difference in proportions shows a reduction with OCR 600 treatment that is statistically significant not including or including CDPW12 events. The relative reduction is 36% without imputation for the CDPW12 patients and 33% when they are included.

Table 91: Reviewer table: Number and proportion of subjects with at least one IDP and CDP12 or CDPW12, RMS pooled, ITT

	OCR 600 ITT		Rebif ITT	
PARAMCD	N	%	N	%
No CDP12	752	91%	716	86%
No CDP12 or CDPW12	745	90%	705	85%

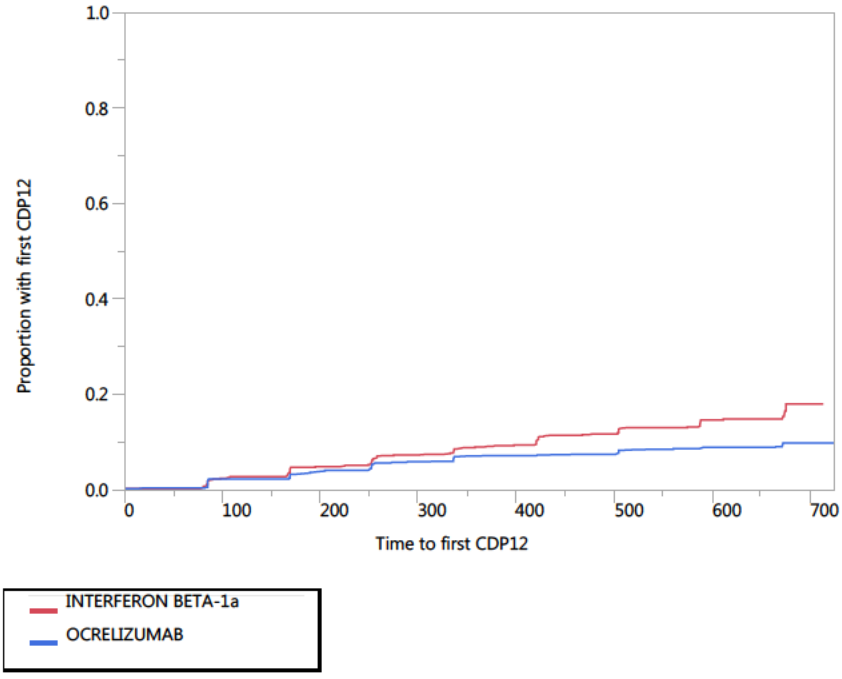
PARAMCD	OCR 600 ITT		Rebif ITT	
	N	%	N	%
CDP12	75	**9%***	113	**14%**
CDPW12	7		11	
CDP12 or CDPW12	**82**	**10%****	**124**	**15%**
Total	827	100.0%	829	100.0%

Source: ACDP dataset
CDP12: Confirmed Disability Progression 12 weeks; CDPW12: imputed CDP12 at withdrawal from treatment
*: p=0.0041 OCR vs Rebif, Fisher's exact test
**: p=0.0022 OCR vs Rebif, Fisher's exact test

The time to the first CDP12 alone, the pre-specified endpoint (Figure 16) or to the first CDP12 or CDPW12, comparable to the calculation in study WA25046 (Figure 17) both show a statistically significant benefit from treatment with OCR 600.

Figure 16: Time to first CDP12, pooled WA21092 and WA21093, ITT

Failure Plot



Summary

Group	CDP12	No CDP12
Rebif	113	715
OCR 600	75	752
Combined	188	1467

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	11.2519	1	0.0008*
Wilcoxon	9.5844	1	0.0020*

Source: Join CDP12orCDPW12 with TRTorSCR EDSSatADYrevmax inclNM with ADSL.jmp

The influence of the stratification and other baseline demographic or disease characteristics is shown in **Table 92.** In general, when there is an adequate sample size there is a statistically significant benefit with OCR 600 treatment for most subgroups.

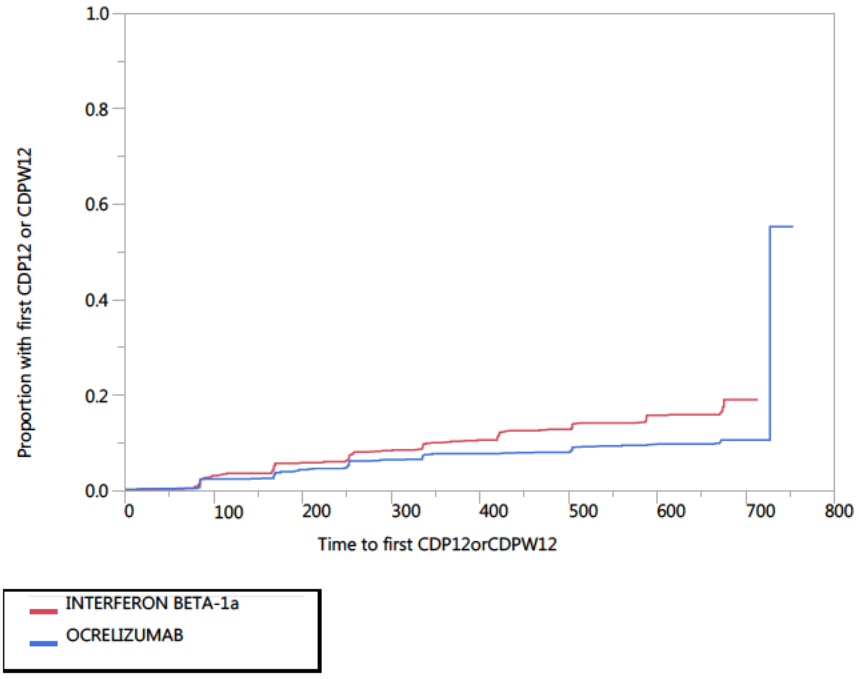
Table 92: Influence of stratification and other key baseline factors – CDP12 – pooled WA21092 and 21093, ITT

	OCR		Rebif		
	Failed	Censored	Failed	Censored	Log Rank
Sex					
M, N=563	27	259	43	234	0.0144
F, N=1092	48	493	70	481	0.0176
IXRS Age					
≤45, N=1304	52	598	82	572	0.0031
>45, N=351	23	154	31	143	0.1087
IXRS Region					
OUS, N=1220	45	565	79	531	0.0004
US, N=435	30	187	34	184	0.3784
Relapse free during treatment (NPDRCAT)					
Yes, N=1271	47	635	50	539	0.1768
No, N=384	28	117	63	176	0.0561
Baseline EDSS category					
<4, N=	64	565	87	540	0.0178
≥4, N=	11	187	26	175	0.0067
Race					
White, N=1370	68	675	100	565	0.0045
Black or African American, N=72	6	34	5	27	0.6833
Ethnic group					
Hispanic or Latino, N=213	9	92	24	88	0.0088
Not Hispanic or Latino, N=1315	59	604	81	571	0.0130
Not Reported, N=127	7	56	8	56	0.7899
Baseline T1 Gd Enhanced Lesions Category					
0, N=979	43	442	65	429	0.0164
1, N=236	9	113	18	96	0.0308
2, N=131	5	58	9	59	0.3190
3, n=65	7	28	5	25	0.8807
≥4, N=228	11	102	15	100	0.2832
Baseline gadolinium-enhancing lesions (yes/no) (BGDLESFL)					
Yes, N=660	32	301	47	280	0.0288
No, N=979	43	442	65	429	0.0162
Baseline Number of T2 Lesions category					
0-5, N=57	2	25	4	26	0.6044
6-9, N=70	2	34	2	32	0.7596
>9, N=1518	71	688	107	652	0.0011
Baseline Weight category					
<75kg, N=885	28	422	61	374	<0.0001
≥75kg, N=756	46	324	52	334	0.4860
Previous MS treatment					

	OCR		Rebif		
	Failed	Censored	Failed	Censored	Log Rank
Yes, N=446	22	201	31	192	0.1117
No, N=1209	53	551	82	523	0.0030
Per Protocol Population Flag					
Yes, N=1578	72	724	109	673	0.0007
No, N=77	3	28	4	42	0.8654

Figure 17: Time to first CDP12 or CDPW12, pooled WA21092 and WA21093, ITT

Product-Limit Survival Fit
Failure Plot



Summary

Group	CDP12/CDPW12	N0 CDP12/CDPW12
Rebif	123	705
OCR 600	82	745
Combined	205	1450

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	11.8652	1	0.0006*
Wilcoxon	10.3409	1	0.0013*

Source: Join CDP12orCDPW12 with TRTorSCR EDSSatADYrevmax inclNM with ADSL.jmp

Confirmed Disability Progression – 24 Weeks (CDP24)

During the 96 weeks of double blind treatment an initial progression of disability (IDP) event occurred 367 times (0.44 per patient) in 264 (31.9% of 829) patients being treated with Rebif and 266 times (0.32 per patient) in 194 patients (23.5% of 827) being treated with OCR 600. An IDP event was confirmed as a CDP24 event for 22% of IDPs in the OCR group and for 24% of IDPs in the Rebif group (Table 93).

Table 93: Reviewer table: Summary of progression to CDP24 or CDPW24 at subject and event level, pooled RMS, ITT

	OCR		Rebif	
	Subjects	Events	Subjects	Events
IDPs	194	266	264	367
CDP24	57 (29%)	59 (22%)	87 (33%)	89 (24%)
CDPW24	7	7	15	15
Total CDP24	64 (33%)	66(25%)	102 (39%)	104 (28%)
Unconfirmed IDPs	130 (67%)	200 (75%)	162 (61%)	263 (72%)

The simple proportion of patients in the ITT with a 24 week confirmed progression of disability is shown in Table 94. For the RMS studies progression was not imputed for those who discontinued treatment following an initial progression (CDPW24). Since CDPW24 was included in the calculation of this endpoint in the PPMS trial (WA25046) both methods are included in the table. The difference in proportions shows a reduction with OCR 600 treatment that is statistically significant without including the CDPW24 events (the pre-specified method for the pooled analysis). It is also significant if these events are included. The relative reduction is 36% without imputation for the CDPW24 patients and 33% when they are included.

Table 94: Number and proportion of subjects with at least one IDP and CDP24 or CDPW24, RMS pooled, ITT

	OCR 600 ITT		Rebif ITT	
PARAMCD	N	%	N	%
No CDP24	770	93%	742	90%
No CDP24 or CDPW24	763	92%	727	88%
CDP24	**57**	**7%***	**87**	**11%**
CDPW24	7		15	
CDP24 or CDPW24	**64**	**8****	**102**	**12%**
Total	827	100.0%	829	100.0%

Source: ACDP dataset
CDP24: Confirmed Disability Progression 24 weeks; CDPW24: imputed CDP24 at withdrawal from treatment
*: p=0.0112 OCR vs Rebif, Fisher's exact test

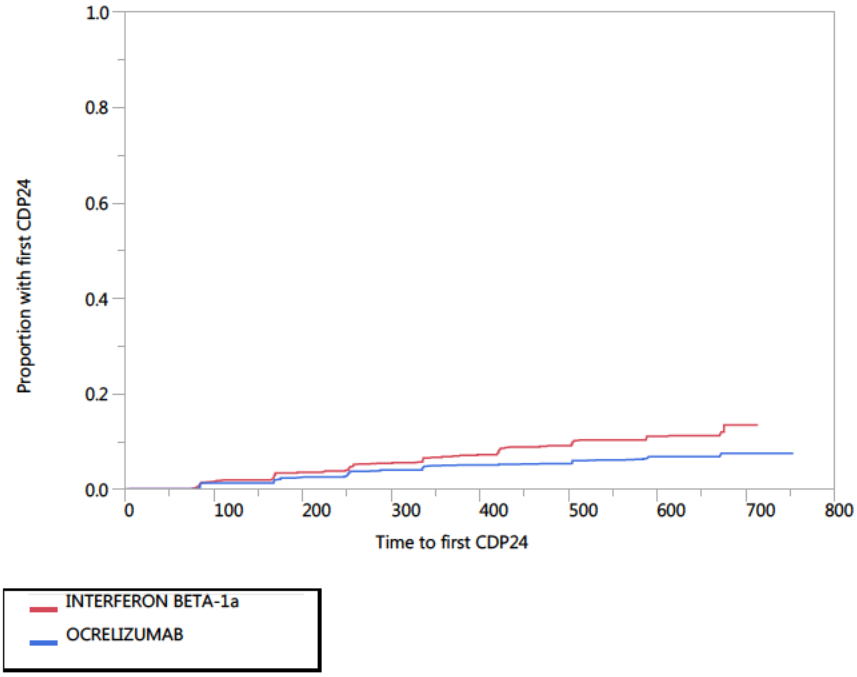
**: p=0.0024 OCR vs Rebif, Fisher's exact test

Time to first CDP24

The proportion of patients with progression of disability confirmed at 24 weeks is low but the time to first CDP24 event remains significantly lower in the pooled studies of RMS without (Figure 18) or with (Figure 19) inclusion of those initial progression that lack a confirmatory assessment because of discontinuation.

Figure 18: Reviewer figure: Time to first CDP 24, Pooled WA21092 and 21093, ITT

Product-Limit Survival Fit
Failure Plot



Summary

Group	CDP24	No CDP24
Rebif	87	741
OCR 600	57	770
Combined	144	1511

Tests Between Groups

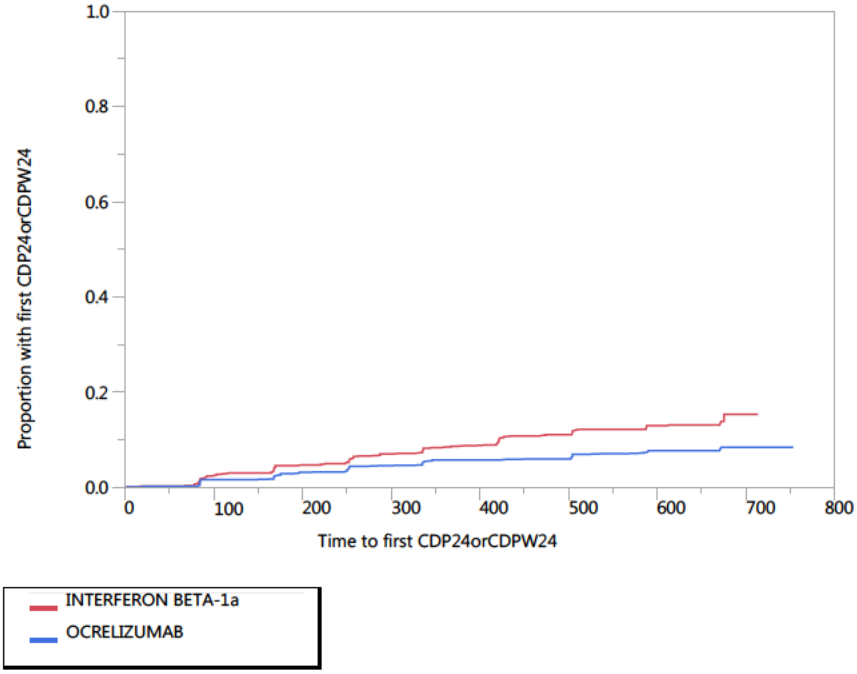
Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	8.7597	1	0.0031*
Wilcoxon	8.0148	1	0.0046*

Source: Join CDP24orCDPW24 with TRTorSCR EDSSatADYrevmax inclNM with ADSL.jmp

Time to first CDP24 or CDPW24

Figure 19: Reviewer figure: Time to first CDP24 or CDPW24, pooled WA21092 and WA21093, ITT

Product-Limit Survival Fit
Failure Plot



Summary

Group	CDP24/CDPW24	No CDP24/CDPW24
Rebif	102	726
OCR 600	64	763
Combined	166	1489

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	11.7208	1	0.0006*
Wilcoxon	11.0387	1	0.0009

Source: Join CDP24orCDPW24 with TRTorSCR EDSSatADYrevmax inclNM with ADSL.jmp

CDP Duration

The duration of the periods during which the patients met the criteria for disability progression were essentially the same for the two treatment groups (Table 95). The difference between the two treatment groups was the number of such periods.

Table 95: Reviewer table: Duration of periods of disability following an IDP, WA21092 and WA21093 pooled, ITT

Treatment	CDP Duration (Days) (AVAL)						
	N	Mean	Std Dev	Median	Min	Max	N Missing
Rebif	367	119.65	125.99	85	1	597	0
OCR 600	266	119.77	119.22	85	1	671	0

Source: PARAMCD_CDPDUR Subset of Pooled RMS ACDP CDPDUR By (TRT01P).jmp

The proportion of confirmed disability progression that continued to meet the criteria for disability progression to the last EDSS assessment in the blinded treatment period was 9.34% for the OCR 600 group and 13.2% for the Rebif group.

CDP last

For those treated with Rebif there were 77 patients who met the criteria for progression of disability for every EDSS from the IDP to the last EDSS score at the end of the double blind treatment period (26.5% of the patients with an IDP and 9.3% of the treatment group) and for those treated with OCR 600 there were 41 such patients (19.7% of the patients with an IDP and 5.0% of the treatment group).

Table 96: Proportion of patients with an IDP who continued to meet the criteria for confirmed progression to the last EDSS assessment, WA21092 and WA21093 pooled, ITT

Analysis Value C	Rebif		OCR 600	
Y, n	77		41	
	% of CDLAST	% of TRT grp	% of CDLAST	% of TRT grp
Total	26.5%	9.3%	19.7%	5.0%

Source: JRevCtab PooledACDP AVALCbyTRT01PfilterPARAMCD_CDLAST.xls

Reviewer Comment: In the RMS population about 75% to 80% periods of "confirmed disability progression" no longer meet the criteria over the course of a two year trial, regardless of treatment. For the pooled dataset for the two RMS trials, the proportion of patients who met this criterion was about 9% in the Rebif group and 5% in the OCR 600 group suggesting a reduction in those with longer term disability progression with OCR 600 treatment.

Confirmed Disability Improvement

Disability improvement was defined as a reduction in EDSS score of 1 or more for those with a baseline EDSS of 2 to ≤5.5 and as a reduction of 0.5 for those with a baseline EDSS of more than 5.4. This analysis was limited to those with a baseline EDSS of 2 or more. A greater proportion of patients treated with OCR 600 met the criteria for an initial disability improvement (IDI) (35.8%) compared to those treated with Rebif (28.9%). The improvement was confirmed 12 weeks later (CDI12) for 58.6% of subjects treated with OCR 600 with an IDI and for 40.1% of those treated with Rebif. The overall proportion of patients treated with OCR 600 and who met the CDI12 criteria was 20.7% compared to 15.4% for those treated with Rebif. The comparable rates for CDI24 were 15.6% and 11.4% for the OCR 600 and Rebif groups respectively. The mean and median duration of the period during which a patient continued to meet the criteria for CDI was essentially the same for the two treatment groups. The proportion of patients who continued to meet the criteria from the time of the IDI to the end of the double-blind treatment period was also the same for the two groups at about 35% (Table 97).

Table 97: Reviewer table: Occurrence of CDI12 and CDI24 following period of initial disability improvement, pooled WA21092 and WA21093, population with baseline EDSS≥2

Population Baseline EDSS ≥2, N	Rebif 624		OCR 628	
	Events	Subjects	Events	Subjects
IDI (% of pop)	246	180 (28.9%)	325	225 (35.8%)
CDI12 (% of IDIs) % of population	105/236 (44.5%)	96/172 (40.1%) 15.4%*	155/321 (48.3%)	130/222 (58.6%) 20.7%
CDI24 (% of IDIs) % of population	76/228 (33.3%)	71/169 (42.0%) 11.4%**	108/309 (35.0%)	98/219 (44.8%) 15.6%
CDIDUR, Mean (SD), days Median, days	246	166.27 (159.9) 86	325	166.89 (159.4) 87
CDILAST	87/246 (35.4%)		112/325 (34.5%)	

Source: Pooled WA21092and3 revACDI.jmp
*: p=0.0153
**: p=0.0315

6.4. WA25046: 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.

6.4.1. Study Design

Overview and Objective

The primary objective of Study WA25046 was to assess the efficacy of ocrelizumab compared to placebo for the treatment of primary progressive multiple sclerosis.

Trial Design

WA25046 was a randomized placebo-controlled trial. The study planned to enroll 630 patients randomized 2:1 to ocrelizumab 600mg (OCR 600) or placebo. Randomization was stratified by region (US vs OUS) and age group (≤45 vs. >45 years old).

The study consisted of a screening period, a blinded treatment period, an open label treatment period and a safety follow-up period. Following informed consent subjects entered a screening period of up to 8 weeks to determine eligibility.

Key eligibility criteria

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 either less than 15 years in patients with an EDSS at screening > 5.0 or 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:

- elevated IgG index
- one or more IgG oligoclonal bands detected by isoelectric focusing

Specific exclusions for those treated with drugs targeting the immune system
Treatment with β-interferons, glatiramer acetate, IV immunoglobulin, plasmapheresis, or other immunomodulatory therapies within 12 weeks prior to randomization
Systemic corticosteroid therapy within 4 weeks prior to screening

Treatment

The first IV infusion of ocrelizumab or placebo was administered on study Day 1. To reduce potential infusion reactions, patients received prophylactic treatment with 100 mg of methylprednisolone, administered by slow IV infusion, to be completed approximately 30 minutes before the start of each ocrelizumab or placebo infusion. Prophylactic treatment with an analgesic/antipyretic such as acetaminophen/paracetamol (1 g) and an IV or oral antihistamine (such as IV diphenhydramine 50 mg; or equivalent dose of alternative) was recommended 30 to 60 minutes prior to the start of the infusion to reduce potential infusion reactions (protocol Section 6.4.)

During the blinded treatment period patients were to receive at least 5 treatment cycles given every 24 weeks for a total of at least 120 weeks of treatment. The schedule for drug administration is shown in **Table 98**. The initial protocol called for OCR 600 to be administered as two IV infusions of 300 mg on Days 1 and 15 for the first treatment cycle followed by single IV infusions of 600 mg every 24 weeks. In an amendment submitted in sequence 0325 (SDN 332) – 3/14/2011 - WA25046B – 03Mar2011) ocrelizumab was to be administered every 24 weeks as dual IV infusions of 300 mg x2 separated by 14 days for all treatment cycles. The rationale for this change was:

"Primary efficacy results from a recent Phase III trial in patients with RA (Study WA20496/ACT4394g, FEATURE) indicate that a single infusion of 400mg did not significantly reduce the signs and symptoms of RA, while a dual infusion of 200 mg of ocrelizumab administered 14 days apart did show significant efficacy compared to placebo on the primary efficacy endpoint. Previous successful double-blinded efficacy trials with ocrelizumab (and rituximab) in RA and MS have employed a dual infusion approach in demonstrating efficacy. Therefore, to maintain the potential for efficacy with ocrelizumab in PPMS, a dual infusion treatment paradigm will be instituted for all treatment cycles of Study WA25046."

An additional rationale for the divided doses also stated in the same amendment was:

"In order to assure adequate initial and sustained B-cell depletion, minimize potentially dose-dependent infusion associated events particularly upon the first infusion, avoid early production of HAHA, and maintain potential for efficacy, a dual infusion of ocrelizumab is administered for all treatment cycles."

Prior to the first dose of each cycle, if any of the following criteria were not met further administration of ocrelizumab should have been suspended until the criteria were met or held indefinitely:

- Severe allergic or anaphylactic reaction to a previous ocrelizumab infusion
- Any significant or uncontrolled medical condition or treatment-emergent, clinically significant laboratory abnormality
- Active infection
- Absolute neutrophil count < 1.5 x 103/µL
- CD4 cell count < 250/µL
- Hypogammaglobulinemia IgG < 4.0 g/L

In addition, prior to the second infusion of each treatment cycle patients were to be evaluated for the following conditions. If any of these were present prior to re-dosing, further administration of ocrelizumab should have been suspended until resolved or held indefinitely:

- Severe allergic or anaphylactic reaction to a previous ocrelizumab infusion
- Any significant or uncontrolled medical condition or treatment-emergent, clinically significant laboratory abnormality
- Active infection

In the event any infusion was delayed, a 20-week period was to be maintained between the last infusion of one treatment cycle and the first infusion of the next treatment cycle.

Blinded treatment was continued until the study was considered completed and treatment unblnded. This was to occur when the last enrolled subject completed at least 120 weeks of treatment. However if the target number of 12 week confirmed progressions had not occurred at that point then the blinded treatment period would be extended until at least 253 confirmed progressions occurred.

> ***Reviewer Comment: Note that reconsent was required for those patients who reached the 24 Week Confirmed Disability Progression endpoint.***

There were "Non-infusion visits" at Week 12 and at the midpoint of each treatment cycle thereafter through the end of the Blinded Treatment Period (i.e. at weeks 36, 60, 84, and at the midpoint of an additional treatment cycles). In addition, a structured telephone interview was conducted on a 4-week basis between study visits from Week 8 through the end of the Blinded Treatment Period to identify any new or worsening neurological symptoms that could warrant an unscheduled visit. Additional unscheduled visits for the assessment of potential relapses, new neurological symptoms or safety events could occur at any time.

An assessment of disability was conducted for all patients by an independent Examining Investigator at screening and every 12 weeks during the blinded treatment period of the study, and at any unscheduled withdrawal from treatment visit.

A brain MRI scan was obtained in all patients at baseline and at weeks 24, 48 and 120. In addition, patients who remained in the treatment period through week 144 were to have a brain MRI scan performed at week 144. If patients had received corticosteroids for a relapse, the scan should have been done prior to the first steroid dose if the pre-steroid scan was within 1 week of the scheduled visit. For patients who have received corticosteroids, there should have been an interval of 3 weeks between the last dose of corticosteroids and the scan. MRI scans were be read by a centralized reading center for both efficacy and safety endpoints. The centralized reading center was blinded to the treatment assignment and the reading was performed in the absence of clinical information. All MRI scans were also reviewed locally by a radiologist for safety and the MRI scan report containing only non-MS pathology was to be provided to the Treating Investigator. The Treating Investigator was instructed not to review the MRI scans unless there was a safety concern. In the event that the Treating Investigator did become aware of the MRI results, this was to be documented in the eCRF, indicating the reason.

Following unblinding subjects were eligible to enter an open label treatment period if the investigator determined that the subject could benefit from continued (for those who were on ocrelizumab) or initiation of treatment with ocrelizumab.

Patients who discontinued treatment for any reason were to be followed up for at least 48 weeks after the last infusion in the Safety Follow-Up Period with visits every 12 weeks until 48 weeks had elapsed since the last infusion of study drug. If the subject's B-cell count had not returned to baseline or the lower limit of the normal range (whichever was lower) then assessments would continue every 24 weeks until the B-cell counts met those criteria.

The end of study is defined as either the last patient last visit (LPLV) of the OLE phase or the LPLV of the B-cell monitoring of Safety Follow-Up Period, whichever is later.

The full schedule of assessments during the blinded treatment phase is shown in **Table 99**. The assessments during added treatment cycles are in **Table 100**.

Assessment of Relapse (Protocol Section 5.5.4.2)

Patients were to be evaluated for possible relapses by the Treating Investigator at each visit throughout the study and at any unscheduled visits to confirm relapses occurring between the visits.

All new or worsening neurological events compatible with MS representing a clinical relapse were reported in the eCRF. Patients with clinical relapses should have been referred to the Examining Investigator who was to assess the FSS/EDSS independently to allow confirmation as to whether or not the clinical relapse met the criteria for protocol defined relapse(s).

A protocol-defined relapse was defined as the occurrence of new or worsening neurological symptoms attributable to MS and immediately preceded by a relatively stable or improving neurological state of least 30 days. Symptoms must have persisted for more than 24 hours and could not be attributable to confounding clinical factors such as a fever, infection, injury, or adverse reactions to concomitant medications. The new or worsening neurological symptoms had to be accompanied by objective neurological worsening consistent with an increase of at least half a step on the EDSS, or 2 points on one of the appropriate FSS, or 1 point on two or more of the appropriate FSS. The change must have affected a specific 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.

It should be noted that all patients with new neurological symptoms defined at a visit or over the phone should have been referred to the Examining Investigator unless the Treating Investigator considers the symptoms consistent with an intensification of neurological symptoms from a transient systemic infection.

Clinical relapses (i.e., regardless of whether they meet criteria for a protocol-defined relapse) should have been recorded on the eCRF “MS relapse” eform; these were also to be reported as adverse events. However relapses were not necessarily reported as an SAE. An MS relapse was not reported as an SAE if the reason for hospitalization was to receive standard treatment with IV methylprednisolone. When the MS relapse resulted in hospitalization for any reason other than for routine treatment of the relapse or when hospitalization was prolonged, then the MS relapse should have been reported as an SAE.

Table 98: Schedule for administration of study drug, WA25046

Randomization group	Blinded Treatment Period												Open Label period[1]		Safety follow-up period
	5 Treatment Cycle (120 week) minimum[2]												Variable		Variable
	Cycle														
	1		2		3		4		5		Added Cycles		Open label		
	Weeks 0 - 24		Weeks 24 - 48		Weeks 48 - 72		Weeks 72 - 96		Weeks 96 - 120		Every 24 weeks		Every 24 weeks		
	Infusion week														
	1	2	24	26	48	50	72	74	96	98	120+	120+	OLE	OLE	
OCR	OCR 300 mg IV	OCR 300 mg IV	OCR 300 mg IV	OCR 300 mg IV	OCR 300 mg IV	OCR 300 mg IV	OCR 300 mg IV	OCR 300 mg IV	OCR 300 mg IV	OCR 300 mg IV	OCR 300 mg IV	OCR 300 mg IV	OCR 300 mg IV	OCR 300 mg IV	
PLACEBO	Placebo IV	Placebo IV	Placebo IV	Placebo IV	Placebo IV	Placebo IV	Placebo IV	Placebo IV	Placebo IV	Placebo IV	Placebo IV	Placebo IV	Placebo IV	Placebo IV	

1: The open label treatment period for eligible patients begins after the interim database lock (primary unblinding) at the end of the Blinded Treatment Period and will last until a market authorization decision is made.
2. 100 mg of methylprednisolone IV will be administered prior to ocrelizumab or placebo infusions.

Table 99: Schedule of Assessments: Screening through the End of Treatment Period, WA25046

	Screening	Blinded Treatment Period															
Visit	1	2 (BL)	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Week	-4 to -1	1	2	12	24	26	36	48	50	60	72	74	84	96	98	108	120
OCR admin		✓	✓		✓	✓		✓	✓		✓	✓		✓	✓		
PE	X	X	X		X	X		X	X		X	X		X	X		X
Neuro exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EDSS	X	X		X	X		X	X		X	X		X	X		X	X
Routine Safety Labs	X	X		X	X		X	X		X	X		X	X		X	X
Telephone interview[1]				X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X	X						X									X
MRI[2]		X			X			X									X
Pgx test	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs	SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Potential relapses recorded		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis B viral DNA	X			X	X		X	X		X	X		X	X		X	X
CD4 count	X			X			X			X			X			X	
IgG				X			X			X			X			X	
Total Ig, IgA, IgG, IgM	X				X			X			X			X			X
Plasma and Urine JCV		X		X	X		X	X		X	X		X	X		X	X

1: A structured telephone interview will be done on a 4-week basis between visits from Week 8 through the Blinded Treatment Period (and Open Label Treatment Period, if applicable) to identify any new or worsening neurological symptoms that warrant an unscheduled visit.
2: MRI scans: If applicable brain MRI's will be obtained in patients who complete Week 144 during the blinded treatment period.

Table 100: Schedule of Assessments: Additional Treatment Cycles, Delayed dosing, unscheduled, WA25046

	Additional Treatment Cycles			Delayed Dosing Visit	Unscheduled Visit	Withdrawn from Treatment visit
	Day 1±2	Day 1±2	12 weeks post-day 1±4			
OCR infusion	✓	✓		✓		
Physical exam	X	X	X	X	X	X
ECG						X
EDSS	X		X		X	X
AEs	X	X	X	X	X	X
Potential relapses recorded	X	X	X	X	X	X
Telephone Inteview[1]	X	X	X			X
MRI[2]						X
Pgx test	X	X	X	X	X	X
Total Ig, IgA, IgG, IM	X					X
Safety labs[3]	X		X		X	X

1: A structured telephone interview will be done on a 4-week basis between visits from Week 8 through the Blinded Treatment Period (and Open Label Treatment Period, if applicable) to identify any new or worsening neurological symptoms that warrant an unscheduled visit.

2: MRI scans: If applicable brain MRI's will be obtained in patients who complete Week 144 during the blinded treatment period.

3: Routine safety lab. Hematology, chemistry, and urinalysis: On infusion visits, all urine and blood samples should be collected prior to the infusion of methylprednisolone. At other times, samples may be taken at any time during the visit.

Reviewer Comment: A "structured" telephone interview was done every 4 weeks from Week 8 through the Blinded Treatment Period (and Open Label Treatment Period, if applicable) to identify any new or worsening neurological symptoms that warrant an unscheduled visit.

Table 101: Schedule of Assessments: Safety Follow Up Period (including additional B cell monitoring if required), WA25046

	Safety Follow Up Period					End of Safety Follow Up or Withdrawal from Study
	Through 48 weeks after the last infusion: visits occur every 12 weeks				Continued B-cell monitoring visits occur every 24 weeks[1]	
	Weeks after final treatment visit					
Assessment	12	24	36	48	Every 24 weeks	End of observation
Routine safety labs[2]	X	X	X	X	X	X
Urine Pgx test	X	X	X	X	X	X
Total Ig, IgA, IgG, IgM		X		X		X
Neuro Exam	X	X	X	X	X	X
Potential relapses recorded	X	X	X	X	X	X
ECG		X		X		X
AEs	X	X	X	X	X	X
Telephone interview recorded[3]	X	X	X	X	X	X

1: Patients whose B-cells have not been repleted (returned to baseline or to the lower limit of normal, whichever is lower) 48 weeks-post last infusion will continue safety follow up for B-cell monitoring until B-cells have repleted. Assessments will be performed every 24 weeks (± 14 days) until B-cell repletion.

2: Hematology, chemistry, and urinalysis.

3: A structured telephone interview will be done on a 4-week basis between visits until 48 weeks after the last infusion to identify any new or worsening neurological symptoms that warrant an unscheduled visit. If additional Safety Follow Up for B-cell monitoring is required beyond 48 weeks after the last infusion, telephone interviews will be done every 12 weeks between visit

Blinding

Each site was to have two blinded investigators: A Treating Investigator and an Examining Investigator. The Treating Investigator had access to both safety and efficacy data. The treating investigator made all treatment decisions based on the patient's clinical response and laboratory findings. The following laboratory results were provided to the Treating Investigator because they were Criteria for Retreatment with Ocrelizumab (See Section 6.2.3 of the Protocol)

- Absolute neutrophil count < 1.5 x 103/µL
- CD4 cell count < 250/µL
- Hypogammaglobulinemia IgG < 4.0 g/L

Any critical blinded laboratory values for IgG, absolute neutrophil count and CD4 count were provided to the Treating Investigator and the Medical Monitor. Investigators notified of their patient's critical laboratory test result were instructed to suspend further treatment with study drug until the patient could be further evaluated.

The Examining Investigator was the efficacy assessor and should have been a neurologist or other qualified health care practitioner trained and certified in administering and scoring the Functional System Scores (FSS) and Kurtzke Expanded Disability Status Scale (EDSS). The Examining Investigator was responsible for administration of the EDSS including screening assessment and access to the subject's clinical data was to be limited to EDSS data. Patients were to be instructed not to discuss any symptoms related to the study treatment with the Examining Investigator; the Examining Investigator was instructed to remind the patient at the start of the examination

MRI scans in all patients were read in a blinded fashion at the central reading center.

Laboratory parameters which could have made the investigator aware of treatment assignment, such as FACS cell counts including CD19+ cells, lymphocyte count, and IgM and IgG levels were not provided to the Treating Investigator unless necessary for safety until the interim data lock for the primary analysis.

Study Endpoints

The primary measure of efficacy was the time to the first 12 week confirmed progression of disability. Progression of disability was defined as an increase of one point or more on the Expanded Disability Status Scale (EDSS) from a baseline EDSS score of 5.5 or less or an increase of 0.5 points from a baseline of more than 5.5.

Secondary efficacy endpoints were:

- change from baseline to Week 120 in the total volume of T2 lesions (mean change in total volume of T2 lesions from baseline up to Week 120 using a Mixed-Effect Model Repeated Measures (MMRM) analysis
- change from baseline to Week 120 in the timed 25 foot walk (differences in the mean change from baseline up to Week 120 using an MMRM analysis)
- time to sustained disability progression - 24 week confirmation (same method as for the primary endpoint).

Statistical Analysis Plan

For changes in the SAP see the Biometrics review by Dr. Yan.

Primary efficacy endpoint (Protocol Section 8.1.1)
The primary efficacy endpoint was the time to sustained disability progression during the treatment period. Disability progression was defined as an increase of ≥ 1.0 point from baseline EDSS, if the baseline EDSS was less than or equal to 5.5 points, or an increase of ≥ 0.5 points, if the baseline EDSS is > 5.5 points. The change could not be attributable to another etiology such as a fever, concurrent illness, MS relapse or exacerbation, or concomitant medication. Confirmation of disability progression was required at a regularly scheduled visit that was at least 12 weeks after the initial disease progression. The non-confirmatory EDSS assessments (if any) between the initial and confirmation of disability progression had to be at least as high as the minimum change required for progression.

The primary analysis was assessed in the Intent to Treat (ITT) population which included all randomized patients as randomized.

The primary analysis was to be conducted when the treatment period ended. An interim data lock was to occur when the last patient had completed the Week 120 assessment. If additional treatment cycles were instituted due to lower than anticipated disease progression rates at 120 weeks, then the interim data lock was to occur when approximately 253 sustained disability progression events had occurred. An additional analysis comprising of both safety and efficacy endpoints was planned at the end of the follow-up period to investigate the maintenance of the treatment effect and/or the potential for a withdrawal effect.

Time to 12 week confirmed disability progression (12 week confirmation) was defined as the time from Baseline (Day 1) to the first disability progression which was confirmed at the next regularly scheduled visit ≥ 12 weeks (84 days) after the initial disability progression. An assessment that occurred within 30 days after a protocol-defined relapse was not to be used for confirmation of sustained disability progression.

Patients who did not have initial disability progression at the time of interim data lock, time of early discontinuation, or loss to follow up were censored at the date of their last EDSS assessment. Patients who had initial disability progression with no confirmatory EDSS assessment at time of interim data lock were censored at the date of their last EDSS assessment. Patients who had initial disability progression and then discontinued the treatment early with no confirmatory EDSS assessments were considered as having sustained disability progression.

> ***Reviewer Comments:***
> ***Note that for the primary analysis a progression could begin at a relapse. In a subsequent revision of the SAP a sensitivity analysis was added that excluded progressions that began at a relapse.***
>
> ***For patients who had an initial disability progression but who did not have a confirmatory visit at the time of the interim database lock the primary analysis assumes that these patients did not meet the criteria for confirmed progression. Sensitivity analyses using alternate imputation methods were planned (SAP Section 4.4.4).***

Time to sustained disability progression was compared using a two-sided log-rank test stratifying by geographic region (US vs. OUS) and age (≤45 vs. >45). The proportion of patients with sustained disability progression was to be estimated using Kaplan-Meier methodology. The overall hazard ratio was to be estimated using a stratified Cox regression model with the same stratification factors used in the stratified log-rank test above.

<u>EDSS Cleaning Process (SAP version 4 Section 3.3)</u>

> ***Reviewer Comment: In describing the EDSS "cleaning" process in Appendix 1 of the SAP it is stated that "Between Jan 1, 2011 and Jan 31, 2012*** (b) (4) ***Experts reviewed 1082 EDSS assessments rated by 267 examining investigators at 160 study sites participating in the Roche trials WA25046, WA21092 and WA21093. They found in 23% of the cases***

inconsistencies in the last step of the assessment, namely the combination of the Functional Systems and the ambulation scores to the final EDSS step". This new process was applied to all previous and following EDSS scores. The sponsor subsequently proposed the "cleaning" process in an amendment dated February 25, 2013. DNP provided written comments to the proposed procedure and essentially agreed that the process was acceptable (see letter to sponsor dated 3/21/13).

The primary efficacy endpoint was derived from the EDSS values recorded at any visit. Only EDSS assessments that had been performed by an examining investigator (not the treating investigator) were entered into an electronic device, and then transferred to the central database for the "data-cleaning" process. All EDSS results were then checked in accordance with a standard operating procedure entitled "EDSS Assessment Check for the Roche Trials WA25046, WA21092, and WA21093". For details of this process see Appendix **13.4**.

The secondary efficacy endpoints were:

- Time to sustained disability progression over the treatment period, defined as an increase of ≥ 1.0 point from baseline EDSS, if the baseline EDSS was less than or equal to 5.5 points, or an increase of ≥ 0.5 points, if the baseline EDSS was > 5.5 points, was confirmed at least 24 weeks after the initial progression.

- Change in timed 25-foot walk from baseline to Week 120

- Change in total volume of T2 lesions on 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 SF-36v2 PCS score from baseline to Week 120*

- *To evaluate the safety and tolerability of ocrelizumab 300 mg × 2 (over 24 week treatment cycles) compared with placebo in patients with PPMS*

Reviewer Comment: The last three secondary endpoints in italics were added in Version E of the protocol. Secondary efficacy endpoints were tested in the hierarchical order listed above, if the primary endpoint and each preceding endpoint reached the significance level of 0.05.

The sample size for the confirmed disability progression (12-week confirmation) was estimated on the basis of data from a previous rituximab Phase II/III trial in adults with PPMS (Study U2786g[12]). For the current study, the 2-year progression rate in patients receiving ocrelizumab is predicted to be 30%, compared with 43% in patients receiving placebo (hazard ratio = 0.635). In addition, the following assumptions were made for the study conduct: a 2:1 randomization ratio between the ocrelizumab and placebo arms, a 1-year accrual period with a 3.5-year maximum blinded treatment period, and a dropout rate of 20% over 2 years. On the basis of these assumptions, the predicted power and number of events for the originally planned sample size (N = 630) were calculated.

Sample Size	Planned
N	630
Type 1 error rate	0.01
Power (%)	80
No. of expected events	253

Reviewer Comment: The sponsor reports that "due to a late screening boost" the actual number of patients randomized was 732. Assuming the same rate for CDP12 events, 295 events were expected at study unblinding if performed 120 weeks after the last patient randomized. This results in a power of 87% at alpha 0.01, and 96% at alpha 0.05.

Protocol Amendments

Table 102: Amendments to Protocol WA25046

Protocol version	Release Date	Changes	Number of subjects randomized
A	23 June 2010	1. Split dosing for first dose only 2. Eligibility limit of ≤ 50 years old	0
B	3 March 2011 (sequence 0325 (SDN 332)	1. Revise dosing to split doses of 300mg each given 15 days apart for all doses 2. Increase eligible age to ≤55 years old 3. Assessments within 30 days of a relapse would not be used to confirm disability progression	407
C	Not released –replaced by version D		
D	15 June 2012	1. Increased screening period to up to 8 weeks	All remaining subjects
E	6 February 2016	1. Limit maximum blinded treatment period to 3 years 2. Replace analysis of continuous efficacy endpoints over time	

Protocol version	Release Date	Changes	Number of subjects randomized
		using ranked analysis of covariance with Mixed-Effect Model Repeated Measures method.	

Data Quality and Integrity: Sponsor's Assurance

The sponsor reports that 3 sites were audited by the sponsor and 8 by the co-development partner/contract research organization [redacted] (b) (4) Site 208368 (Dr. Sokolova) failed to perform some EDSS assessments in a valid manner. An inspection was performed by the [redacted] (b) (4), which reported a critical finding of 20% over-enrollment of patients due to an unexpected increase in screening of new patients when the closing of enrollment into the study was announced. The SAP was subsequently amended to reflect the new statistical assumptions. A sensitivity analysis of the primary endpoint using the originally planned patient sample size (630 patients) was performed (SAP Section 4.4.4). Other findings included the performance of EDSS assessments being undertaken by treating investigators (the Sponsor confirmed that these were isolated cases and the site was retrained) and the use of paper work sheets for data entry. Although the Sponsor's intent was to use the Trial Slate [redacted] APPEARS THIS WAY ON ORIGINAL ☐ as the primar to enter their assessment first on paper work sheets and then entered the data into the Trial Slate™. "The protocol was ambiguous as to whether this was permissible or only allowed in cases of technical failure. Following the inspection the protocol was amended to clarify that this was allowed".

6.4.2. Study Results

Compliance with Good Clinical Practices

The sponsor reports that the study was conducted in accordance with the GCP principles of the International Conference on Harmonization. Investigators were trained according to applicable Standard Operating Procedures. Approvals were obtained from the appropriate regulatory authorities and from the local IRB/IEC.

Financial Disclosure

The sponsor provided an overview of financial disclosures in module 1.3.4.1. A total of 1738 out of 1740 (99.9%) principal investigators and sub-investigators responded by disclosing their financial interests in Roche/Genentech. The sponsor reports that 8 investigators for study WA25046 reported financial arrangements or interests "of other sorts". From these sites there was a total of 10 placebo and 16 OCR 600 patients with 4 and 5 respectively with a 12 week

confirmed progression of disability. The 12-week CDP treatment effect at sites without disclosable financial interest (HR=0.76, p=0.0360) did not differ from the result for those with financial interest (HR=0.6439). Investigators with disclosable financial interests did not unduly influence the primary outcome in the PPMS study.

Patient Disposition

First patient randomized: 3 March, 2011
Last patient randomized: 27 December, 2012
Clinical Cut-off date (CCOD) for primary analysis: 24 July 2015
Database lock (DBL): 18 September, 2015

A total of 732 patients were randomized at 182 investigational sites in 29 countries. Approximately 14% of patients were from the United States (USA) and 86% for outside the USA (OUS) (Table 103). The countries with the 10 highest number of patients randomized are shown in (Table 104). In general, randomization was balanced by treatment group and region or country with the exception of a disproportionate number of patients randomized to placebo in Germany where the randomization ratio was approximately 1:1. No single site accounts for this difference.

Table 103: Reviewer table: Randomization by Region and treatment group, WA25046, ITT

REGION	Total ITT		OCR 600		Placebo	
	N	%	N	%	N	%
OUS	631	86.2%	421	86.3%	210	86.1%
USA	101	13.8%	67	13.7%	34	13.9%
Total	732	100.0%	488	100.0%	244	100.0%

Source: WA25046 ASL By (REGION).xlsx

Table 104: Reviewer table: Randomization by country and treatment group, WA25046, ITT

COUNTRY	Total		OCR 600		Placebo	
	N	%	N	%	N	%
FRA	106	14.5%	69	14.1%	37	15.2%
USA	101	13.8%	67	13.7%	34	13.9%
ESP	74	10.1%	50	10.2%	24	9.8%
UKR	74	10.1%	48	9.8%	26	10.7%
POL	58	7.9%	39	8.0%	19	7.8%
DEU	57	7.8%	29	5.9%	28	11.5%
CAN	32	4.4%	20	4.1%	12	4.9%
GBR	29	4.0%	24	4.9%	5	2.0%

COUNTRY	Total		OCR 600		Placebo	
	N	%	N	%	N	%
CZE	20	2.7%	17	3.5%	3	1.2%
HUN	20	2.7%	12	2.5%	8	3.3%

Source: WA25046 ASL by Country and TRT01P descending.xlsx

The disposition of patients in the study is summarized in Figure 20. 725 of the 732 randomized patients received treatment. Six patients in the OCR 600 mg group and 1 in the placebo group withdrew before receiving treatment. The time from informed consent/screening and randomization was to be 4 weeks but could be extended to 8 weeks (protocol section 5.1). The actual duration from the start of screening to randomization is shown in Table 105. Nine patients in the OCR 600 group and 4 in the placebo group exceeded the allowed interval from screening to randomization.

> *Reviewer Comment: The original definition of the ITT was all randomized patients who received at least one dose of investigational treatment. This was changed in submission SDN 619 to all randomized patients.*

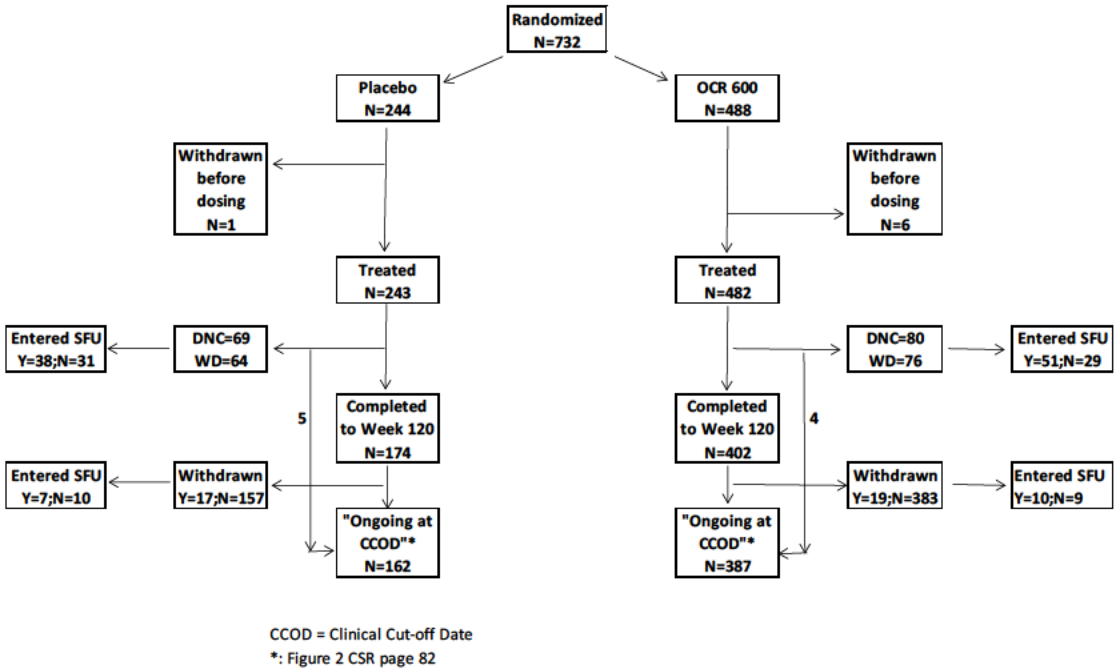
Table 105: Reviewer table: Time from start of screening to randomization, WA25046, ITT

	Time from informed consent to randomization in days					
TRT01P	N	Mean	Std Dev	Min	Max	Median
OCR 600	488	30.1	15.7	175	0	27
PLACEBO	244	30.4	10.9	69	13	28

Source: ADSL INFCODT minus RANDDT By (TRT01P).jmp

APPEARS THIS WAY ON ORIGINAL

Figure 20: Reviewer Figure: Disposition of subjects in study WA25046



In this study the minimum treatment time was 120 weeks but subjects were to continue blinded treatment until the required number of endpoint events was reached, i.e. 253 CDP12 events. 402 of the 482 (82.4%) treated subjects randomized to OCR 600 completed at least 120 weeks of treatment; 174 of 243 (71.6%) treated with placebo completed 120 weeks of treatment.

95 subjects in the OCR 600 group were withdrawn after the start of treatment (plus 6 prior to start of treatment), 80 (80/482=16.6%) of them prior to week 120 and an additional 15 (3.1%) after week 120 but prior to the Clinical Cut-off Date (CCOD). 81 subjects in the placebo group were withdrawn from treatment (plus 1 prior to the start of treatment), 69 (28.4%) prior to week 120 and an additional 12 (4.9%) after week 120.

Treatment was ongoing at the time of CCOD for 387 patients being treated with OCR 600 and for 162 patients being treated with placebo.

The reasons for discontinuation are shown in **Table 106**.

The most common reason for premature discontinuation of treatment in the placebo group was "Lack of Efficacy". On my review of the comments entered into the CRF for those listed as "Other" and those listed as "Physician decision" there are 8 additional patients treated with placebo whose probable reason was either subject perception of lack of efficacy (7 patients) or physician perception of lack of efficacy (1 patient).

In addition to the 21 (4.3%) of patients in the OCR 600 group who discontinued due to lack of efficacy, on my review of the comments entered into the CRF for those listed as "Other" and those listed as "Physician decision" there are 8 additional patients treated with OCR 600 whose probable reason was either subject perception of lack of efficacy (8 patients) or physician perception of lack of efficacy (0 patient).

The most common reason for premature discontinuation of treatment in the OCR 600 group was Withdrawal by Subject. On my review of the comments entered into the CRF, 6 of the 22 withdrawals by subjects in the OCR group were due to lack of efficacy and 7 of the 21 withdrawals by subjects in the placebo group were due to lack of efficacy. The majority of the "Withdrawals by Subject" in both treatment groups were due to logistic or personal reasons.

The total number of withdrawals that were most likely due to lack of efficacy were 35 (7.2%) in the OCR 600 group and 42 (17.2%) of those in the placebo group.

Table 106: Reasons for discontinuation of treatment by treatment group, ITT

Reason for Treatment Discontinuation	OCR 600	PLACEBO	Subjects
Did Not Discontinue Treatment	387 (79.30%)	162 (66.39%)	549 (75.00%)
Lack Of Efficacy	21 (4.30%)	27 (11.07%)	48 (6.56%)
Withdrawal (of consent) By Subject	22 (4.51%)	21 (8.61%)	43 (5.87%)
Adverse Event	18 (3.69%)	12 (4.92%)	30 (4.10%)
Physician Decision	6 (1.23%)	2 (0.82%)	8 (1.09%)
Death	3 (0.61%)	1 (0.41%)	4 (0.55%)
Lost To Follow-Up	4 (0.82%)	1 (0.41%)	5 (0.68%)
Non-Compliance	2 (0.41%)	2 (0.82%)	4 (0.55%)
Non-Compliance With Study Drug	2 (0.41%)	2 (0.82%)	4 (0.55%)
Pregnancy	1 (0.20%)	1 (0.41%)	2 (0.27%)
Protocol Violation	2 (0.41%)	0 (0.00%)	2 (0.27%)

Reason for Treatment Discontinuation	OCR 600	PLACEBO	Subjects
Other	20 (4.10%)	13 (5.33%)	33 (4.51%)
Subjects	488 (100.00%)	244 (100.00%)	732 (100.00%)

Source: JRev WA25046 TRTDiscReason.xls

The adverse events that resulted in premature discontinuation of treatment (DAE) are listed by SOC in Table 107. 33 DAEs in 32 subjects resulted in an action taken with study treatment of "drug withdrawn". Discontinuation of treatment occurred more commonly in the placebo group but for a relatively small proportion (2.5%) of all subjects treated compared to 0.4% of subjects treated with OCR. Discontinuation of treatment was due to malignant neoplasm in 7 patients treated with OCR 600 one patient treated with placebo.

Reviewer Comment: See the review of safety by Dr. Boehm for an analysis of the occurrence of neoplasms in patients treated with ocrelizumab.

Table 107: Reviewer table: Adverse events leading to discontinuation by SOC and treatment group, ITT.

AEBODSYS	Total		OCR 600		PBO	
	N	% of treated	N	% of treated	N	% of treated
NERVOUS SYSTEM DISORDERS	9	1.2%	3	0.6%	6	2.5%
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	8	1.1%	7	1.5%	1	0.4%
INFECTIONS AND INFESTATIONS	7	1.0%	4	0.8%	3	1.2%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	3	0.4%	2	0.4%	1	0.4%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2	0.3%	2	0.4%	0	0.0%
CARDIAC DISORDERS	1	0.1%	1	0.2%	0	0.0%
GASTROINTESTINAL DISORDERS	1	0.1%	1	0.2%	0	0.0%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1	0.1%	0	0.0%	1	0.4%
PSYCHIATRIC DISORDERS	1	0.1%	1	0.2%	0	0.0%
	33	4.6%	21	4.4%	12	4.9%

Source: AEACN_drugWD by SOC and TRT01P.xlsx

Protocol Violations/Deviations

There were 100 protocol violations considered major compared to 64 in the placebo group. The violation involved eligibility criteria 47 times in 42 subjects in the OCR 600 group and 22 times in 22 patients in the placebo group. The criteria typically not met involved either disease duration for the baseline EDSS score, the presence of oligoclonal bands in cerebrospinal fluid or the use of reliable means of contraception.

> *Reviewer Comment: It is unlikely that inclusion of the above patients affects interpretation of study results.*

Demographic Characteristics

The demographics of the patients in the trial are summarized in the tables below. The average age of subjects in this trial was approximately 44 years with 75% of the patients 40 years or older. Approximately half the patients were female. The race category for over 90% of patients was white and the ethnic category was non-Hispanic or Latino in over 90%. The treatment arms were balanced for all of these baseline characteristics. Only about 14% of patients in the trial were from the United States.

> *Reviewer Comment: The approximately equal number of males and females is typical of the PPMS population.*

Table 108: Summary of baseline demographic characteristics, WA25046, ITT

	OCR 600	Placebo
SEX, n, %		
Female	237, 48.6%	124, 50.8%
Male	251, 51.4%	120, 49.2%
AGE		
Mean (SD)	44.6 (7.9)	44.3 (8.3)
Median	46	46
Min, Max	20, 56	18, 55
<40	120, 24.6%	68, 27.9%
≥40	368, 75.4%	176, 72.1%
RACE, n, %		
White	454, 93.0%	235, 96.3%
Other	18, 3.7%	4, 1.6%
Black or African American	9, 1.8%	5, 2.0%

	OCR 600	Placebo
American Indian or Alaska native	5, 1.0%	0, 0.0%
Unknown	2, 0.4%	0, 0.0%
ETHNIC GROUP		
Not Hispanic or Latino	385, 78.9%	206, 84.4%
Not reported	51, 10.5%	16, 6.6%
Hispanic or Latino	32, 6.6%	14, 5.7%
Unknown	18, 3.7%	8, 3.3%
Missing	2, 0.4%	0, 0.0%
Country group		
OUS	421, 86.3%	210, 86.1%
US	67, 13.7%	34, 13.9%
Region		
EU/Switzerland/Norway	315, 64.5%	157, 64.3%
USA/Canada/Australia/New Zealand	96, 19.7%	49, 20.1%
Non-EU/Israel/Africa	61, 12.5%	32, 13.1%
Latin America	16, 3.3%	6, 2.5%

Baseline Medical History

At baseline depression was the most common reported medical illness followed by hypertension (Table 109).

Table 109: Reviewer table: Medical history at baseline by treatment group

Dictionary Derived Term	OCR 600	PLACEBO	Subjects
Depression	94 (19.26%)	50 (20.49%)	144 (19.67%)
Hypertension	75 (15.37%)	39 (15.98%)	114 (15.57%)
Back Pain	36 (7.38%)	23 (9.43%)	59 (8.06%)
Drug Hypersensitivity	36 (7.38%)	16 (6.56%)	52 (7.10%)
Headache	33 (6.76%)	16 (6.56%)	49 (6.69%)
Insomnia	29 (5.94%)	19 (7.79%)	48 (6.56%)
Hypercholesterolaemia	27 (5.53%)	12 (4.92%)	39 (5.33%)
Seasonal Allergy	26 (5.33%)	10 (4.10%)	36 (4.92%)
Anxiety	22 (4.51%)	13 (5.33%)	35 (4.78%)
Constipation	24 (4.92%)	10 (4.10%)	34 (4.64%)

Source: JRev WA25046 AMH MHDECOD by TRT01P filter MHCAT_GenMedHx.xls

Approximately 7.4% of patients at baseline had a history of a thyroid disorder. 4.1% had diabetes at baseline.

The most common previous or concomitant medications at baseline are shown in Table 110.

Table 110: Reviewer table: Most common previous or concomitant medications at baseline by treatment group, ITT

Medication Class	OCR 600	PLACEBO	Subjects
CORTICOSTEROIDS	213 (43.74%)	118 (48.36%)	331 (45.22%)
MUSCLE RELAXANTS	226 (46.41%)	103 (42.21%)	329 (44.95%)
NSAIDs	224 (46.00%)	102 (41.80%)	326 (44.54%)
VITAMINS AND MINERALS	207 (42.51%)	103 (42.21%)	310 (42.35%)
ANALGESICS	208 (42.71%)	97 (39.75%)	305 (41.67%)
MISC. NEUROLOGICAL AGENTS	133 (27.31%)	74 (30.33%)	207 (28.28%)
ANTISPASMODICS AND ANTICHOLINERGICS	138 (28.34%)	64 (26.23%)	202 (27.60%)
SSRIs	139 (28.54%)	62 (25.41%)	201 (27.46%)
SUPPLEMENTS	122 (25.05%)	73 (29.92%)	195 (26.64%)
ANTICONVULSANTS	129 (26.49%)	60 (24.59%)	189 (25.82%)
PENICILLINS	126 (25.87%)	63 (25.82%)	189 (25.82%)
BENZODIAZEPINES	113 (23.20%)	58 (23.77%)	171 (23.36%)
INVESTIGATIONS	122 (25.05%)	48 (19.67%)	170 (23.22%)
PROTON PUMP INHIBITORS	110 (22.59%)	56 (22.95%)	166 (22.68%)
ANTIHISTAMINES	120 (24.64%)	32 (13.11%)	152 (20.77%)

Source: JRev ACM CMCLASSbyTRT01PfilterCMCAT_PrevConTRT.xls

Baseline Characteristics of PPMS

The mean number of years since the onset of MS was slightly longer for the OCR 600 group compared to the placebo group, both over 6 years (Table 111).

Table 111: Mean number of years since the onset of MS symptoms, ITT

	Duration since MS Symptom Onset years				
Treatment group	subjects	mean	std.dev.	min	max
OCR 600	488	6.66	4.01	1.1	32.9
PLACEBO	244	6.14	3.59	0.9	23.8

Source: WA25046ADSL BLDursinceonset.xls

Baseline EDSS score

The baseline EDSS score (Table 112) was the average of the score at screening and the score at baseline/day 1. The mean score at baseline was approximately 4.5. Approximately 75% of subjects had a baseline EDSS score of 4[1] or more and

[1] 4.5: Fully ambulatory without aid, up and about much of the day, able to work a full day, may

approximately 30% had a baseline EDSS greater than 5.5[2]. (See Appendix 13.3 for the full EDSS scale). The ambulation score is of interest in that it may be a somewhat more objective and meaningful measure of function. At baseline the mean score for this FSS was approximately 3 with a wide range of scores from 2.5 to 6.75 (Table 113); See Appendix 13.3 for FSS ambulation scores).

Table 112: Reviewer table: Baseline EDSS score by treatment group, WA25046, ITT

Treatment	Baseline EDSS					
	subjects	mean	std.dev.	min	max	median
OCR 600	488	4.70	1.18	2.5	6.75	4.5
PLACEBO	244	4.70	1.17	2.5	6.5	4.5

Source: JRevCtab WA25046 ADSL BLEDSS by TRT01P.xls

Table 113: Reviewer table: Baseline FSS ambulation score, WA25046, ITT

Treatment	Baseline FSS Ambulation Score				
	subjects	mean	std.dev.	min	max
OCR 600	488	3.23	2.85	0	10
PLACEBO	244	3.15	2.75	0	9

Source: WA25046ADSL BLFSSAMBScore.xls

The timed 25 foot walk test (T25WT) is another measure of walking ability and is a secondary endpoint for this trial. At baseline the placebo group had a slightly shorter time (i.e. better function) on this test compared to the OCR 600 group (Table 114).

Table 114: Reviewer table: Baseline 25 Foot Walk Test result in seconds, WA25046, ITT

Treatment	Baseline 25 Foot Walk Test (BT25FW) time in seconds						
	N	Mean	Std Dev	Min	Max	Median	N Missing
OCR 600	488	14.83	21.17	3.30	180.00	7.75	0.00
PLACEBO	244	12.94	15.51	2.60	145.00	7.38	0.00

Source: WA25046 ADSL BT25FW By (TRT01P).jmp

Baseline MRI

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otherwise have some limitation of full activity or require minimal assistance: characterized by relatively severe disability usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters.

[2] 5.5: Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities: (usual FS equivalents are one grade 5 alone, others 0 or 1: or combination of lesser grades usually exceeding those for step 4.0).

The number of gadolinium-enhancing lesions at baseline was much lower for the placebo group. The T2 lesion volume in the placebo group was approximately 14% lower than that in the OCR 600 group. The normalized brain volume and T2 lesion counts were similar (Table 115).

Table 115: Baseline MRI scan characteristics, WA25406, ITT

Treatment	Total	Mean	Std Dev	Median	Min	Max
Number gadolinium enhancing lesions (AVAL)						
Placebo	244	0.60	1.55	0	0	77
OCR 600	488	1.21	5.14	0	0	10
Normalized Brain Volume, cm^3						
Placebo	244	1469.86	88.73	1462.23	1214.3	1711.1
OCR 600	488	1462.91	83.95	1462.23	1214.3	1701.7
T2 Lesion Count						
Placebo	244	48.2	39.3	43	0	208
OCR 600	488	48.7	38.2	42	0	249
T2 Lesion Volume						
Placebo	244	10.91	12.95	6.2	0.037	81.07
OCR 600	488	12.67	15.11	7.3	0.009	90.32

Source: WA25046 ADSL and subsets of ABLFL_Y Subset of AMRI AVAL By (TRT01P)

Reviewer Comment: The large difference in the number of gadolinium-enhancing lesions may bias the result in favor of OCR 600 if in fact OCR 600 is more effective in the presence of gadolinium-enhancing lesions – see Table 126 and Table 130 and subsequent discussion of the impact of this imbalance between the treatment groups.

Previous treatment

Approximately 14% of subjects had been treated for MS previously. Excluding the use of corticosteroids only 12% had been treated previously. The specific previous treatments are listed in Table 116.

Table 116: Reviewer table: Previous treatment for MS, WA25046, ITT

Standardized Medication Name	OCR 600	PLACEBO	Subjects
GLATIRAMER ACETATE	21 (4.31%)	10 (4.10%)	31 (4.23%)
INTERFERON BETA-1A	19 (3.90%)	15 (6.15%)	34 (4.64%)
INTERFERON BETA-1B	16 (3.29%)	8 (3.28%)	24 (3.28%)
AZATHIOPRINE	2 (0.41%)	2 (0.82%)	4 (0.55%)

Standardized Medication Name	OCR 600	PLACEBO	Subjects
CYCLOPHOSPHAMIDE	3 (0.62%)	1 (0.41%)	4 (0.55%)
FINGOLIMOD	1 (0.21%)	2 (0.82%)	3 (0.41%)
Total subjects	487 (100.00%)	244 (100.00%)	732 (100.00%)

Source: JRevACM CMDECODbyTRT01PfilterCMCAT_Prev CMSCAT_MSTx CMCLAS_cyto.xls
Source: JRevACM CMDECOD2byTRT01PfilterCMCAT_Prev CMSCAT_MSTx CMCLAS_alk.xls
Source: JRevACM CMDECODbyTRT01PfilterCMCAT_Prev CMSCAT_MSTx CMCLAS_immod.xls
Source: JRevACMCMDECOD2byTRT01PfilterCMCAT_PrevCMSCAT_MSTxCMCLAS_immsupp.xls

Twenty-three (23) patients (4.7%) in the OCR 600 group and 31 patients (12.7%) in the placebo had a history of treatment with intravenous corticosteroids for an indication of an MS relapse.

> *Reviewer Comment: Eligibility criteria required a Diagnosis of PPMS in accordance with the revised McDonald criteria (2005) which require one year of disease progression. Therefore treatment for a relapse that occurred more than one year prior to enrollment would be compatible with those criteria.*

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Of 732 randomized, 725 subjects were treated.

For 4 subjects whose planned treatment was OCR – each received one dose of placebo. For 4 subjects whose planned treatment was PBO – each received one dose of OCR. Therefore there are 733 entries for various measures of exposure. The duration from first to last dose of investigational treatment was greater than the protocol minimum of 120 weeks but slightly longer for the OCR 600 group (Table 117). The duration of exposure, the number of doses (Table 118) and total dose (Table 119) were slightly lower for the group assigned to placebo. The number of patients receiving each treatment cycle declined gradually through the course of the trial. 81.7% of those assigned to OCR 600 and 74.9% of those assigned to placebo completed the target number of 5 cycles of treatment (Table 120).

Table 117: Reviewer table: Duration of exposure in weeks by treatment group, WA25046, safety population*

Treatment	Duration of Exposure in weeks (EXTDUR2N)						
	N	Mean	Std Dev	Min	Max	Median	N Missing
OCR 600	486	137.35	49.89	0.00	219.75	146.01	0
PLACEBO	247	123.89	54.91	0.01	218.15	123.42	0

Source: EXTCAT_OVERALL Subset of WA25046 AEX EXTDUR2N By (TRT01P).xlsx

*: includes infusion of incorrect drug in 4 patients in each group

Table 118: Reviewer table: Total number of doses by treatment group, WA25046, Safety population*

Treatment	EXDOSNT - Total number of doses)					
	N	Mean	Std Dev	Min	Max	Median
OCR 600	486	6.60	2.07	1	10	7
PLACEBO	247	6.04	2.28	1	10	6

Source: EXTCAT_OVERALL Subset of WA25046 AEX EXDOSNT By (TRT01P).xlsx
*: includes infusion of incorrect drug in 4 patients in each group

Table 119: Reviewer table: Total dose by Treatment group, WA25046, safety population*

Treatment	Total dose (EXDOST)					
	N	Mean	Std Dev	Min	Max	Median
OCR 600	486	3867.96	1251.28	0	6000	4200
PLACEBO	247	4.86	37.94	0	300	0

Source: EXTCAT_OVERALL Subset of WA25046 AEX EXDOST By (TRT01P).xlsx
*: includes infusion of incorrect drug in 4 patients in each group

Table 120: Reviewer table: Percent of subjects with treatment by treatment cycle, WA25046, safety population*

Infusion (AINFC)	Total treated		OCR 600		Placebo	
	n	% of treated	n	% of treated	n	% of treated
CYCLE 1 INFUSION 1	725	100.0%	482	98.8%	243	100.0%
CYCLE 1 INFUSION 2	712	98.2%	473	96.9%	239	98.4%
CYCLE 2 INFUSION 1	692	95.4%	461	94.5%	231	95.1%
CYCLE 2 INFUSION 2	668	92.1%	445	91.2%	223	91.8%
CYCLE 3 INFUSION 1	668	92.1%	448	91.8%	220	90.5%
CYCLE 3 INFUSION 2	647	89.2%	433	88.7%	214	88.1%
CYCLE 4 INFUSION 1	640	88.3%	435	89.1%	205	84.4%
CYCLE 4 INFUSION 2	627	86.5%	426	87.3%	201	82.7%
CYCLE 5 INFUSION 1	616	85.0%	424	86.9%	192	79.0%
CYCLE 5 INFUSION 2	592	81.7%	410	84.0%	182	74.9%
CYCLE 6 INFUSION 1	576	79.4%	402	82.4%	174	71.6%
CYCLE 6 INFUSION 2	541	74.6%	378	77.5%	163	67.1%
CYCLE 7 INFUSION 1	411	56.7%	293	60.0%	118	48.6%
CYCLE 7 INFUSION 2	388	53.5%	277	56.8%	111	45.7%

Infusion (AINFC)	Total treated		OCR 600		Placebo	
	n	% of treated	n	% of treated	n	% of treated
CYCLE 8 INFUSION 1	254	35.0%	180	36.9%	74	30.5%
CYCLE 8 INFUSION 2	230	31.7%	161	33.0%	69	28.4%
CYCLE 9 INFUSION 1	100	13.8%	72	14.8%	28	11.5%
CYCLE 9 INFUSION 2	77	10.6%	56	11.5%	21	8.6%
CYCLE 10 INFUSION 1	9	1.2%	7	1.4%	2	0.8%
CYCLE 10 INFUSION 2	9	1.2%	7	1.4%	2	0.8%

Source: EXTCAT_INDIVID subset WA25046 AEX AINFCbyTRT01P desc.xlsx
*: includes infusion of incorrect drug in 4 patients in each group

The duration of the individual infusions was about 2.5 hours and generally similar for the two treatment groups. However the duration was more than 4 hours in 56 OCR infusions but for only 4 placebo infusions. 35 of these events match to an AE of an IRR, 34 of them occurring in 25 OCR patients and one in a placebo patient. When the infusion was modified it was most often interrupted or slowed rather than discontinued (Table 121).

Table 121: Reviewer table: Changes to drug infusion by treatment group, WA25046, safety population

FASTRESC	Total	OCRELIZUMAB	PLACEBO
	N	N	N
Interrupted	169	121	48
Slowed Down	87	79	8
Discontinued	13	11	2
Total	269	211	58

Source: FATEST_method Subset of Join FACAT_EXP FA with ASL By (FASTRESC).jmp

The reasons for adjustment of the infusion from the above dataset are summarized in the table below (Table 122)

Table 122: Reviewer table: Reason for adjustment of infusion of study drug, WA25046, safety population

Reason For Dose Adjustment (FAEXADJ)	Total	OCRELIZUMAB	PLACEBO
	N	N	N
Infusion Reaction	147	135	12
Other (subject related and/or technical)	121	76	45
Total	268	211	57

Source: Join OccurEXP FA with ASL TRT01P By (FAEXADJ).xlsx

Adjustments to the infusion were more common at the first infusion for those being treated with OCR but were much less common and evenly distributed across visits in the placebo group (Table 123). This correlates with the higher incidence of IRRs with the first few infusions. See the Safety review by Dr. Boehm for details regarding IRRs.

Table 123: Reviewer table: Adjustments to infusion by visit and treatment group, WA25046, safety population

VISIT	Total treated N=725		OCR 600 N=482		PLACEBO N=243	
BASELINE/DAY 1	72	9.9%	65	13.5%	7	2.9%
WEEK 2	19	2.6%	10	2.1%	9	3.7%
WEEK 24	32	4.4%	25	5.2%	7	2.9%
WEEK 26	14	1.9%	10	2.1%	4	1.6%
WEEK 48	19	2.6%	15	3.1%	4	1.6%
WEEK 50	13	1.8%	6	1.2%	7	2.9%
WEEK 72	16	2.2%	13	2.7%	3	1.2%
WEEK 74	2	0.3%	1	0.2%	1	0.4%
WEEK 96	15	2.1%	13	2.7%	2	0.8%
WEEK 98	16	2.2%	15	3.1%	1	0.4%
CY1_ADDL_TX_D1/W120	13	1.8%	9	1.9%	4	1.6%
CY1_ADDL_TX_D15	10	1.4%	6	1.2%	4	1.6%
CY2_ADDL_TX_D1	12	1.7%	11	2.3%	1	0.4%
CY2_ADDL_TX_D15	2	0.3%	2	0.4%	0	0.0%
CY3_ADDL_TX_D1	4	0.6%	3	0.6%	1	0.4%
CY3_ADDL_TX_D15	4	0.6%	2	0.4%	2	0.8%
DELAYED DOSING	5	0.7%	5	1.0%	0	0.0%
Total	**268**		**211**		**57**	

Source: Join OccurEXP FA with ASL TRT01P By (VISIT).jmp

Efficacy Results - Primary Endpoint

An Initial disability progression (IDP) must have met the criteria for an increase in the EDSS score compared to baseline and must have occurred on treatment. An IDP occurred 355 times (0.73 IDPs per patient randomized) in 225 patients being treated with OCR 600 and 191 times (0.78 per patient randomized) in 133 patients being treated with placebo.

Of the 355 IDPs that occurred in 225 patients being treated with OCR 600, 174 (49%) met the criteria for a CDP12 (Confirmed Disability Progression – 12 weeks) event. Of the 191 IDPs that

occurred in 133 patients being treated with placebo, 94 (49.2%) met the criteria for a CDP12 event.

> *Reviewer Comment: The nearly identical confirmation rates support a lack of bias in the automated confirmation process.*

The 174 CDP12 events in the OCR group occurred in 151 subjects (67.1% of the 225 subjects with at least one IDP). The 94 CDP12 events in the placebo group occurred in 84 subjects (63.2% of the subjects with at least one IDP). 22 IDPs that occurred in 22 subjects who did not have a confirmatory assessment were imputed as progressions (CDPW12) because the patient discontinued prematurely. (Since one OCR subject had a CDP12 and a CDPW12, only the CDP12 is counted for that patient.) Of the remaining IDPs there were 172 that occurred in 65 patients treated with OCR that were not confirmed; there were 85 IDPs that occurred in 37 placebo patients that were not confirmed. Overall, for all IDP events, about half were confirmed 12 weeks later. Of all subjects with one or more IDPs, about 70% had at least one CDP. Table 124 summarizes the outcome of IDPs.

Table 124: Reviewer table: Outcome of IDPs to CDP12, CDPW12 or no CDP12, WA25046, ITT

Progression category	OCR		Placebo	
	Subjects	Events	Subjects	Events
IDPs	225	355	133	191
CDP12 (% of IDPs)	151 (67%)	174 (49%)	84 (63%)	94 (49%)
CDPW12	9	9	12	12
Total CDP12 (% of IDPs)	160 (71.1%)	183 (51.6%)	96 (71.2%)	106 (55.5%)
Unconfirmed IDPs	65 (28.9%)	172 (48.5%)	37 (27.8%)	85 (44.5%)

Source: ACDP dataset.

The numbers of patients with a CDP12 and CDPW12 and those who did not meet the criteria for CDP12 are listed in Table 125. The proportion of patients with a 12 week confirmed progression in the OCR group was 32.8% and it was 39.3% in the placebo group, an absolute reduction of 6.5% (p-value for the difference = 0.0846, Fisher's exact test, 2-sided). The reduction relative to the rate in the placebo group was 16.5%.

> *Reviewer Comment: The relative percent reduction in the simple proportion of subjects with a CDP12 or CDPW12, 16.5%, is slightly lower than the percent reduction of 24% found when using the Kaplan-Meier model with a hazard ratio based on Cox proportional hazards.*

Table 125: Reviewer table: Number and proportion of subjects with at least one IDP and CDP12 or CDPW12, WA25046, ITT

	Total ITT		OCR 600 ITT		Placebo ITT	
PARAMCD	**N**	**%**	**N**	**%**	**N**	**%**
No CDP	476	65.0%	328	67.2%	148	60.7%
CDP12	**235**	**32.1%**	**151**	**30.9%**	**84**	**34.4%**
CDPW12	21	2.9%	9*	1.8%	12	4.9%
Total CDP12	256	35%	160**	**32.8%****	96	**39.3%**
95% CI				28.6, 37.2		33.2, 45.8
Total	732	100.0%	488	100.0%	244	100.0%

Source: Join ADESSMaxADYwithConcatAVALC_Y CDR12andCDPW12 incl NM plus TRT01P PARAMCD By (TRT01P) ITT.xlsx
CDP12: Confirmed Disability Progression 12 weeks; CDPW12: imputed CDP12 at withdrawal from treatment
*: one patient had both a CDP12 and a CDPW12 and is counted only once
**: p=0.0846: OCR vs PBO, Fisher's exact test;

Reviewer Comment: The number and proportions of subjects with at least one IDP, CDP12 and CDPW12 are essentially the same as those reported by the sponsor in the CSR, Table 13 page 98/8131 – see Table 128 below.

One patient in the placebo group and 6 patients in the OCR 600 group were randomized but not treated. For the ITT analysis these patients are included as having not progressed. Inclusion of these patients favors the OCR 600 group. If it is assumed that the overall proportion of subjects progressed in Table 125 applies to these 7 patients then the one untreated placebo patient would be imputed as not progressed and 2 of the 6 untreated OCR 600 patients would be imputed as progressed. The proportion progressed would be changed to 162/488 or 33.2% for the OCR 600 group and would remain at 39.3% for the placebo group (p-value for the difference = 0.1017, Fisher's exact test). Similarly, if the 7 patients are excluded, the proportion with a CDP12 or CDPW12 are 33.2% and 39.5% for the OCR 600 and placebo groups respectively (p=0.100 for the difference, Fisher's exact test, 2-tailed).

Reviewer Comment: In the Kaplan-Meier analysis the 7 untreated patients have less of an effect on the result since they only contribute one day each to the time to event analysis.

Proportion of patients with CDP12 or CDPW12 by Subgroups

The simple proportion of patients who had either a CDP12 or CDPW12 during the treatment phase is shown in Table 126. In general, the treatment effect favored OCR in all major subgroups. The effect was more prominent in males (CDP12 rate 21.3% in the placebo group compared to 15.3% in the OCR group) and in those who were 45 years old or younger (CDP12 rate 20.1% in the placebo group compared to 15.0% in the OCR group). The benefit is also most prominent in those with more recent onset and slightly more prominent for those with less evidence of activity on MRI scan. There was no major difference based on baseline EDSS score. There does not appear to be a major difference by weight category. There are too few subjects who had been treated prior to the trial, who were relapse free during the trial and who were from the US to make a meaningful assessment of the influence of these factors on the treatment effect.

Reviewer Comment: See Table 130 for analyses of the same subgroups using the Kaplan-Meier time to event method, particularly for further analysis of the impact of the large difference in baseline gadolinium-enhancing lesions.

Table 126: Reviewer table: Proportion of patients with CDP12 or CDPW12 by subgroup, WA25046, ITT

Subgroup	OCR 600 N=488				Placebo N=244				Treatment Effect (Overall = 6.3%)
	N	CDP12/ CDPW12	Rate in subgroup	% of treated	N	CDP12/ CDPW12	Rate in subgroup	% of treated	
Sex									
Female	237	85	35.9%	17.4%	124	44	35.5%	18.0%	0.6%
Male	251	75	29.9%	15.4%	120	52	43.3%	21.3%	5.9%
Age Group									
≤45	234	73	31.2%	15.0%	118	49	41.5%	20.1%	5.1%
>45	254	87	34.3%	17.8%	126	47	37.3%	19.3%	1.4%

Subgroup	OCR 600 N=488				Placebo N=244				Treatment Effect (Overall = 6.3%)
	N	CDP12/ CDPW12	Rate in subgroup	% of treated	N	CDP12/ CDPW12	Rate in subgroup	% of treated	
Baseline weight category									
<75kg	290	93	32.1%	19.1%	142	53	37.3%	21.7%	2.7%
≥75kg	196	67	34.2%	13.7%	101	43	42.6%	17.6%	3.9%
Time since diagnosis									
≤2 yrs	279	91	32.6%	18.6%	143	63	44.1%	25.8%	7.2%
>2 to ≤5 yrs	117	42	35.9%	8.6%	53	18	34.0%	7.4%	-1.2%
> 5 to <= 10 Years	68	22	32.4%	4.5%	37	11	29.7%	4.5%	0.0%
> 10 Years	22	4	18.2%	0.8%	10	3	30.0%	1.2%	0.4%
Time since onset of MS symptoms									
≤ 3 yrs	79	25	31.6%	5.1%	53	24	45.3%	9.8%	4.7%
>3 to ≤5 yrs	82	39	47.6%	8.0%	36	20	55.6%	8.2%	0.2%
>5 to ≤ 10 yrs	111	60	54.1%	12.3%	52	34	65.4%	13.9%	1.6%
>10 yrs	202	30	14.9%	6.1%	96	15	15.6%	6.1%	0.0%
Baseline T1 Gd Enhanced Lesions category									
0	351	115	32.8%	23.6%	183	68	37.2%	27.9%	4.3%
1	62	25	40.3%	5.1%	29	9	31.0%	3.7%	-1.4%
2	22	10	45.5%	2.0%	15	10	66.7%	4.1%	2.0%
3	17	1	5.9%	0.2%	5	4	80.0%	1.6%	1.4%
≥4	32	7	21.9%	1.4%	11	4	36.4%	1.6%	0.2%
Baseline T1 gadolinium enhanced lesions flag (Y/N)									
Yes	133	43	32.3%	8.8%	60	27	45.0%	11.1%	2.3%
No	351	115	32.8%	23.6%	183	68	37.2%	27.9%	4.3%
Baseline Number of T2 Lesions category									

Subgroup	OCR 600 N=488				Placebo N=244				Treatment Effect (Overall = 6.3%)
	N	CDP12/ CDPW12	Rate in subgroup	% of treated	N	CDP12/ CDPW12	Rate in subgroup	% of treated	
0-5	50	17	34.0%	3.5%	29	14	48.3%	5.7%	2.3%
6-9	11	2	18.2%	0.4%	6	3	50.0%	1.2%	0.8%
>9	425	140	32.9%	28.7%	208	78	37.5%	32.0%	3.3%
Baseline EDSS category									
<4	130	33	25.4%	6.8%	66	24	36.4%	9.8%	3.1%
≥4	357	127	35.6%	26.0%	178	72	40.4%	29.5%	3.5%
Baseline EDSS category 2									
≤5	348	100	28.7%	20.5%	163	61	37.4%	25.0%	4.5%
>5	139	60	43.2%	12.3%	81	35	43.2%	14.3%	2.0%
Relapse free									
Yes	457	144	31.5%	29.5%	204	77	37.7%	31.6%	2.0%
No	31	16	51.6%	3.3%	40	19	47.5%	7.8%	4.5%
Previous MS treatment									
Yes	55	18	32.7%	3.7%	30	15	50.0%	6.1%	2.5%
No	433	142	32.8%	29.1%	214	81	37.9%	33.2%	4.1%
Region stratification									
OUS -N=631	421	145	34.4%	29.7%	210	84	40.0%	34.4%	4.7%
USA-N=101	67	15	22.4%	3.1%	34	12	35.3%	4.9%	1.8%

Time to event analyses

Actual time to the primary endpoint (CDP12 or CDPW12)

The actual time to the first CDP12 or CDPW12 is shown in Table 127. The mean actual times to a confirmed progression are numerically earlier for the placebo group although not statistically significantly different from the times in the OCR group. OCR 600 patients with no CDP12 have a longer time to the last EDSS score compared to placebo patients with no CDP12.

Table 127 : Reviewer table: Time to the first CDP12 or CDPW12 or to the last EDSS assessment during the treatment phase, ITT

Treatment	Time to first CDP12 or CDPW12					
	N OUSs	Mean	Std Dev	Median	Min	Max
OCR 600	160	492.27*	305.07	504.5	1	1267
PLACEBO	96	464.15	329.58	422.5	1	1107
Time to Last EDSS if no CDP12 or CDPW12						
OCR 600	328	1009.3**	338.21	1087	1	1518
PLACEBO	148	948.88	363.59	1008	1	1514

Source: Censor_1 Subset of Join CDP12orCDPW12PlusTRTorSCR ADYrevmax inclNM with ADSL.jmp; Censor_0 Subset of Join CDP12orCDPW12PlusTRTorSCR ADYrevmax inclNM with ADSL.jmp

*: p=0.4912, unpaired t-test

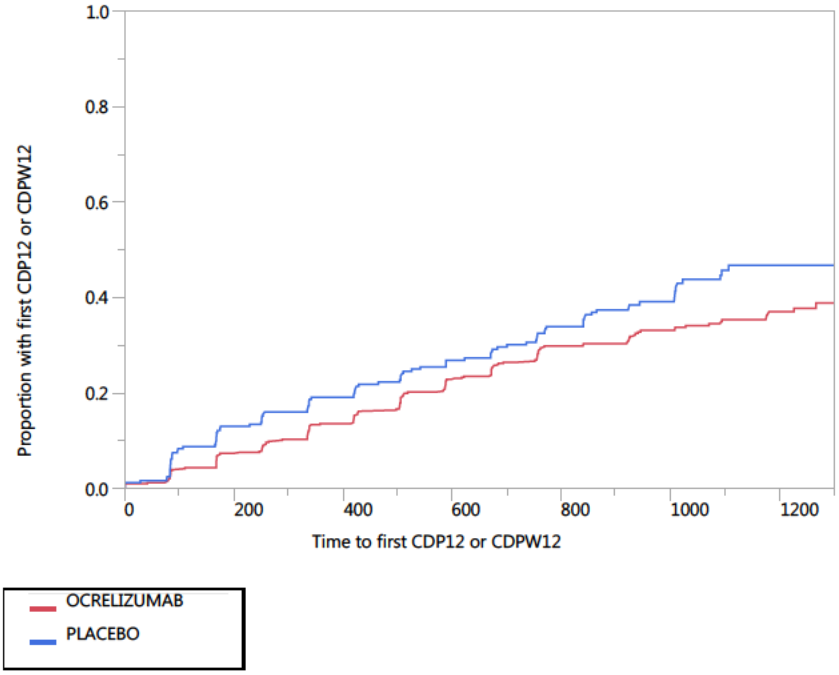
**: p=0.0759, unpaired t-test

Kaplan-Meier analysis

Using the Kaplan-Meier model, the time to the first CDP12 or CDPW12 shows a statistically significant difference in favor of the group treated with OCR 600 (Figure 21). This result is comparable to that of the sponsor (see Table 128 below).

Figure 21: Reviewer Figure: Unadjusted Time to first CDP12 or CDPW12, WA25046, ITT

Product-Limit Survival Fit
Failure Plot



Source: CDP12orCDPW12 Plus TRTorSCR ADYrevmax inclNM.jmp

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	4.5670	1	0.0326*
Wilcoxon	4.4401	1	0.0351*

Source: CDP12orCDPW12 Plus TRTorSCR ADYrevmax inclNM.jmp

Reviewer Comment: The result is similar for the "all treated" population (i.e. excluding the 7 patients who were not treated) with a p-value of 0.0328 (log-rank). See the Biometrics review by Dr. Yan for the FDA analysis of the Kaplan-Meier estimate of the hazard ratio using the stratification variables and the Cox proportional hazards model. The sponsor's estimates of the proportions and hazard ratio are in Table 128 below.

Table 128: Sponsor Table 13: Time to Onset of Confirmed Disability Progression for at Least 12 Weeks

	OCR 600	Placebo
Patients, N (%)	487 (100%)	244 (100%)

CDP12, N	160 (32.9%)	96 (39.3%)
No CDP12, N	327 (67.1%)	148 (60.7%)
p-value, stratified analysis(log-rank)	0.0321	
Hazard ratio (95%CI)	0.76 (0.59, 0.98)	

Source: WA25046 CSR Table 13, page 98/8131
Stratified by Geographical Region (US vs. OUS) and Age (<= 45, >45 years).
Hazard ratios were estimated by stratified Cox regression.
Patient with missing baseline EDSS excluded from analysis. Patients with an initial disability progression during the blinded treatment period who discontinue the treatment early and do not have a subsequent visit with EDSS measurement are imputed as having a CDP event.

Reviewer Comment: The sponsor did conduct a number of sensitivity analyses of interest. These are shown in Table 129 below.

Table 129: Sponsor table: Sensitivity Analyses of Primary Endpoint (Time to Onset of Confirmed Disability progression for at Least 12 Weeks during the Double-Blind Treatment Period)

Analysis	Patients with event/N		Hazard ratio (95% CI)	p-value
	OCR 600	Placebo		
Primary Analysis	160/488	96/244	0.76 (0.59, 0.98)	0.0321
ITT with multiple imputation	#	#	0.78 (0.60, 1.02)	#
ITT without imputation	151/487	84/244	0.82 (0.63, 1.07)	0.1477
Exclude progression beginning ≤83 days after randomization	160 /487	94 /244	0.78 (0.60, 1.00)	0.0500
Exclusion of patients with clinical relapses (including protocol-defined relapses)	144 /456	77/204	0.74 (0.56, 0.98)	0.0324

Source: WA25046 CSR Table 14, page 101/8131
#: No p-value calculated for multiple imputation results (50% of events are randomly imputed across groups, therefore the number of events in each group differs with each imputation).

Reviewer Comment: The p-value and confidence interval of the hazard ratio is sensitive to changes in the imputation method. For example, 9 patients in the OCR group and 12 in the placebo group lacked a confirmation visit due to premature discontinuation – a difference of only 3 patients. In the pre-specified primary analysis it is assumed that these patients progressed. When it is assumed that these patients did not progress the result is no longer statistically significant. If progressions that started in the first 12 weeks are excluded then the difference becomes more significant. If patients who had a protocol-defined relapse during the treatment phase of the trial are excluded then the result also becomes more significant.

Kaplan-Meier analyses of the primary endpoint by subgroups are summarized in Table 130. OCR 600 appears to be more effective in males and in those who were 45 years old or younger. There were relatively few patients who did have gadolinium-enhancing lesions at baseline but the reduction in CDP12/CDPW12 events in that subgroup appears to be greater than that in those who did not have gadolinium-enhancing lesions.

Reviewer Comment: There was a large imbalance in the number of gadolinium-enhancing lesions at baseline with nearly 50% less in the placebo group (Table 115). If OCR 600 in fact is more effective when there is acute inflammation such as might be shown be the presence of gadolinium-enhancing lesions, then this imbalance may bias the efficacy result in favor of OCR 600. The sponsor discusses this issue in the CSR Section 5.2.3, page 103/8131). Using multivariate analysis methods the sponsor notes that the interaction of baseline gadolinium-enhancing lesions at baseline and treatment effect was significant as was the interaction with sex. All other interactions were not significant.

Table 130: Reviewer table: Kaplan-Meier analysis of time to first CDP12 or CDPW12 by subgroups, WA25046, ITT

	OCR 600		Placebo		Simple Odds Ratio (OCR/PBO)	p-value (Log Rank)
	CDP12/CDPW12	No CDP12/CDPW12	CDP12/CDPW12	No CDP12/CDPW12		
Sex						
F, N=361	85	152	44	80	1.02	0.7892
M, N=371	75	176	52	68	0.557	0.0054
IXRS Age						
≤45, N=352	73	161	49	69	0.638	0.0208
>45, N=380	87	167	47	79	0.876	0.4295
IXRS Region						
OUS, N= 631	145	276	84	126	0.784	0.0834
US, N= 101	15	52	12	22	0.529	0.1296
Relapse free						
Yes, N= 661	144	313	77	127	0.759	0.0338

	OCR 600		Placebo		Simple Odds Ratio (OCR/PBO)	p-value (Log Rank)
	CDP12/CDPW12	No CDP12/CDPW12	CDP12/CDPW12	No CDP12/CDPW12		
No, N=71	16	15	19	21	1.18	0.3622
Baseline EDSS category						
≤ 5.5, N=511	100	248	61	102	0.674	0.0488
>5.5, N=220	60	79	35	46	1.00	0.4982
Race						
White, N=689	148	306	94	141	0.726	0.0215
Ethnic group						
Hispanic or Latino, N=46	14	18	6	8	1.04	0.7369
Not Hispanic or Latino, N=591	121	264	80	126	0.721	0.0385
Not reported, N = 67	16	35	6	10	0.762	0.5680
Baseline T1 Gd Enhanced Lesions flag						
Y, N=193	43	90	27	33	0.584	0.0330
N, N=534	115	236	68	115	0.824	0.2132
Baseline Number of T2 Lesions category						
0-5, N=79	17	33	14	15	0.552	0.2729
6-9, N=20	2	9	3	3	0.222	0.1803
>9, N=633	140	285	78	130	0.818	0.1027
Baseline Weight category						
<75, N=432	93	197	53	89	0.792	0.1408
≥75, N=297	67	129	43	58	0.700	0.1400
Baseline Body Mass Index category						
<25	91	198	57	82	0.661	0.0213
≥25	69	128	39	64	0.885	0.5102
Baseline FSS Ambulation Score Category						
5 or less*, N=524	104	251	61	108	0.733	0.1012
More than 5	56	77	34	39	0.834	0.2165
Per Protocol Population Flag						
Y, N=702	153	317	91	141	0.749	0.0250
N, 30	7	11	5	7	0.891	0.4478
Previous MS trt. excl. Corticosteroids						

	OCR 600		Placebo		Simple Odds Ratio (OCR/PBO)	p-value (Log Rank)
	CDP12/CDPW12	No CDP12/CDPW12	CDP12/CDPW12	No CDP12/CDPW12		
Y, N=85	18	37	15	15	0.487	0.2285
N, N=647	142	291	81	133	0.801	0.0788

Source: Join CDP12orCDPW12PlusTRTorSCR ADYrevmax inclNM with ADSL.jmp
*: No assistance

CDP duration

The duration of any period of progression of disability from the initial progression to either the last EDSS assessment date (if all met the criteria for progression) or to date of the first EDSS assessment that did not meet the criteria is shown in Table 131. There is no difference between the treatment groups in the duration of episodes of disability. The progression of disability was sustained to the last EDSS in a lower proportion of patients treated with OCR 600, 43.1%, compared to those treated with placebo, 54.5% (Table 132).

Table 131: Duration of periods of disability progression, WA25046, ITT

	Duration in days (AVAL)					
TRT01P	N	Mean	Std Dev	Median	Min	Max
OCRELIZUMAB	355	230.3	239.8	99	1	1193
PLACEBO	191	236.2	266.9	106	1	1260

Source: CDPDUR Subset of WA25046 ACDP AVAL By (TRT01P).jmp

Table 132: Proportion of patients whose initial disability progression continued to the last EDSS, WA25046, ITT

Disability criteria to last EDSS (AVALC)	N(OCRELIZUMAB)	N(PLACEBO)

Disability criteria to last EDSS (AVALC)	N(OCRELIZUMAB)	N(PLACEBO)
NO	202	87
YES	153, 43.1%	104, 54.5%
Total	355	191

Source: CDPLAST Subset of WA25046 ACDP AVALC By (TRT01P).jmp

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Data Quality and Integrity - Reviewers' Assessment

The rate at which an IDP met the criteria for a CDP12 event was 49% for both treatment groups which suggests that the processing of IDPs using the "EDSS cleaning process" did not introduce significant bias in the analysis of the primary endpoint.

Efficacy Results - Secondary and other relevant endpoints

CDP24

A summary of the rate of confirmation of IDPs to CDP24 is shown in **Table 133.** Approximately 40% of IDPs were confirmed 24 weeks later. A slightly higher proportion of subjects in the OCR group (57%) with an IDP were confirmed 24 weeks later compared to 53% in the placebo group.

Table 133: Reviewer table: Outcome of IDPs to CDP24, CDPW24 or no CDP24, WA25046, ITT

Progression category	OCR		Placebo	
	Subjects	Events	Subjects	Events
IDPs	225	355	133	191
CDP24 (% of IDPs)	128 (57%)	138 (39%)	71 (53%)	76 (40%)
CDPW24	16	16	16	16
Total CDP24	144 (64%)	154 (43%)	87 (65%)	92 (48%)
Unconfirmed IDPs	81 (36%)	201 (57%)	46 (35%)	99 (52%)

Source: JMP and JReview PARAMCD subsets of ACDP

Of the 488 patients treated with OCR, 144 (29.5%) had a CDP24 or CDPW24 and 344 did not have an event; of the 244 patients treated with placebo 87 (35.7%) had a CDP24 or CDPW24 event and 157 did not have an event, an absolute reduction of 6.2% and a reduction relative to the rate in the placebo group of 17.4%. The difference in the proportion of subjects with a CDP24/CDPW24 event is not statistically significant, p=0.0926, Fisher's exact test, 2-tailed.

Table 134: Reviewer table: proportion of patients with CDP24, CDPW24 or no CDP24, ITT

PARAMCD	Total ITT		OCR 600 ITT		Placebo ITT	
	N	%	N	%	N	%
No CDP	501	68.4%	344	70.5%	157	64.3%
CDP24	199	27.2%	128	26.2%	71	29.1%
CDPW24	32	4.4%	16	3.3%	16	6.6%
Total CDP24	231	31.6%	144	**29.5%***	87	**35.7%**

PARAMCD	Total ITT		OCR 600 ITT		Placebo ITT	
	N	%	N	%	N	%
95% CI				25.5, 33.8		29.7, 42.0
Total	732	100.0%	488	100.0%	244	100.0%

Source: JRevCtab ACDP AVALCbyTRT01PfilterPARAMCD_CDP24orCDPW24.xls
*: p=0.0926, Fisher's exact test, 2-sided

Reviewer Comment: The results in Table 70 above are the same as those reported by the sponsor (CSR Table 17, page 108/8131). The difference in proportions would be slightly less for the all treated population.

As was the case for CDP12, the treatment effect of OCR 600 based on the results for CDP24, indicate a greater benefit for males compared to females and for those who were 45 years old or younger (Table 135).

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Table 135: Summary of proportion of subjects with CDP24 or CDPW24 by subgroup

	OCR 600				Placebo				Treatment Effect (Overall = 6.2%)
	488				244				
	N	CDP24/ CDPW24	Rate in subgroup	% of treated	N	CDP24/ CDPW24	Rate in subgroup	% of treated	
Sex									
Female	237	76	32.1%	15.6%	124	41	33.1%	16.8%	1.2%
Male	251	68	27.1%	13.9%	120	46	38.3%	18.9%	4.9%
Age Group									
≤45	234	67	28.6%	13.7%	118	46	39.0%	18.9%	5.1%
>45	254	77	30.3%	15.8%	126	41	32.5%	16.8%	1.0%
Baseline weight category									
<75kg	290	86	29.7%	17.6%	142	48	33.8%	19.7%	2.0%
≥75kg	196	58	29.6%	11.9%	101	39	38.6%	16.0%	4.1%
Time since diagnosis									
≤2 yrs	279	80	28.7%	16.4%	143	57	39.9%	23.4%	7.0%
>2 to ≤5 yrs	117	38	32.5%	7.8%	53	16	30.2%	6.6%	-1.2%
> 5 to <= 10 Years	68	21	30.9%	4.3%	37	10	27.0%	4.1%	-0.2%
> 10 Years	22	4	18.2%	0.8%	10	3	30.0%	1.2%	0.4%
Time since onset of MS symptoms									
≤ 3 yrs	79	22	27.8%	4.5%	53	23	43.4%	9.4%	4.9%
>3 to ≤5 yrs	82	36	43.9%	7.4%	36	18	50.0%	7.4%	0.0%
>5 to ≤ 10 yrs	111	52	46.8%	10.7%	52	29	55.8%	11.9%	1.2%
>10 yrs	202	28	13.9%	5.7%	96	14	14.6%	5.7%	0.0%
Baseline Gadolinium enhancing lesion flag									

	OCR 600				Placebo				Treatment Effect (Overall = 6.2%)
	488				244				
	N	CDP24/ CDPW24	Rate in subgroup	% of treated	N	CDP24/ CDPW24	Rate in subgroup	% of treated	
No	351	103	29.4%	21.1%	183	63	34.4%	25.8%	4.7%
Yes	133	39	29.3%	8.0%	60	23	38.3%	9.4%	1.4%
Baseline T1 Gd Enhanced Lesions category									
0	351	103	29.3%	21.1%	183	63	34.4%	25.8%	4.7%
1	62	23	37.1%	4.7%	29	7	24.1%	2.9%	-1.8%
2	22	8	36.4%	1.6%	15	10	66.7%	4.1%	2.5%
3	17	1	5.9%	0.2%	5	3	60.0%	1.2%	1.0%
≥4	32	7	21.9%	1.4%	11	3	27.3%	1.2%	-0.2%
Baseline Number of T2 Lesions category									
0-5	50	15	30.0%	3.1%	29	10	34.5%	4.1%	1.0%
6-9	11	2	18.2%	0.4%	6	3	50.0%	1.2%	0.8%
>9	425	126	29.6%	25.8%	208	73	35.1%	29.9%	4.1%
Baseline EDSS category									
<4	130	30	23.1%	6.1%	66	23	34.8%	9.4%	3.3%
≥4	357	114	31.9%	23.4%	178	64	36.0%	26.2%	2.9%
Baseline EDSS category 2									
≤5	348	90	25.9%	18.4%	163	55	33.7%	22.5%	4.1%
>5	139	54	38.8%	11.1%	81	32	39.5%	13.1%	2.0%
Relapse free									
Yes	457	128	28.0%	26.2%	204	71	34.8%	29.1%	2.9%
No	31	16	51.6%	3.3%	40	16	40.0%	6.6%	3.3%
Previous MS treatment									
Yes	55	16	29.1%	3.3%	30	14	46.7%	5.7%	2.5%

	OCR 600				Placebo				Treatment Effect (Overall = 6.2%)
	488				244				
	N	CDP24/ CDPW24	Rate in subgroup	% of treated	N	CDP24/ CDPW24	Rate in subgroup	% of treated	
No	433	128	29.6%	26.2%	214	73	34.1%	29.9%	3.7%
Region stratification									
OUS -N=631	421	131	31.1%	26.8%	210	77	36.7%	31.6%	4.7%
USA-N=101	67	13	19.4%	2.7%	34	10	29.4%	4.1%	1.4%

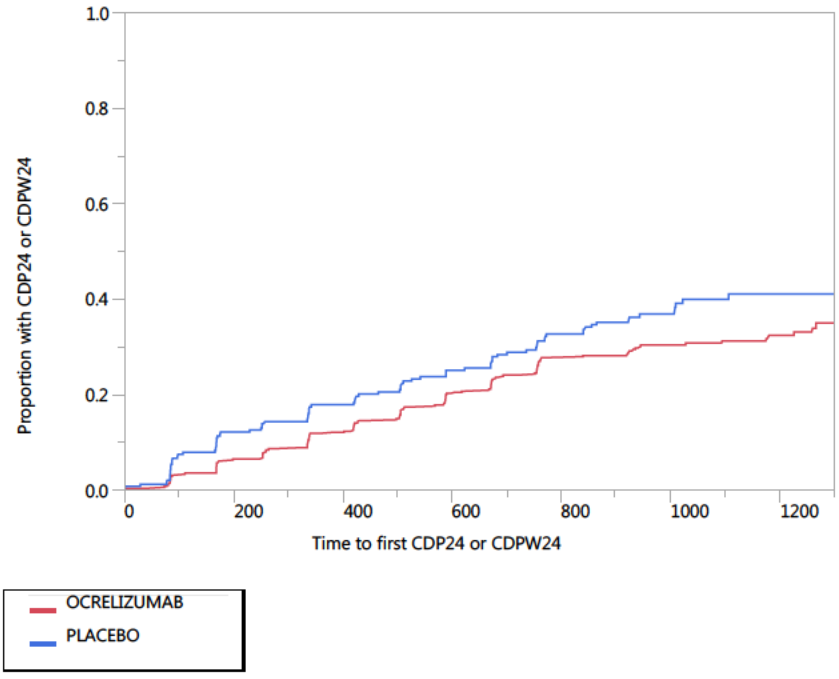
Source: JRevCtab ACDP AVALCbyTRT01Pand (subgroups as above) filterPARAMCD_CDP24orCDPW24.xls

APPEARS THIS WAY ON ORIGINAL

Time to CDP24 event analysis

Visual inspection of the unadjusted Kaplan-Meier analysis of time to first CDP24 or CDPW24 (**Figure 22**) shows earlier onset of progression in the placebo group and the difference is statistically significant.

Figure 22: Reviewer Figure: Unadjusted Time to first CDP24 or CDPW24, WA25046, ITT



Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	4.2868	1	0.0384*
Wilcoxon	4.7748	1	0.0289*

Source: Join CDP24orCDPW24 Plus TRTorSCR ADYrevmax inclNM with ADSL.jmp

Reviewer Comment: The result is similar for the all treated group (p=0.0385). See the Biometrics review by Dr. Yan for the Kaplan-Meier analysis of time to CDP24 event and hazard ratio adjusted for the stratification factors.

The time to CDP24 event by subgroup is shown in Table 136. The benefit of treatment with OCR 600 is most prominent in males and in those who are 45 years old or less.

Table 136: Reviewer table: Time to first CDP24 or CDPW24 by subgroup, WA25046, ITT

	OCR		Placebo		
	Failed	Censored	Failed	Censored	Log Rank
Sex					
F, N=361	76	161	41	83	0.5893
M, N=371	68	183	46	74	0.0160
IXRS Age					
≤45, N=352	67	167	46	72	0.0140
>45, N=380	77	177	41	85	0.5595
IXRS Region					
OUS, N= 631	131	290	77	133	0.0775
US, N= 101	13	54	10	24	0.2079
Relapse free					
Yes, N= 661	128	329	71	133	0.0207
No, N=71	16	15	16	24	0.1370
Baseline EDSS category					
≤ 5.5, N=511	90	258	55	108	0.0576
>5.5, N=220	54	85	32	49	0.4680
Race					
White, N=689	132	322	86	149	0.0177
Ethnic group					
Hispanic or Latino, N=46	11	21	5	9	0.7412
Not Hispanic or Latino, N=591	112	273	72	124	0.0813
Not reported, N = 67	8	10	4	4	0.5584
Baseline T1 Gd Enhanced Lesions flag					
Y, N=193	39	94	23	37	0.0890
N, N=534	103	248	63	120	0.1624
Baseline Number of T2 Lesions category					
0-5, N=79	15	35	10	19	0.6875
6-9, N=17	2	9	3	3	0.1803
>9, N=633	126	299	73	135	0.0639

Source: Join CDP24orCDPW24 Plus TRTorSCR ADYrevmax inclNM with ADSL.jmp

Change in Timed 25-foot Walk from Baseline to Week 120

The value for the Timed 25-foot Walk Test is the average of two trials performed at each visit. The primary analysis was to assess the change from baseline to Week 120. The last observation was to be carried forward for those with missing assessments after baseline. Those without a baseline assessment are excluded. If the assessment was not done because of physical inability to perform the task then a value of 180 seconds was imputed. Using simplified analysis

methods the mean change from baseline to the last assessment in the double-blind period was an increase of 3.08 (median 0.8) seconds for the group treated with OCR 600 compared to an increase of 2.97 seconds (median 1.0) in the placebo group (Table 137). The ratio of the two means was 0.964. To address the wide variability in this measure the percent change from baseline was assessed. The simple mean percent change was an increase of 40.12% (median 10.26%) in the group treated with OCR 600 compared to a 35.18% (median 16.11%) increase in the placebo group (Table 138).

Table 137: Reviewer table: absolute change from baseline to Week 120 or last observation in Timed 25 foot walk test, WA25046, ITT

Treatment	Change from baseline to last assessment (seconds)					
	Total	Mean	Std Dev	Median	Min	Max
OCR 600	481	3.08	17.4	0.8	-143.2	98.2
PLACEBO	243	2.97	14.2	1	-108.45	116.8

Source: Join Join Baseline FT1and2 with Last FT1and2 Subset of ZATESTCD_WLK25FT1 and 2 Subset of T25WT Subset of WA25046 ZA with ADSL LastminusBaseline By (TRT01P).jmp

Table 138: Reviewer table: percent change from baseline to Week 120 or last observation in Timed 25 foot walk test, WA25046, ITT

Treatment	Percent change from baseline					
	Total	Mean	Std Dev	Median	Min	Max
OCR 600	481	40.12*	109.3	10.26	-96.42	1020
PLACEBO	243	35.18	74.9	16.11	-95.76	585.71

Source: Join Join Baseline FT1and2 with Last FT1and2 Subset of ZATESTCD_WLK25FT1 and 2 Subset of T25WT Subset of WA25046 ZA with ADSL Percent change By (TRT01P).jmp
p=0.5267, unpaired t-test

Table 139: Sponsor table 21: Ratio and Percentage Change of Timed 25-Foot Walk Relative to Baseline and Relative Reduction Compared with Placebo from Baseline to Week 120 during the Double-Blind Treatment Period

	OCR 600, N=488	Placebo, N=244
Baseline		
n	473	239
Mean (sec)	12.781	14.573
Week 120 (ratio relative to baseline		
n	397	174
Adjused Geometric Mean (% change)	1.389 (39.93)	1.551 (55.10)
95% CI Adjusted Geometric Mean	1.292, 1.494	1.399, 1.720
Ratio of Adjusted Geometric Means	0.896	

	OCR 600, N=488	Placebo, N=244
95% CI for Ratio of Adjusted Geometric Means	0.792, 1.013	
Relative Reduction (%)	29.337	
95% CI for Relative Reduction	-1.618, 51.456	
p-value (Ranked ANCOVA)	0.0404	

Source: CSR WA25046 Table 21 page 117/8131

Reviewer Comment: See the Biometrics review by Dr. Yan for an analysis of this endpoint using all of the conditions and the analysis method pre-specified in the SAP. The percent improvement over placebo is less than the 20% that the division typically considers a clinically relevant improvement in walking speed.

Change in Total Volume of T2 Lesions on MRI Scans of the Brain from Baseline to Week 120

The absolute and relative change in the volume of T2 lesions from baseline to week 120 are shown in Table 140 and Table 141 below. The assessment is missing for 86 and 60 patients in the OCR 600 and placebo groups respectively. There was an approximately 10% increase in the placebo group compared to a small decrease in those treated with OCR 600.

Table 140: Volume of T2 lesions, change from baseline to week 120, WA25046, ITT

Treatment	Absolute Change from BL to WK120 (AVAL)(cm^3)						
	Total	Mean	Std Dev	Median	Min	Max	N Missing
OCR 600	487	-0.393	1.37	-0.12	-10.407	5.244	86
PLACEBO	243	0.788	2.53	0.123	-2.601	19.806	60

Source: Join T2LESV SCRBL with WK120 WA25046 AMRI AVAL By (TRT01).jmp

Table 141: Volume of T2 lesions, percent change baseline to week 120, WA25404, ITT

	Percent change from BL to WK120						
TRT01P	N Rows	Mean	Std Dev	Median	Min	Max	N Missing
OCRELIZUMAB	487	-2.89	11.6	-3.23	-40	68.3	86
PLACEBO	243	10.44	30.0	3.00	-37.9	170.8	60

Source: Join T2LESV SCRBL with WK120 WA25046 AMRI Percent change By (TRT01P).jmp

Reviewer Comment: The results are comparable to those of the sponsor, CSR WA25046, Table 23, page 122/8131.

Last EDSS score

The comparison of the last EDSS score on treatment by treatment group is seen in Table 142 below. The last EDSS score on treatment is not significantly different comparing the two treatment groups. There is a greater increase in the EDSS score compared to baseline while on treatment in the placebo group compared to the group treated with OCR (Table 143) (p-value 0.0737 unpaired t-test).

Table 142: Reviewer table: Last EDSS score by treatment group, all treated

	EDSS Score (QSSTRESN)					
TRT01P	N	Mean	Std Dev	Min	Max	Median
OCRELIZUMAB	482	5.02*	1.50	1	8	5.5
PLACEBO	243	5.14	1.53	1.5	8.5	5.5

Source: Join TRTsubsetEDSSsubsetAEDSS ADYmaxbyUSUBJID with TRTSubset EDSSsubsetAEDSS matchUSUBJIDandADYwithmaxADY QSSTRESN By (TRT01P).jmp
*:p=0.3128, unpaired t-test

Table 143: Reviewer table: Change from baseline to last EDSS on treatment, all treated*

	Last EDSS minus Baseline EDSS					
Treatment	N	Mean	Std Dev	Min	Max	Median
OCRELIZUMAB	481	0.307**	0.98	-4.25	3	0
PLACEBO	243	0.449	1.06	-2.5	4.25	0.5

Source: Join Last and BL EDSS By (TRT01P of Join EDSS subset of AEDSS by MaxADYbyUSUBJID with EDSS subset AEDSS match USUBJID and ADY to QSDY).jmp
*: one OCR subject with a baseline EDSS excluded
**: p=0.0737

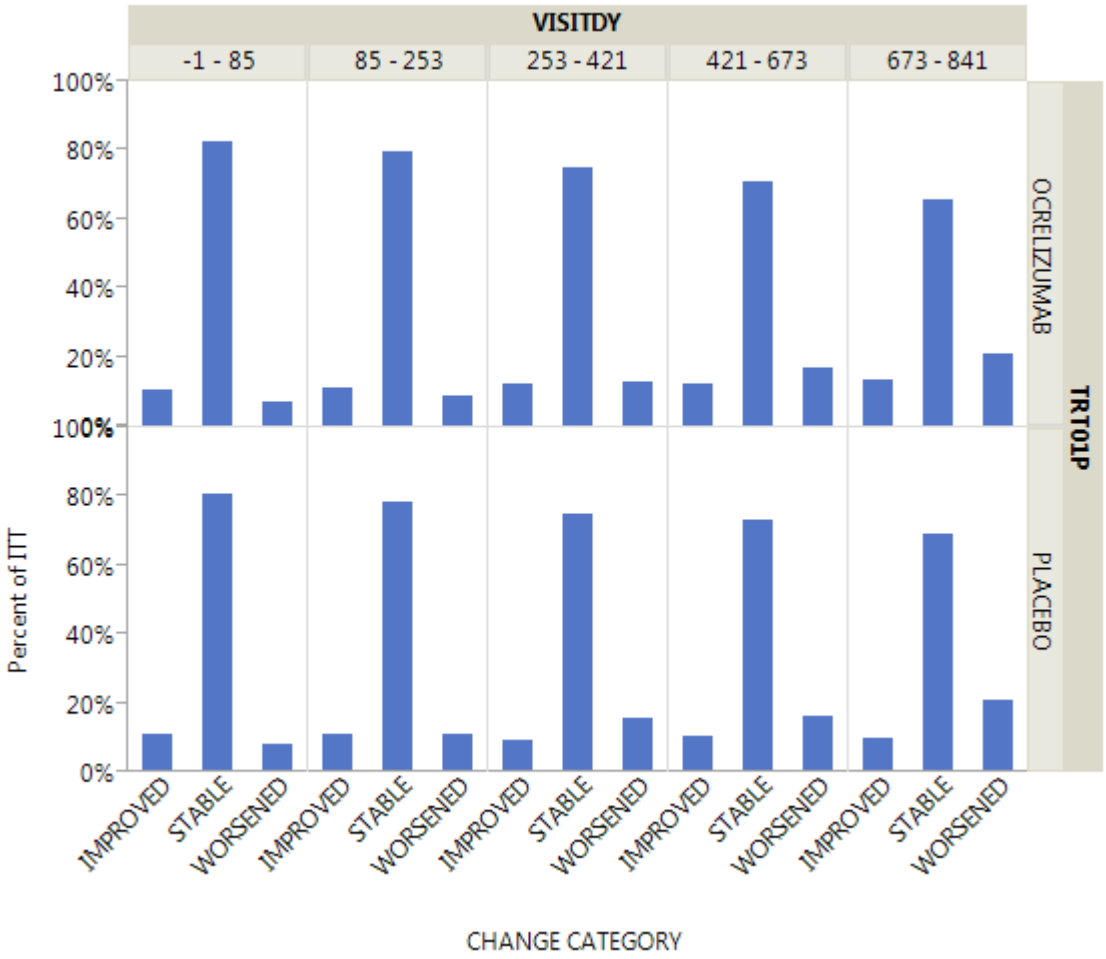
Improvement, stable or worsening EDSS score

Table 144: Reviewer table: proportion of patients whose EDSS improved, remained stable or worsened* at each major visit, by treatment group, ITT

Analysis Visit	Improved, % of ITT		Stable, % of ITT		Worsened, % of ITT		Subjects	
	OCR	Placebo	OCR	Placebo	OCR	Placebo	N	% of ITT
WEEK 12	10.5%	11.5%	78.1%	76.6%	6.6%	7.8%	699	95.5%
WEEK 24	9.6%	11.1%	76.0%	74.2%	8.6%	9.0%	691	94.4%
WEEK 36	11.1%	9.8%	73.6%	71.7%	8.6%	11.1%	682	93.2%
WEEK 48	10.7%	7.8%	69.5%	67.6%	11.7%	14.8%	669	91.4%
WEEK 60	11.9%	8.2%	66.6%	66.0%	11.3%	13.5%	653	89.2%
WEEK 72	10.5%	9.0%	64.3%	63.5%	13.9%	12.3%	641	87.6%
WEEK 84	9.6%	7.4%	62.3%	61.1%	14.8%	13.5%	624	85.2%
WEEK 96	11.1%	8.6%	60.2%	55.7%	15.4%	14.8%	617	84.3%
WEEK 108	11.7%	7.8%	55.3%	51.2%	17.6%	15.6%	596	81.4%
CY1_D1/W120	10.9%	6.6%	53.7%	50.8%	17.0%	15.6%	577	78.8%

Source: JRevCTabWA25046AEDSSCHGCATbyTRT01PbyAVISITfilterPARAMCD_EDSS.xls
*: Worsening= increase from baseline of ≥0.5; Improved= decrease from baseline ≥0.5

Figure 23: Reviewer Figure: Change Category by treatment group and visit day, ITT



Source: JRevCTabWA25046AEDSSCHGCATbyTRT01PbyAVISITfilterPARAMCD_EDSS.xls

Dose/Dose Response

A single dose was studied.

Durability of Response

Durability of response was not assessed.

Persistence of Effect

Persistence of effect was not assessed.

Additional Analyses Conducted on the Individual Trial

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

RMS population - Annualized Relapse Rate

The population in these two studies was nearly identical (Table 89). The reduction in ARR was also essentially identical in the two RMS trials (Table 145).

Table 145: Summary of ARR reduction in Trials WA21092 and WA21093

	WA21092		WA21093	
Efficacy measure	**OCR 600 N=410**	**Rebif N=411**	**OCR 600 N=417**	**Rebif N=418**
Unadjusted ARR *	0.136	0.245	0.138	0.254
Adjusted ARR **	0.156	0.292	0.155	0.290
95% CI of adjusted ARR	(0.122, 0.200)	(0.235, 0.361)	(0.121, 0.198)	(0.234, 0.361)
Adjusted ARR ratio **	0.536		0.532	
95% CI of adjusted ARR ratio	(0.400, 0.719)		(0.397, 0.714)	
p-value	<.0001		<0.0001	

* The total number of relapses for all patients in the treatment group divided by the total patient-years of exposure to that treatment.

** Adjusted by Baseline EDSS (<4.0 vs. >=4.0) and Geographical Region (US vs. OUS).

Log-transformed exposure time is included as an offset variable.

Source: CSR WA21092 Table 19, page 112/6491; CSR WA21093 Table 19, page 111/6798

PPMS population - Progression of Disability

The reduction is progression of disability is demonstrated in a single trial in the PPMS population. Whether the reduction in disability seen in the RMS population can support the benefit seen in study WA25046 is problematic. The demographic features of the population in

the trial in PPMS differ from those of the pooled RMS population (Table 146). The population with PPMS is approximately 10 years older than the RMS population. Whereas the RMS population is predominantly female, the sexes are equally represented in the PPMS population. The duration from onset of symptoms is similar. The mean number of gadolinium-enhancing lesions at baseline is greater in the RMS population but the median number is the same at zero. The T2 lesion count is about the same. The PPMS population had been previously treated for MS only slightly less often than those with RMS.

Table 146: Comparison of demographic and baseline disease characteristics of the RMS and PPMS populations studied.

	WA25046		Pooled RMS	
	OCR N=488	Rebif N=244	OCR N=827	Rebif N=829
Age				
Mean (SD)	44.6 (7.9)	44.3 (8.3)	37.5 (9.2)	37.5 (9.2)
Median	46	46	38	38
Sex				
F	237, 48.6%	124, 50.8%	552 (66.8%)	541 (65.3%)
M	251, 51.4%	120, 49.2%	277 (33.5%)	286 (34.5%)
Race				
White	454, 93.0%	235, 96.3%	743 (89.9%)	757 (91.3%)
All others	34, 7.0%	9, 3.7%	84 (10.2%)	72 (8.7%)
Region				
OUS	421, 86.3%	210, 86.1%	610 (73.8%)	610 (73.6%)
US	67, 13.7%	34, 13.9%	217 (26.2%)	219 (26.4%)
Duration since onset (years)				
Mean	6.66 (4.01)	6.14 (3.59)	6.47±6.2	6.47±6.1
Median	5.95	5.51	5.1	4.8
Baseline EDSS score				
Mean	4.70 (1.18)	4.70 (1.17)	2.77±1.26	2.75±1.33
Median	4.5	4.5	2.5	2.5
Baseline Gadolinium enhancing lesions				
Mean	1.21 (5.14)	0.60 (1.55)	1.76±4.6	1.91±5.0
Median	0	0	0	0
T2 lesion count				
Mean	48.7 (38.2)	48.2 (39.3)	50.1 (38.8)	51.0 (37.8)
Median	42	43	40	42
T2 lesion volume				
Mean	12.67 (15.11)	10.91 (12.95)	10.79 (14.1)	10.18 (11.8)
Median	7.3	6.2	5.4	6.2

	WA25046		Pooled RMS	
	OCR N=488	Rebif N=244	OCR N=827	Rebif N=829
Number of relapses in the past year				
Mean	n/a	n/a	1.32±0.67	1.34±0.69
Median	n/a	n/a	1	1
Previous MS treatment				
No	433, 88.7%	214, 87.7%	604, 73.0%	605, 73.0%
Yes	55, 11.3%	30, 12.3%	223, 27.0%	224, 27.0%

The differences in the periods of disability may be more relevant to the issue. Periods of disability in the PPMS population last considerably longer than those in the RMS population. As seen in **Table 147,** the mean duration of any period meeting the criteria for CDP12 was over 100 days longer in the PPMS group. The number of patients who met the criteria for CDP12 was about 9-13% in the RMS population compared to about 33-40% in the PPMS population. The proportion of subjects with an initial progression of disability that lasted to the final EDSS assessment was 31-43% in the PPMS group and only 5-9% in the RMS group. The relative reduction in the proportion of patients who met the CDP12 endpoint was greater in RMS patients, 33.1%, compared to that in PPMS patients, 16.3%. Using the time to event analysis methods the hazard ratio favoring treatment with OCR 600 was 0.60 in the pooled RMS population (p=0.0006) and 0.76 in the PPMS population (p=0.0321). The differences in the nature of the periods of disability in these two populations do not support the assertion that a reduction in periods of disability in the RMS population can support a reduction in disability in PPMS patients. Therefore a comparison of the primary endpoint in the single trial in PPMS patients to the comparable endpoint in the two trials in RMS patients would not be a valid assessment of the same endpoint across trials.

Table 147: Comparison of the CDP12 endpoint in WA25046 and the pooled RMS population

	WA 25046		RMS pooled	
	OCR 600	Placebo	OCR 600 N=827	Rebif N=829
CDP12[1,2]				
Proportion	32.9%	39.3%	9.1%	13.6%
Hazard ratio	0.76		0.60	
95% CI	0.59, 0.98		0.45, 0.81	
p-value	0.0321		0.0006	
CDP 24[3,4]				
Proportion	29.6%	35.7%	6.9%	10.5%
Hazard ratio	0.75		0.60	
95% CI	0.58, 0.98		0.43, 0.84	
p-value	0.0365		0.0025	
CDP duration				

	WA 25046		RMS pooled	
	OCR 600	Placebo	OCR 600 N=827	Rebif N=829
Mean	230 (240)	236 (267)	119 (119)	120 (126)
Median	99	106	85	85
CDP last (% of treatment group, ITT)				
Yes	153/488=31.4%	104/244=42.6%	41/828=5.0%	77/829=9.3%

1: CSR WA25046, Table 13, page 98/8131; with imputation
2: CSR WA21092/21093 pooled, Table 10, page 57/1515; no imputation
3: CSR WA25046, Table 17, page 108/8131
4: CSR WA21092/21093 pooled, Table 12, page 63/1515; no imputation

7.1.2. Secondary and Other Endpoints

RMS population

The reduction in the rate of disability progression confirmed at 12 or 24 weeks was consistent across the two trials in RMS patients (Table 148). Time to event analyses showed similar results (Table 149).

Table 148: Proportion of patients with disability progression confirmed at 12 or 24 weeks, RMS population

Category of progression	WA21092			WA21093		
	OCR 600	Rebif	p-value*	OCR 600	Rebif	p-value*
CDP12	8%	12%	0.0346	11%	15%	0.0620
CDP12/CDPW12**	8%	13%	0.0215	12%	17%	0.0624
CDP24	6%	10%	0.0657	8%	12%	0.1012
CDP24/CDPW24**	6%	10%	0.0407	9%	14%	0.0319

*: Fisher's exact test
**: i.e. "with imputation"

Table 149: Time to first disability progression confirmed at 12 or 24 weeks, RMS population

Category of progression	WA21092		WA21093	
	OCR 600	Rebif	OCR 600	Rebif
	Odds ratio*	p-value**	Odds ratio*	p-value**
CDP12	0.590	0.0169	0.663	0.0162
CDP12/CDPW12	0.586	0.0139	0.663	0.0133
CDP24	0.8	0.0347	0.662	0.0360
CDP24/CDPW24	0.57	0.0213	0.613	0.0104

*: simple odds ratio
**: estimated from Kaplan-Meier analysis

PPMS population

Given the differences between the PPMS and RMS populations, comparison of comparable secondary endpoints cannot be made between the trials in these two populations.

7.1.3. Subpopulations

For the pooled RMS population there was no indication of a reduced effect size in those with 4 or more gadolinium-enhancing lesions at baseline. This was an issues raised by the results of study WA21943.

Table 150: Unadjusted ARR by Baseline gadolinium-enhancing lesion, pooled WA21092 and WA21093

Treatment	Unadjusted ARR										
	Total	0		1		2		3		>= 4	
		RLP, n	ARR	RLP, n	ARR	RLP, n	ARR	RLP, n	ARR	RLP, n	ARR
Rebif	829	164	0.195	43	0.219	36	0.307	14	0.304	64	0.340
OCR 600	827	126	0.149	25	0.116	11	0.100	12	0.197	22	0.110
% reduction		23.6%		47.0%		67.4%		35.2%		67.6%	

7.1.4. Dose and Dose-Response

A single dose was studies in the RMS and PPMS populations.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

The time to onset of the first relapse and to the first CDP12 or CDP24 was significantly earlier in the group treated with OCR 600 in studies WA21092 and WA21093. The time to onset of the first CDP12 and to the first CDP24 was earlier in the group treated with OCR 600 in study WA25046. Duration and durability of benefit were not studied.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Post-market Setting

RMS indication: No post-market efficacy studies are recommended.
PPMS indication: If Ocrevus is approved for the treatment of PPMS based on the results of study WA25046 supported by studies WA21092 and WA21093 then the long term efficacy should be assessed in post-marketing studies.

7.2.2. Other Relevant Benefits

There are no additional relevant benefits

7.3. Integrated Assessment of Effectiveness

RMS population
A reduction in the Annualized relapse rate is consistent across two adequate and well-controlled trials
A reduction in periods of disability lasting 12 and 24 weeks in patients with RMS is consistent across two adequate and well controlled trials
A reduction in various MRI measures of disease activity in RMS patients is consistent across two adequate and well controlled trials.

PPMS population
A reduction in disability in the PPMS population cannot be compared to that seen in the RMS population. An across-trials analysis cannot be assessed.

8 Review of Safety

8.1. Safety Review Approach

See the review of safety by Dr. Boehm

8.2. Review of the Safety Database

8.2.1. Overall Exposure

8.2.2. Relevant characteristics of the safety population:

8.2.3. Adequacy of the safety database:

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

8.3.2. **Categorization of Adverse Events**

8.3.3. **Routine Clinical Tests**

8.4. Safety Results

8.4.1. **Deaths**

8.4.2. **Serious Adverse Events**

8.4.3. **Dropouts and/or Discontinuations Due to Adverse Effects**

8.4.4. **Significant Adverse Events**

8.4.5. **Treatment Emergent Adverse Events and Adverse Reactions**

8.4.6. **Laboratory Findings**

8.4.7. **Vital Signs**

8.4.8. **Electrocardiograms (ECGs)**

8.4.9. **QT**

8.4.10. Immunogenicity

8.5. Analysis of Submission-Specific Safety Issues

8.5.1.

8.6. Safety Analyses by Demographic Subgroups

8.7. Specific Safety Studies/Clinical Trials

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

8.8.2. Human Reproduction and Pregnancy

8.8.3. Pediatrics and Assessment of Effects on GOUSth

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

8.9.2. Expectations on Safety in the Postmarket Setting

8.10. Additional Safety Issues From Other Disciplines

8.11. Integrated Assessment of Safety

9 Advisory Committee Meeting and Other External Consultations

The need for an Advisory Committee Meeting has not been determined at this time.

10 Labeling Recommendations

10.1. Prescribing Information

The label has not been finalized at the time of this review.

10.2. Patient Labeling

The label has not been finalized at the time of this review.

10.3. Nonprescription Labeling

N/A

11 Risk Evaluation and Mitigation Strategies (REMS)

11.1. Safety Issue(s) that Warrant Consideration of a REMS

The need for a REMS has not been determined at the time of this review

11.2. Conditions of Use to Address Safety Issue(s)

11.3. Recommendations on REMS

12 Postmarketing Requirements and Commitments

The necessity of post-marketing requirements or commitments has not been determined at the time of this review.

13 Appendices

13.1. References

1. Kurtzke JF. On the evaluation of disability in multiple sclerosis. Neurology 1961;11:686-94.
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(b) (4)

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13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): WA21493, WA21092, WA21093, WA25046

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: WA21493-724 ; WA21092-1374; WA21093-1743 ; WA25046- 1740		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): WA21493 - 3 ; WA21092 - 3 ; WA21093 - 6 ; WA25046 - 8		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 20		

Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) WA21493 - 711 ; WA21092 - 1369 ; WA21093 - 1736 ; WA25046 - 1738		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. Kurtzke Expanded Disability Status Scale

Note 1: EDSS steps 1.0 to 4.5 refer to patients who are fully ambulatory, and the precise step number is defined by the Functional System (FS) score(s). EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation, and usual equivalents in Functional System scores are provided.

Note 2: EDSS should not change by 1.0 step unless there is a change in the same direction of at least one step in at least one FS. Each step (e.g., 3.0 to 3.5) is still part of the DSS scale equivalent (i.e., 3). Progression from 3.0 to 3.5 should be equivalent to the DSS score of 3.

0 - Normal neurological exam (all grade 0 in FS).
1.0 - No disability, minimal signs in one FS (i.e., grade 1).
1.5 - No disability, minimal signs in more than one FS (more than on FS grade 1).
2.0 - Minimal disability in one FS (one FS grade 2, others 0 or 1).
2.5 - Minimal disability in two FS (two FS grade 2, others 0 or 1).
3.0 - Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory.
3.5 - Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1).
4.0 - Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest 500 meters.

4.5 - Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance: characterized by relatively severe disability usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters.
5.0 - Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions): (usual FS equivalents are one grade 5 alone, others 0 or 1: or combinations of lesser grades usually exceeding specifications for step 4.0).
5.5 - Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities: (usual FS equivalents are one grade 5 alone, others 0 or 1: or combination of lesser grades usually exceeding those for step 4.0).
6.0 - Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting: (usual FS equivalents are combinations with more than two FS grade 3 +).
6.5 - Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting (usual FS equivalents are combinations with more than two FS grade 3 +).
7.0 - Unable to walk beyond approximately 5 meters even with aid, essentially restricted to a wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (usual FS equivalents are combinations with more than one FS grad 4 +; very rarely pyramidal grade 5 alone).
7.5 - Unable to take more than a few steps; restricted to wheelchair, may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair; (usual FS equivalents are combinations with more than one FS grade 4 +).
8.0 - Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day, retains many self-care functions; generally has effective use of arms; (usual FS equivalents are combinations, generally grade 4 + in several systems).
8.5 - Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions; (usual FS equivalents are combinations generally 4 + in several systems).
9.0 - Helpless bed patient: can communicate and eat; (usual FS equivalents are combinations, mostly grade 4 +).
9.5 - Totally helpless bed patient; unable to communicate effectively or eat/swallow; (usual FS equivalents are combinations, almost all grade 4 +).
10.0 - Death due to MS.

13.3. FSS Ambulation Score

0- Unrestricted

1- Full ambulatory
2- ≥300 meters, but < 500 meters, without help or assistance (EDSS 4.5 or 5.0)
3- ≥200 meters, but < 300 meters, without help or assistance (EDSS 5.0)
4- ≥100 meters, but < 200 meters, without help or assistance (EDSS 5.5)
5- Walking range < 100 meters without assistance (EDSS 6.0)
6- unilateral assistance, ≥50 meters (EDSS 6.0)
7- bilateral assistance, ≥120 meters (EDSS 6.0)
8- unilateral assistance, < 50 meters (EDSS 6.5)
9- bilateral assistance, ≥5 meters, but < 120 meters (EDSS 6.5)
10- Uses wheelchair without help; unable to walk 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day (EDSS 7.0)
11- Uses wheelchair with help; unable to take more than a few steps; restricted to wheelchair; may need some help in transferring and in wheeling self (EDSS 7.5)
12- essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms (EDSS 8.0)

13.4. EDSS Assessment check for the Roche Trials WA25046, WA21092 and WA21093

1. The EDSS score data from the assessment by the examining investigator are captured by using (b) (4) (an electronic data capturing device). Range checks are performed during data entry onto the device. The data are then transferred via LAN or Mobile network to (b) (4) web portal (the database).
2. (b) (4) checks the data on (b) (4) for plausibility and inconsistencies of the EDSS using automated consistency checks. The rules for these checks are given in the (b) (4) Scoring booklet, version (b) (4). A scoring sheet consisting of the results of the EDSS assessments is generated by (b) (4) and uploaded to (b) (4) The scoring sheet will flag inconsistencies in the EDSS assessment. If the scoring sheet does not identify any inconsistencies, the assessment remains unchanged in (b) (4)
3. The (b) (4) expert will review the scoring sheet with the EDSS assessments within 2 working days from upload to (b) (4). The EDSS assessments with flagged inconsistencies in the scoring sheet are manually reviewed by the (b) (4) Expert. If after review by the (b) (4) expert, the flagged EDSS assessment is determined to be consistent then It will remain on (b) (4) unchanged. If after review by the (b) (4) expert, the flagged EDSS assessments are confirmed to be inconsistent a manual query (b) (4)

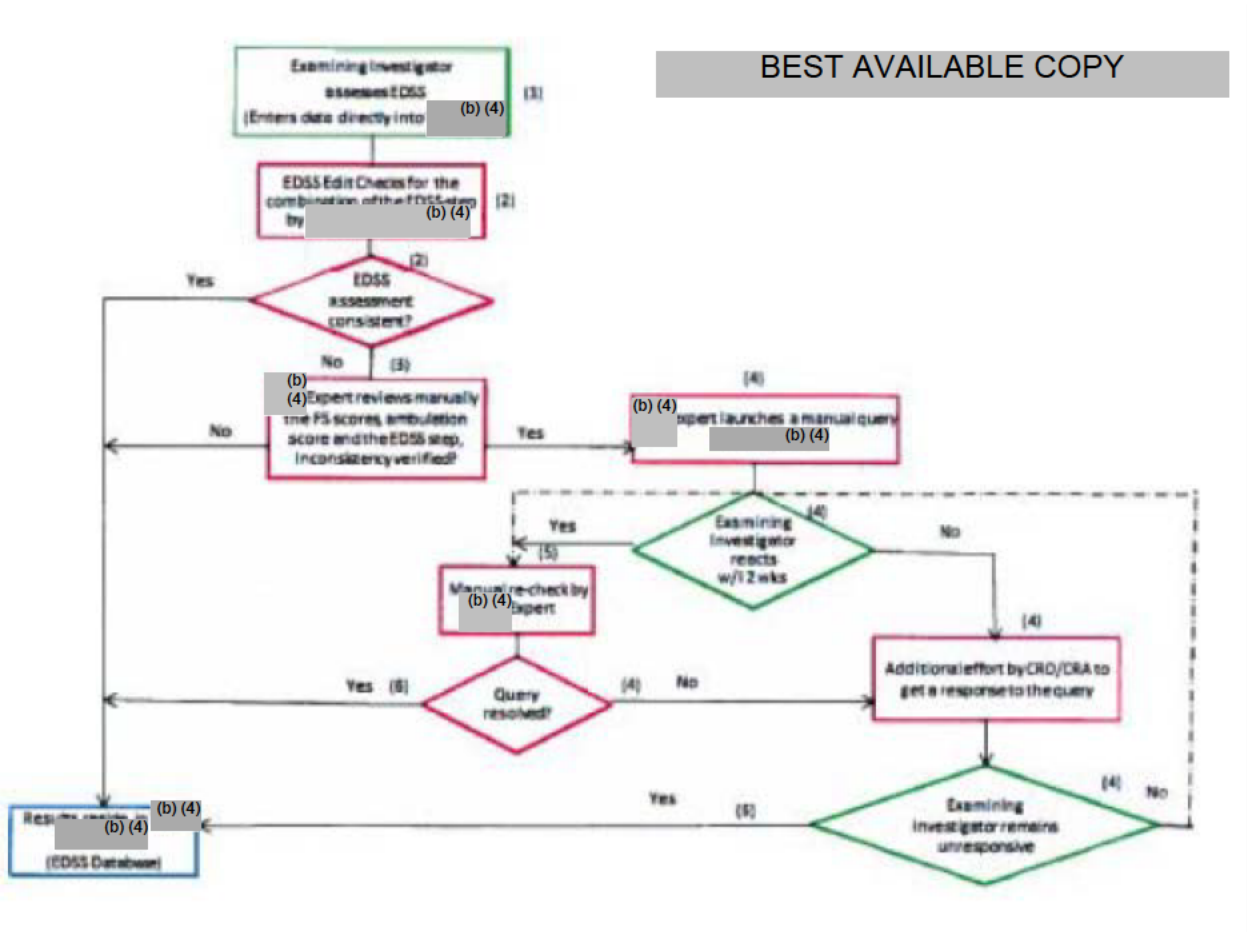
will be generated in [redacted] The query [redacted] will be reviewed and responded to by the examining Investigator (See Step 4)

4. The [redacted] are queries described in the study manual query process. The [redacted] expert is responsible for the content of the [redacted]
   a. [redacted] is responsible for processing all TrialDCFs related to the EDSS assessment captured in [redacted]
   b. The Monitor/CRA will log into [redacted] at least once per week for any new [redacted] If new [redacted] have been issued, sites will be notified by the monitor/CRA that a response to the [redacted] is required by the examining investigator within two weeks via [redacted]
   c. If the examining investigator does not respond to the initia [redacted] within the two weeks as stated above, the monitor/CRA will contact the examining investigator to request to resolve the outstanding [redacted] as per the agreed monitoring plan.
   d. The Examining investigator and/or monitor/CRA can ask for support by the [redacted] expert via email or telephone to ask any question to enable resolution of the [redacted]
   e. All outstanding [redacted] will be followed up by the monitor/CRA as per the agreed monitoring plan. The Study Management Team (SMT) will review unresolved [redacted] (as defined in study Integrated Data Review Plan (iDRP)) and will decide to close or continue to follow up the outstanding [redacted].
   f. Any [redacted] that are not answered/resolved will have their status changed as defined by [redacted] (following authorisation from the Roche SMT during the course of the study (see Step 6).
5. All answered [redacted] will be re-checked manually by the same [redacted] Expert who issued the initial [redacted] Trial Manger will generate a report to notify the [redacted] expert of the response from examining investigator at the site and he/she will review the response.
6. If the [redacted] is resolved, the EDSS assessment will be considered final and [redacted] will implement and verify the change in [redacted] The final status of a [redacted] will be either
   a. "Resolved with change and closed"- [redacted] is answered and revised data are entered by the examining investigator into [redacted]
   b. "Resolved without change and closed" - [redacted] is answered by the Examining Investigator who confirms his original assessment in the [redacted]
   c. "unresolved and closed" - [redacted] is not answered and the SMT authorizes to close due to unresponsiveness

   In all cases the examining investigator remains the final decision maker on the EDSS assessment.

7. Handling of EDSS assessments checked prior to the Implementation of the process outlined in this SOP. All previous EDSS assessments, that had gone through the previous

automated (b) (4) process, whether they had been changed or not as a result of this process will go through this new revised (b) (4) edit check process again and the process steps outlined in this current SOP 2-6 will be applied. Automated and new (b) (4) data will be stored in (b) (4)



13.5. Relapse Confirmation Process

A clinical relapse was confirmed as a PDR if the following conditions were met:

1. Clinical relapse is reported on eCRF.
2. On the MS relapse eCRF page the question "Did symptoms persist for >24 hours and were not being attributable…" is checked 'Yes'.

3. The EDSS at the first EDSS assessment at a visit (unscheduled or scheduled) on or after the onset date of the relapse is increased by ≥ 0.5 steps from the previous EDSS; OR FSS domains relevant to the relapse event (pyramidal, ambulation, cerebellar, brainstem, sensory, or converted visual) are increased by ≥ 2 points on one domain or ≥ 1 point on two or more domains.

   For each relapse that satisfied the 3 criteria above, it was then determined whether the potential relapse was within 30 days (i.e., the onset dates are ≤ 30 days apart) of a previous PDR. If a potential relapse was within 30 days, then the potential relapse was not a protocol-defined relapse.

13.6. Karnofsky Performance Score

Functional level	Score	Clinical criteria
Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

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/s/

LAWRENCE D RODICHOK
09/19/2016

JOHN R MARLER
12/12/2016

Cross-Discipline Team Leader Review

Date	November 27, 2016
From	John R. Marler, MD
Subject	Cross-Discipline Team Leader Review
Application Number	BLA 761053
Applicant	Genentech
Date of Submission	April 28, 2016
PDUFA Goal Date	December 28, 2016
Proprietary Name (Non-Proprietary)	Ocrevus (ocrelizumab)
Dosage form	600 mg IV every 24 weeks
Applicant's Proposed Indication	Relapsing and primary progressive forms of multiple sclerosis
Recommended Regulatory Action	Complete Response pending final product quality review
Recommended Indication	The treatment of patients with relapsing forms of multiple sclerosis (RMS).

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Ocrelizumab is a humanized monoclonal antibody that binds to a cluster of differentiation 20 (CD20) cell membrane protein that is found on most B-lymphocytes and some T-lymphocytes. Ocrelizumab causes significant depletion of circulating B-lymphocytes soon after infusion. The depletion lasts for months. This review assesses the effectiveness of ocrelizumab despite unresolved manufacturing problems that prevent consistent production of a potent and stable product that may delay approval.

The application asks for two indications:

Relapsing forms of multiple sclerosis (RMS) (b) (4)

Primary progressive multiple sclerosis (PPMS) (b) (4)

This review's benefit risk assessments for these two indications are as follows:

Ocrelizumab is a safe and effective treatment for **RMS** over two years

There is insufficient information in the application to conclude that ocrelizumab is a safe or effective treatment for **PPMS**.

There is only one PPMS trial. As it is, the trial results count events that may not have occurred, show inconsistencies among important subgroups, and lack independent confirmation. In women, no beneficial effect balances the potential risk of breast cancer. In addition, there are problems with trial conduct and reasons to suspect the quality of the data.

Infusion reactions, malignancies, infection, and depression-associated events are the most significant adverse events for both indications.

Relapsing multiple sclerosis

Two 800-patient adequate and well-controlled clinical trials provide substantial evidence of effectiveness. Compared to Rebif, an interferon β-1a drug approved for MS, ocrelizumab reduces the rate of relapses by 46% from 0.29 to 0.16 relapses per year with a 13% absolute difference in the number of patients with no relapses for 96 weeks. Rebif itself is FDA-approved because, compared to placebo, it reduces the rate of both relapse and confirmed disability progression events. Over two years, the proportion of patients with disability progression events is 40% less, 15.2% in the Rebif group compared to 9.8% in the ocrelizumab group. The absolute difference in proportions is 5.4% of patients.

The two RMS trials added innovative design features that may have reduced the effect of bias on the clinical outcomes. Nevertheless, the high and unbalanced drop-out rates in the two trials (17% vs 11%, and 23% vs 14%, Rebif vs ocrelizumab) and the high percentage of disclosing side effects in the Rebif groups are likely to have introduced bias in clinical assessments and post-randomization medical care decisions. The bias increases the uncertainty about the point estimates of the relative effect of ocrelizumab compared to Rebif for relapse rate and the rate of disability progression events.

Primary progressive multiple sclerosis

For PPMS, the application contains evidence from one 732-patient 2-to-1 randomized placebo-controlled clinical trial. For confirmatory evidence, the application refers to the evidence from the two RMS trials that ocrelizumab reduces disability progression events.

DNP granted breakthrough designation for ocrelizumab because of positive topline results of one PPMS trial. As the review of the application has proceeded, the review team has identified a number of serious problems with the evidence to support approval of ocrelizumab for PPMS. The problems relate to the protocol-specified primary analysis, the conduct of the study, and the degree of relatedness to PPMS of the RMS trial results the applicant uses to confirm the PPMS results.

The PPMS trial design did not adequately control for bias. The primary outcome event is an increase above baseline in EDSS disability rating lasting at least twelve weeks. In the PPMS trial, 21 patients who experienced the start of a disability event dropped out of the trial before a second increased EDSS score confirmed the duration of the event 12 or more weeks later. The applicant's statistical analysis for the trial imputed these events as confirmed disability progression (CDP) events; however not all patients who had an initial increased EDSS in the trial and did not dropout sustained that increase at a second EDSS. This imputation is unusual in MS trials. For instance, the analyses for the two ocrelizumab RMS trials did not use imputation for CDP events. The statistical reviewer notes that in a pre-specified sensitivity analysis that corrected for potential bias introduced by imputation, the p-value for the trial increased from 0.03 to **0.15.** If the usual definition of a CDP event is used, the trial results are not statistically significant.

The results of the trial are of questionable clinical significance. Slightly more women on ocrelizumab experienced poor outcomes compared to those on placebo. Because of this lack of benefit in women and the fact that 4 women in the PPMS trial developed breast cancer compared to none in the placebo group, the risk benefit assessment favors placebo in women with PPMS. In addition, for all patients, the Kaplan-Meier curves indicate that the rate of CDP events is the same for placebo and ocrelizumab for 2 years after the initial 18 weeks of treatment. All the treatment effect occurred by 18 weeks or after the patients had been in the trial for two years and the number of active participants began to diminish rapidly. At these early and late times, there is variability in trial participation and investigators and patients lack experience with the protocol procedures. The CDP event rates from 18 weeks to 120 weeks may provide a better estimate of the drug effect--the event rates for placebo and ocrelizumab are essentially the same during this period. In the trial, 120 weeks is the minimum time for participation of all patients. Without imputed events or observations carried forward, all secondary clinical outcomes show no significant beneficial effect using the trial hierarchy.

There are problems with trial conduct. For more than 50% of the patients, investigators did not record the baseline EDSS disability score before randomization as instructed by the applicant. There is a large amount of missing data. With at least 20% dropout, fewer than 195 subjects completed the trial in the control group.

Overall, because of questions about the clinical significance of the findings and problems with trial conduct and design, the PPMS trial WA25046 is not well-controlled and does not provide adequate evidence to support a claim of efficacy for patients with PPMS, particularly women. An alternative conclusion would be that the results are extremely weak and do not provide evidence of a meaningful clinical effect. The overall quality of the data and the trial design is lower than that in the two RMS trials.

The application cites the results of the two ocrelizumab RMS trials to confirm the results of the PPMS trial. Review of the application applying flexibility described in the FDA guidance on clinical evidence finds that there is an insufficient degree of relatedness between the CDP events in the RMS trials and those in the PPMS trial. The evidence of relatedness in the application either depends on the accuracy of the PPMS trial results it is intended to confirm or it depends on reports in the medical literature that do not support the conclusion that progression in RMS is closely related in mechanism and clinical characteristics to progression in PPMS. Although they have the same name and nearly the same definition, confirmed disability progression events in the RMS trial have different characteristics, particularly their duration. Reports in the medical literature provide evidence that the underlying pathological mechanism for disability progression is different in RMS and PMS. Differences in baseline characteristics in the trials support the existence of different pathological mechanisms in RMS and PPMS: compared to RMS, progression is gradual from onset without the relapse episodes that characterize RMS, onset is at an older age, and the female to male ratio is 1 to1 instead of 1 to 2. Finally, trials in PPMS with different drugs that successfully reduce progression event rates in RMS have failed to show significant differences in disability progression. The application has not provided sufficient evidence to conclude that disability progression events in RMS relate closely enough to PPMS events to provide confirmatory evidence that supports the PPMS trial.

Risk Benefit Summary and Conclusion

For relapsing forms of MS (RMS), two adequate and well-controlled trials provide substantial evidence that ocrelizumab reduces the rate of relapses and confirmed disability progression events.

For primary progressive form of MS (PPMS), the application does **not** provide substantial evidence of safety and effectiveness. There was only one efficacy trial. *The trial results count events that may not have occurred, are inconsistent among important subgroups, and lack independent confirmation.* In addition, there are reasons to suspect the quality of the data an, in women, there is no evidence of beneficial effect to balance the potential risk of breast cancer.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Relapsing multiple sclerosis is a chronic and potentially disabling brain disease of unknown etiology characterized by intermittent episodes of focal neurological deficit and scattered lesions of demyelination in the brain. The usual age of onset of RMS is 20 to 50 years. Symptoms include relapsing episodes of diminished sensory or motor function that can be disabling and usually resolve within one month. Over several years, many, but not all, RMS patients experience some degree of persistent disability that may gradually worsen over years. The course varies widely. Some patients have a relatively benign course; others become severely disabled after only a few years. There are no reliable predictors of long-term outcome. • PPMS is generally considered a distinct disease subtype of MS characterized by steady progression of disability without relapses from first onset. Treatments that have a robust benefit in RMS have been ineffective in trials of patients with PPMS and secondary disability progression without relapses. There are a number of clinical and pathological studies that suggest the inflammatory processes in RMS and PPMS are different; however, scientists have not identified the underlying pathophysiology that causes the episodes of disability progression in PPMS patients.	PPMS and RMS are disabling disease subtypes of MS. There is clinical and pathologic evidence that the inflammatory processes involved in RMS and PPMS differ. Several drugs approved for treatment of RMS and tested in PPMS patients have not been effective.
Current Treatment Options	• Twelve different drugs are FDA-approved to treat relapsing forms of multiple sclerosis. Four of the 11 are interferon-β1(a or b) products. All of the drugs reduce relapse rates. The mechanism of action is unknown for all of these approved drugs.	For relapsing MS, the unmet need is a drug or drug combination that prevents long-term disability better than available treatments and does so with fewer adverse effects. Ocrelizumab does not meet an

	• There are no FDA-approved drugs for PPMS; however, FDA has approved mitoxantrone for secondary progressive (SPMS) and relapsing progressive MS. • The major uncertainties are the subjectivity of the clinical outcomes, relapse and disability progression, different operational definitions of the outcomes, and the fact that most of the drugs approved for MS have frequent characteristic side effects that make effective blinding difficult. In some trials, dropout rates are high. Bias may explain some portion of the effects observed in the trials. • Labels for 11 of 12 FDA-approved MS drugs report disability progression outcomes. In some of these labels, all the disability outcomes are not statistically significant but all except the Copaxone and Novantrone labels contain at least one trial that showed a statistically significant effect (p-value less than 0.05) for a disability progression outcome at two years.	unmet need for relapsing forms of MS because there are so many other FDA-approve drugs that meet the same need. None of the approved drugs for relapsing MS prevents the occurrence of relapses or stops progression of disability. For PPMS, the unmet need is a drug that slows progression of disability.
Benefit	• In patients with RMS, there is evidence from two clinical trials that ocrelizumab reduces the frequency of relapses and reduces the frequency but not the duration of short-term periods of disability. • In patients with PPMS the results of one trial are unconvincing. As it is, the results are not substantial. They count events that may not have occurred and are inconsistent across important subgroups. The results show a reduction in the frequency of periods of short-term disability lasting 12 and 24 weeks with a p-value of 0.03 using imputed values. The statistical significance is lost without imputation (p=0.15). Evidence of a reduction of short-term disability in RMS patients does not confirm a claim that there is a benefit in PPMS because the	The two RMS trials provide substantial evidence that ocrelizumab will reduce the relapse rate and reduce the number of confirmed disability progression events in patients with RMS. PPMS trial results do not provide substantial evidence to support a claim that ocrelizumab is safe and effective in PPMS. The PMS trial does not meet the same evidentiary standards met by two RMS trials. For example, a different definition

	populations differ in disease characteristics and in the duration of disability progression events. In women, the PPMS trial results show a slight numerical benefit for placebo (35.5% had CDP events for placebo, 36.0% for ocrelizumab, the hazard ratio is 0.94).[1] In all patients, the slope of the Kaplan-Meier curve is the same from week 18 to week 120, which is consistent with the conclusion that ocrelizumab had no effect on the CDP event rate for a two-year period. The PPMS trial used a definition of the primary outcome that included imputation of events in patients who dropped out of the trial before confirmation of potential events. Imputation for this outcome event is unusual in MS trials. A pre-specified sensitivity test that corrects for this bias shows the p-value for CDP events is 0.1477 instead of 0.032. Investigators randomized many more patients than specified in the protocol. This change affects the primary outcome. The trial would have been negative without inclusion of these subjects. For these reasons and the lack of statistical significance when the primary endpoint did not use imputation, the PPMS trial is not adequate or well controlled. • Trial data show differences between PPMS and RMS that are consistent with medical reports of underlying differences in the inflammatory processes. There is not a sufficiently high degree of relatedness of CDP events in PPMS to those in RMS for the results of the two RMS trials to confirm the weak evidence of benefit in the one PPMS trial. Clinical data quality issues include a 20% or greater dropout rate and poor	of the primary outcome variable, a lack of confirmatory evidence, and an apparent lack of treatment effect in women in general and, for all patients, for a period of two years beginning after the first 18 months of treatment.

[1] Page 49 of 53 in Dr. Yan's review.

	investigator compliance with requirements to record the baseline EDSS prior to randomization and treatment. In 67% of the patients in the trial, baseline investigators recorded EDSS scores after randomization, and, in 20%, after infusion of the first dose of the study drug.	
Risk	**Infusion-related reactions** (IRRs) occurred in 35% of patients in MS trials despite the requirement for prophylactic pretreatment. The IRRs occurred most frequently after the first dose but continued to occur with subsequent infusions. Most of the IRRs were mild and occurred during the infusion period. Some occurred after the patient had left the clinic. **Non-serious infections** occurred more often with ocrelizumab than with placebo or active comparator, but serious infections were less frequent with ocrelizumab. Opportunistic infections were not identified in MS patients treated with ocrelizumab. **Malignancies** occurred three times as often with ocrelizumab than with placebo or active comparator. Six patients taking ocrelizumab developed breast cancer versus none in the control groups. Four of the six breast cancers occurred in the PPMS trial. **Depression** and suicide attempt adverse events occurred only in ocrelizumab patients and not in comparator patients in the MS controlled trials. Although depression adverse events occurred less frequently in ocrelizumab-treated patients than placebo in the PPMS controlled trial, they occurred slightly more frequently than with interferon (8% vs 7%) in the two RMS trials.	Safety data indicates that infusion reactions, infections, malignancies, and depression are significant concerns that warrant inclusion in the list of adverse reactions in labeling.

Risk Management	• Labeling can sufficiently to control the identified safety risks.	A Risk Evaluation and Management Strategy is not necessary to ensure that the benefits of ocrelizumab outweigh the risks of infusion related reactions, infections, and malignancy.

APPEARS THIS WAY ON ORIGINAL

2. Background

Document Purpose

The task for this secondary review is to consolidate the reviews from the different disciplines and make recommendations for approval and labeling.

Application Background

Genentech seeks approval for ocrelizumab to treat relapsing forms of multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS). At a pre-BLA meeting, DNP advised Genentech to submit a single application for both indications. DNP granted breakthrough designation because the topline results of a single trial in PPMS are statistically significant and there are no FDA-approved drugs to treat PPMS.

Review Issues

Of most concern to the review team are drug product potency and stability, the incidence of malignancies, and the weakness of the evidence to support the claim that, for PPMS, ocrelizumab reduces the number of episodes of increased disability lasting 12 weeks or longer.

At the time of this review, the Office of Biologic Products (OBP) is awaiting information that will determine whether the applicant can manufacture a drug product with sufficient potency and stability. The safety reviewers have decided that labeling and a required study of cancer incidence after approval will alleviate their concerns about malignancy.

As the review of efficacy proceeded, the review team identified unexpected weaknesses in the evidence provided in the application to support the PPMS indication. The *primary clinical reviewer* states that, for PPMS, there is "significant uncertainty as to the benefit of treatment with OCR 600 for PPMS."[2] He also does not agree with the applicant that the evidence in the application about disability progression in the RMS trials is sufficient to support the weak evidence provided by the one PPMS trial. Nevertheless, he recommends approval for PPMS because there is an unmet need for a drug to treat PPMS.

The *statistical reviewer* offers no opinion on whether evidence from the two RMS trials is sufficient to support the PPMS results. She concludes "Study WA25046 provided data that were indicative of efficacy in the treatment of ocrelizumab in delaying the disability

[2] Dr. Rodichok's review, page 18 of 194

progression in patients with PPMS. The evidence of the effectiveness was weakened by the failure of the study to withstand an important sensitivity analysis on un-imputed data, which is commonly used as the standard primary data for disability progression endpoint."[3] She states the use of imputed data in the PPMS trials is a possible *source of bias* in the primary analysis.[4] Analysis of disability progression in the RMS trials did not use imputation. She also mentions that ocrelizumab had no treatment benefit numerically or statistically among female patients and identifies weaknesses in the analysis of the Timed 25-Foot Walk Test, a secondary clinical outcome.

Because of the concerns about the PPMS trial WA25046 results and the lack of a second confirming trial in PPMS, this review explores several paths to identify sufficient evidence from the trials in RMS to support the inclusion of the PPMS indication in the ocrelizumab label. See **Structured evaluation of evidence in the application to support the PPMS indication**, page 40, below. The conclusion is that there is not sufficient evidence. In agreement with the primary clinical reviewer, *this review has determined that the RMS trial results do not provide sufficient confirmation of the single trial because the relationship between progression in RMS and PPMS is weak and because drugs that reduce disability progression in RMS have shown no significant effect in trials testing them in PPMS.*

Disease Background for RMS and PPMS

Relapsing multiple sclerosis (RMS) is a chronic and potentially disabling brain disease of unknown etiology characterized by intermittent episodes of focal neurological deficit and scattered lesions of demyelination in the brain. The usual age of onset of RMS is 20 to 50 years. Symptoms include relapsing episodes of diminished sensory or motor function that can be disabling and usually resolve within one month. Over several years, many, but not all, RMS patients experience some degree of persistent disability that may gradually worsen over years. The course varies widely. Some patients have a relatively benign course; others become severely disabled after only a few years. There are no reliable predictors of long-term outcome.

Twelve different drugs are FDA-approved to prevent relapses in RMS.[5] Four of the 12 are interferon β-1a or 1b products. All of the drugs reduce relapse rates. In general, evidence of an effect on disability progression during the two-year exposure in most

[3] Dr. Yan, page 54 of 55.
[4] Dr. Yan, page 52 of 55.
[5] Betaseron, Avonex, Copaxone, Novantrone, Rebif, Tysabri, Gilenya, Aubagio, Tecfidera, Plegridy, Lemtrada, and Zimbryta. Extavia is Betaseron under another name and Glatopa is a generic form of Copaxone.

RMS trials is weaker than the evidence of a reduction in relapse rate. The evidence in RMS drug labels for a reduction in disability progression shows smaller effect sizes and lacks confirmation in a second trial for some drugs.

Primary progressive multiple sclerosis (PPMS) is a distinct clinical subtype of MS characterized by steady progression of disability without relapses from onset of symptoms. Data from clinical trials support the likelihood that the disease mechanisms for RMS are different than those for PPMS. Treatments that have a robust benefit in RMS have been ineffective in trials of patients with PPMS and secondary disability progression without relapses. A number of clinical and pathological studies suggest the inflammatory processes in RMS and PPMS are different. However, scientists have not identified the underlying pathophysiology that causes the episodes of disability progression in PPMS patients and the relationship between disease progression in RMS and PPMS. Therefore, the links between the two forms of the disease remain the subject of ongoing research.

FDA has approved no drugs specific for PPMS; however, FDA has approved mitoxantrone for secondary progressive (SPMS) and relapsing progressive MS.

Labels for 11 of 12 FDA-approved RMS drugs report disability progression outcomes in clinical trials. In some of these labels, all the disability outcomes are not statistically significant but all labels describe at least one trial that showed a statistically significant effect (p-value less than 0.05) at two years except the Copaxone and Novantrone labels.

Reference to subcutaneous interferon β-1a as Rebif

For brevity and specificity, this review and the proposed prescribing information use the trade name for Rebif, the specific product used as an active control in the relapsing multiple sclerosis trials WA21092 and WA21093 because interferon β-1a is the drug substance in several different approved drug products with different formulations, doses, and routes of administration for RMS.

3. Product Quality

At this time, the product quality team review is not final. The team has identified serious concerns with drug product stability and potency at the time of the filing meeting. The team sent information requests to the applicant and made a site visit in order to resolve these problems. They received responses to all their information requests. They have found no satisfactory resolution to the drug substance manufacturing and potency issues. One of the issues is degradation of one of the drug product excipients (polysorbate 20) and drug product stability. At the 18 month time point, all three batches contain visible particles, which Genentech indicates are

composed of free fatty acid (a polysorbate breakdown product). The other issue is variable potency among different drug lots.

4. Nonclinical Pharmacology/Toxicology

Barbara Wilcox, Ph.D., performed the primary nonclinical review. She concluded that ocrelizumab is not approvable because, at the time of her review, she could not confirm that the product used in the reproductive toxicology studies is comparable to the product used in the pivotal clinical studies and to the product intended for market. If the products are not comparable, then the applicant may need to repeat some of the nonclinical studies.

5. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review team is Jagan Parepally, primary reviewer, Angela Men, M.D., Ph.D., Xiaofeng Wang, Ph.D., Kevin Krudys, Ph.D., and Mehul Mehta, Ph.D. The team recommends approval from a clinical pharmacology perspective. They also agree the dose used in the RMS trials (divided first dose as two 300mg infusions 2 weeks apart then 600mg as one infusion every 6 months) would also be effective for PPMS even though the PPMS trial divided all the doses into two 300mg infusions separated by two weeks.

Ocrelizumab is a recombinant humanized monoclonal antibody to the CD20 cell surface antigen found on B-lymphocytes. Ocrelizumab causes B-cell depletion within 14 days of treatment without apparent loss of humoral immunity.

The mechanism of the therapeutic clinical effect is unknown.

General clinical pharmacology: absorption
Ocrelizumab is for intravenous infusion. The dose is 600mg by intravenous infusion every 6 months. The first dose is split: two 300mg intravenous infusions two weeks apart. Subsequent doses are single infusions of 600mg.

General clinical pharmacology: distribution
The estimated volume of distribution for the central compartment is 2.78 liters. Peripheral volume and inter-compartment clearance is 2.68 liters and 0.294 liters per day, respectively by population pharmacokinetics.

Pathway of elimination, half-life, and excretion
The initial time-dependent clearance is 0.0489 liters per day, which declines with a half-life of 33 weeks. The terminal elimination half-life is 26 days.

Factors potentially affecting elimination: age, gender, hepatic impairment, and renal impairment.

The OCP review team recommends no dose adjustments for intrinsic or extrinsic factors, including body weight.

Drug-drug interactions

The clinical pharmacology review team does not anticipate any drug-drug interactions because ocrelizumab is a monoclonal antibody.

Immunogenicity

Out of 1311 patients treated with ocrelizumab, 12 tested positive for treatment-emergent anti-drug antibodies (ADAs). Two patients developed neutralizing ADAs. The OCP team found no effect on safety or efficacy in patients who developed ADAs during treatment.

6. Clinical and Statistical Reviews of Efficacy

This BLA submission requests labeling for two indications:

Relapsing forms of multiple sclerosis (RMS)
Primary progressive multiple sclerosis (PPMS)

The submission provides evidence from **two clinical trials** (WA21092 and WA21093) to support the safety and effectiveness of ocrelizumab in patients with the *relapsing forms of MS* and **one clinical trial** (WA25046) in patients with *primary progressive multiple sclerosis*.

Larry Rodichok, M.D., performed the primary clinical review of efficacy for this BLA application. He concludes that there is convincing evidence that ocrelizumab reduces the relapse rate in patients with RMS compared to Rebif but that there is significant uncertainty that ocrelizumab slows disability progression for PPMS because of weaknesses in the results of the single trial and a lack of sufficient confirmatory evidence from other trials. He concludes that despite uncertain results of the PPMS trial and the lack of confirmatory evidence, the unmet need for an effective treatment for PPMS warrants approval for the PPMS indication. In his clinical review, Dr. Rodichok presents his own analysis of important outcomes. He found no significant discrepancies between his own analyses and those of the sponsor.

The statistical reviewer, Sharon Yan, Ph.D., concludes that for RMS, the data from two trials show similar and consistent efficacy results including results on the annualized relapsing rate and confirmed disability progression. She identified no major issues with the efficacy results.[6]

In contrast, Dr. Yan states that the one PPMS trial in the application Study WA25046 provided data that were "indicative of efficacy in the treatment of ocrelizumab in delaying the disability progression in patients with PPMS. The evidence of the effectiveness was weakened by the failure of the study to withstand an important sensitivity analysis using only un-imputed data… ." This sensitivity analysis is the analysis commonly used as the standard primary analysis for disability progression endpoint.[7] She states that the applicant's primary analysis with imputed events might have contributed bias in favor of the ocrelizumab group in determining the treatment difference and its significance.

This review agrees with Drs. Yan and Rodichok that there is substantial evidence to support approval for the treatment of RMS. After consideration of the standards of evidence required for approval and the extent of **flexibility** that is available under regulations and public guidance documents, this review finds the evidence in the application insufficient to support the indication for PPMS. The results of the single trial submitted as substantial evidence show a statistically significant but clinically small benefit that does not withstand a critical sensitivity test. Using the analysis methods for confirmed disability progression (CDP) events used for the two RMS trials, the results of the PPMS trial are not statistically significant. Weaknesses in the results, conduct, and design preclude the single trial from providing substantial evidence of effectiveness.

For confirmatory evidence, the applicant offers the results of the two RMS trials where ocrelizumab reduces disability progression. The rationale the applicant provides does not describe a high degree of relatedness between disability progression in RMS and disability progression in PPMS. The relationship between PPMS and RMS has not been resolved scientifically and there have been several trials of drugs effective for RMS that showed no significant effect in PPMS. A detailed discussion about the relationship between disability progression in the two forms of MS is presented below.[8] In addition, the PPMS trial results are confounded by an absence of an effect in women (those on

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[6] Dr. Yan's review, page 52 of 55.

[7] Dr. Yan's review page 54 of 55.

[8] See **Structured evaluation of evidence in the application to support the PPMS indication**, page 39, Structured evaluation of evidence in the application to support the PPMS indication.

ocrelizumab had slightly more CDP events those on placebo) and the absence of an effect on the CDP event rate for a two-year period that begins 18 months after the start of treatment.

The summaries of reviews for RMS and PPMS are in separate sections below. Each of the two sections describes pertinent features of the trial designs, presents trial results as reported by the sponsor, and then describes uncertainties in the evidence.

RMS Trials: Design

The two RMS trials, WA21092 and WA21093, have the same clinical protocols. Both trials are 1:1 randomized, 96-week, double-blind, double-dummy, parallel-group, active controlled, Phase III studies with planned sample sizes of 800 patients each, 400 in each of two arms. The primary outcome measure is the number of relapses per year of treatment. The active control is Rebif, an FDA-approved treatment for RMS. The protocols have a double-dummy design because of different routes of administration: patients self-inject Rebif subcutaneously three times per week and receive ocrelizumab 600mg by intravenous infusion every six months.

The patient selection criteria are similar to those of other trials that have supported approval of 12 other drugs for the treatment of RMS. On entry to the studies, patients were in good general health and had experienced at least either two clinically apparent relapses within 2 years or one within 1 year prior to screening. For selection, investigators did not count relapses that occurred less than 30 days before the screening examination.

The protocol scheduled Expanded Disability Status Score (EDSS) ratings every 12 weeks, MRI scans at baseline, 24, 48, and 96 weeks, and Karnofsky disability scores at baseline and 96 weeks. Both trials use the same definitions of relapse and 12-week disability progression, which are the major clinical events used to determine efficacy. If an EDSS rating indicated a possible disability progression event but the patient dropped out before the event was confirmed 12 or 24 weeks later, the statistical analysis did not impute a confirmed disability progression event (CDP). (Note: the analysis of the PPMS trial did impute CDP events when patients dropped out before they provided a confirmatory EDSS score.)

RMS Trials: Results

RMS Trials: Study Population

Baseline characteristics for Trials 20192 and 20193 are side by side in Table 1 for comparison. The two trials randomized populations with similar baseline EDSS, number of enhancing lesions at baseline, and number of relapses in the year prior to

randomization. See Table 1, below. For all of the baseline variables, there are no apparent differences between treatment arms for both trials.

Table 1 Summary of Baseline Characteristics for RMS Trials 21092 and 21093

Trial 20192 and 20193 Summary Table of Baseline Characteristics[9]				
Baseline Characteristic	Trial 21092		Trial 21093	
	Rebif	Ocrelizumab	Rebif	Ocrelizumab
N	411	410	418	417
Age (Years)	36.9	37.1	37.4	37.2
Proportion Age less than 40	59%	59%	57.7	60.4
Proportion Female	66%	66%	67%	65%
Weight (kg)	75.9	74.6	75.0	75.8
BMI	26.4	25.9	26.3	26.4
Mean Years Since MS Onset	6.25	6.74	6.68	6.72
Mean Years Since RMS diagnosis	3.71	3.82	4.13	4.15
Prior MS Treatment (%)	29.0%[10]	26.6%	25.12%	27.34%
Mean Enhancing lesions at baseline	1.87	1.69	1.95	1.82
Volume of T2 lesions (cm^3)	9.74	10.84	10.61	10.73
EDSS Mean	2.75	2.86	2.84	2.78
EDSS Max	6	6	6	6
EDSS Median	2.5	2.5	3.0	2.5
EDSS progression per year[11]	0.440	0.371	0.426	0.414
Proportion from US Center	25.5%	25.6%	27.3%	26.9%

Study Completion. In both trials, the dropout rate at 96 weeks was higher in the Rebif group (17.3% versus 10.7% and 23.4% versus 13.7%, for Rebif and ocrelizumab, respectively). See Table 2, below.

Table 2 96-Week Completion Rate in Two RMS Trials

96-Week Completion Rate in Two RMS Trials				
	Trial 21092[12]		Trial 21093[13]	
	Rebif	Ocrelizumab	Rebif	Ocrelizumab
Subjects Randomized	411	410	418	417

[9] 20160908-resp-req-info.pdf, Tables 25-32, page 93-102 of 108

[10] From table ADSL for 21092 and 21093 by CDTL

[11] Calculated by CDTL: (mean EDSS at baseline)/(mean years since onset of MS)

[12] Csr-wa21092.pdf, page 93 of 6491

[13] Csr-wa21092.pdf, page 92 of 6798

96-Week Completion Rate in Two RMS Trials				
	Trial 21092[12]		Trial 21093[13]	
	Rebif	Ocrelizumab	Rebif	Ocrelizumab
Dropped Out	71	44	98	57
Completed	340	366	320	360
Completion Rate[14]	82.7%	89.3%	76.6%	86.3%
Dropout Rate[14]	17.3%	10.7%	23.4%	13.7%
Difference in completion rate[14]	6.6%		9.7%	

RMS Trials: Primary outcome

Table 3, below, summarizes the sponsor's primary clinical efficacy results for Trials 21092 and 21093. Both trials show a statistically significant reduction in the annualized relapse rate (ARR) in patients with relapsing MS.

Table 3 Primary Outcome for RMS Trials -- Annualized Relapse Rate

Primary Outcome for Relapsing MS Trials[15] Annualized Relapse Rate (ARR)				
Trial	WA21092		WA21093	
Treatment Arm	Rebif	Ocrelizumab	Rebif	Ocrelizumab
ITT (n)				
Modified ITT (n)	411	410	418	417
Total number of relapses	166	96	168	98
Total patient years followed	678.1	706.3	661.0	709.5
Unadjusted ARR	0.245	0.136	0.254	0.138
Adjusted ARR*	0.292	0.156	0.290	0.155
(95% CI)**	(0.235, 0.361)	(0.122, 0.200)	(0.234, 0.361)	(0.121, 0.198)
Adjusted rate ratio		0.536		0.532
(95% CI)		(0.400, 0.719)		(0.397, 0.714)
Risk Reduction		46.4%		46.8%
p-value		< 0.0001		< 0.0001

*Adjusted for baseline EDSS score, below 4 or higher, and geographical region, US or outside US.

The results are similar to the parameters used for the sample size calculation: ARR at 96 weeks 0.165 (standard deviation 0.60) for ocrelizumab and 0.33 (0.80) for Rebif with a relative reduction of 50% with a 20% dropout rate.

[14] Calculated by CDTL.

[15] summary-clin-efficacy-iii.pdf, Table 20, page 74 of 173

RMS Trials: Secondary Outcomes

Table 4, below, shows the results of pre-specified secondary analyses in the hierarchical order of the analysis.

The evidence for ocrelizumab's effect on **disability** in the two RMS trials is a secondary outcome. The pre-specified analysis for confirmed disability progression at 12 weeks was the pooled analysis of outcome events from the two trials. The table shows the independent results from each trial because the analyses for both trials showed statistical significance when analyzed separately. The p-value for the pooled analysis of disability progression confirmed at 12 weeks is 0.0006, the hazard ratio is 0.60, the absolute difference is 5.4% (15.2% compared to 9.8%), and the NNT is 18.4. For disability confirmed at 24 weeks, the pooled analysis p-value is 0.0025, the risk ratio is 0.60, the absolute difference is 4.5%, and the NNT is 22.5. Figure 1 is a survival curve showing the proportion with confirmed disability progression lasting at least 12 weeks. In his review, Dr. Rodichok notes that in the RMS population about 75% to 80% of periods of "confirmed disability progression" no longer meet the criteria over the course of a two year trial, regardless of treatment.[16] In other words, in RMS patients confirmed disability progression events do not represent permanent disability in most cases.

All of the secondary outcomes are closely related. There are three basic domains covered: clinical, MRI, and patient-reported. The relapse rate, the mean EDSS at 96 weeks, and the confirmed disability progression all rely on the same EDSS scores. The MRI outcomes are closely related. A positive finding with one of the different scan types is associated with positive findings in the other MRI outcomes.

[16] Dr Rodichok's review, page 122 of 194.

Table 4 Trial 21092 and 21093 Secondary Outcomes

RMS All Ten Secondary Outcomes for Trials 21092 and 21093[17]						
Hierarchy of Ten Secondary Outcomes 96-week double-blind epoch	Rebif	Ocrelizumab 600	p-value	Rate Ratio (Ocr/Rebif)	Absolute Difference[18]	NNT[18]
	Trial 21092 Result Trial 21093 Result					
1. Disability progression lasting 12 weeks[19,20]	12.2% 17.5%	7.6% 11.1%	0.0139 0.0169	0.57 0.63	4.6% 6.4%	21.7 15.6
2. T1 Gd-enhancing lesions per scan	0.286 0.416	0.016 0.021	0.0001 0.0001	0.058 0.051		
3. New or enlarging T2 hyperintense lesions per scan	1.413 1.904	0.323 0.325	0.0001 0.0001	0.23 0.17		
4. Disability improvement lasting 12 weeks	12.42% 18.83%	20.0% 21.38%	0.0106 0.0370	1.61 1.14	7.6% 2.55%	13.2 39.2
5. Disability progression lasting 24 weeks	10.57% 13.63%	6.51% 8.60%	0.0278 0.0370	0.57 0.63	4.1% 5.0%	24.4 20.0
6. New T1–hypo-intense lesions per scan	0.982 1.255	0.420 0.449	.0001 .0001	0.428 0.357		
7. Mean MSFC	0.174 0.169	0.213 0.276	0.3261 0.0040			
8. % change in brain volume from week 24	-0.74% -0.75%	-0.57% -0.64%	[0.0042][21] 0.0900	0.77 0.85		
9. Change in SF36 PCS	-0.657 -0.833	0.036 0.326	[0.2193] [0.0404]			
10. No evidence of disease activity[22]	27.1% 24.1%	47.4% 43.9%	[0.0001] [0.0001]	1.74 1.81	20.3% 19.8%	4.9 5.0

[17] Data extracted from clinical-overview.pdf, pages 60-61 of 144; hierarchical order from csr-wa21092.pdf statistical analysis plan pages 4978-79 of 6491

[18] Number needed to treat estimated by CDTL

[19] No imputation performed

[20] The pre-specified outcome is for the pooled disability data for both trials.

[21] Nominal statistical significance only due to p-value greater than 0.05 for seventh outcome in hierarchy (MSFC)

[22] No evidence of disease activity "if no protocol defined relapse, no CDP event, and no 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." Number of subjects estimated by CTDL

Figure 1 Kaplan-Meier Plot of Time to Onset of Confirmed Disability Progression Sustained for at Least 12 weeks, Pooled Analysis of Studies WA21092 and WA21093)[23]

Relevant to the discussion of disability progression for the PPMS indication, this review points out that **the difference in disability progression between the two treatments increases steadily with time** in Figure 1. The two survival curves separate.

RMS Trials: Exploratory Outcomes

The protocol for Trials 21092 lists 19 possible exploratory outcomes. See Table 5, below. Table 6, below, shows the proportion of patients relapse-free and changes in the EDSS and the Karnofsky Performance scores. Dr. Rodichok found that both of these disability scales had similar baseline values and both did not change significantly by week 96. In addition, this review notes that the rate of progression in EDSS score during the 96 weeks in the trial was less than the rate of progression estimated using the number of prior relapses and years since diagnosis at baseline (Table 1, above).

[23] Copied from applicant's clinical-overview.pdf, page 65 of 144.

Table 5 List of Exploratory Outcomes

RMS Exploratory Outcomes[24]
1. % relapse-free
2. Δ[25] T2 hyperintense lesion volume
3. ARR for all[26] relapses
4. ARR requiring IV steroid
5. ARR of severe relapses
6. % change in brain volume
7. Δ timed 25-foot walk
8. Δ 9-hole peg test
9. Δ MFIS[27]
10. Δ depression symptoms
11. Δ Karnofsky Scale
12. % change cortical gray matter volume
13. % change white matter volume
14. % with 24-week CDP
15. % with 12-week CDI
16. Disability improvement duration
17. % improved, stable, or worsened
18. Δ EDSS
19. Δ Mental Component of SF-36

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[24] csr-wa21092.pdf, page 4965 of 6491
[25] Δ = change in
[26] confirmed and unconfirmed
[27] Modified Fatigue Impact Scale

Table 6 Trial 21092 and 21093 Selected Exploratory Outcome Results

Selected Exploratory Outcomes for RMS Trials 21092 and 21093[28]				
Hierarchy of Ten Secondary Outcomes 96-week double-blind epoch	Rebif	Ocrelizumab 600	Rate Ratio (Ocr/Rebif)	Absolute Difference[29]
	Trial 21092 Result Trial 21093 Result			
1. % Relapse Free[30]	68.5% 68.4%	81.6% 81.2%	1.19 1.19	13.1% 12.8%
2. Change in EDSS[31] {0-10]	0.026 0.047	-0.145 -0.145	-5.75 -3.08	
3. Change in Karnofsky Performance Status[32] [0-100]	-2.498 -2.438	-0.521 -0.672	0.21 0.28	

Annualized Relapse Rate (ARR) in Patient Subgroups

For all subgroups analyzed, the applicant reports that the point estimates of the annualized relapse rate in the application in both trials are similar and favor ocrelizumab (see Figure 2). Dr. Rodichok and Dr. Yan agree. Dr. Yan reports that she found no large discrepancies in efficacy among the subgroups. She mentions that high body mass index (BMI) might have a negative effect on the overall efficacy. OCP review found no reason to adjust dose by body weight (see Clinical Pharmacology, above).

[28] Data extracted from clinical-overview.pdf, pages 60-61 of 144; hierarchical order from csr-wa21092.pdf statistical analysis plan pages 4978-79 of 6491

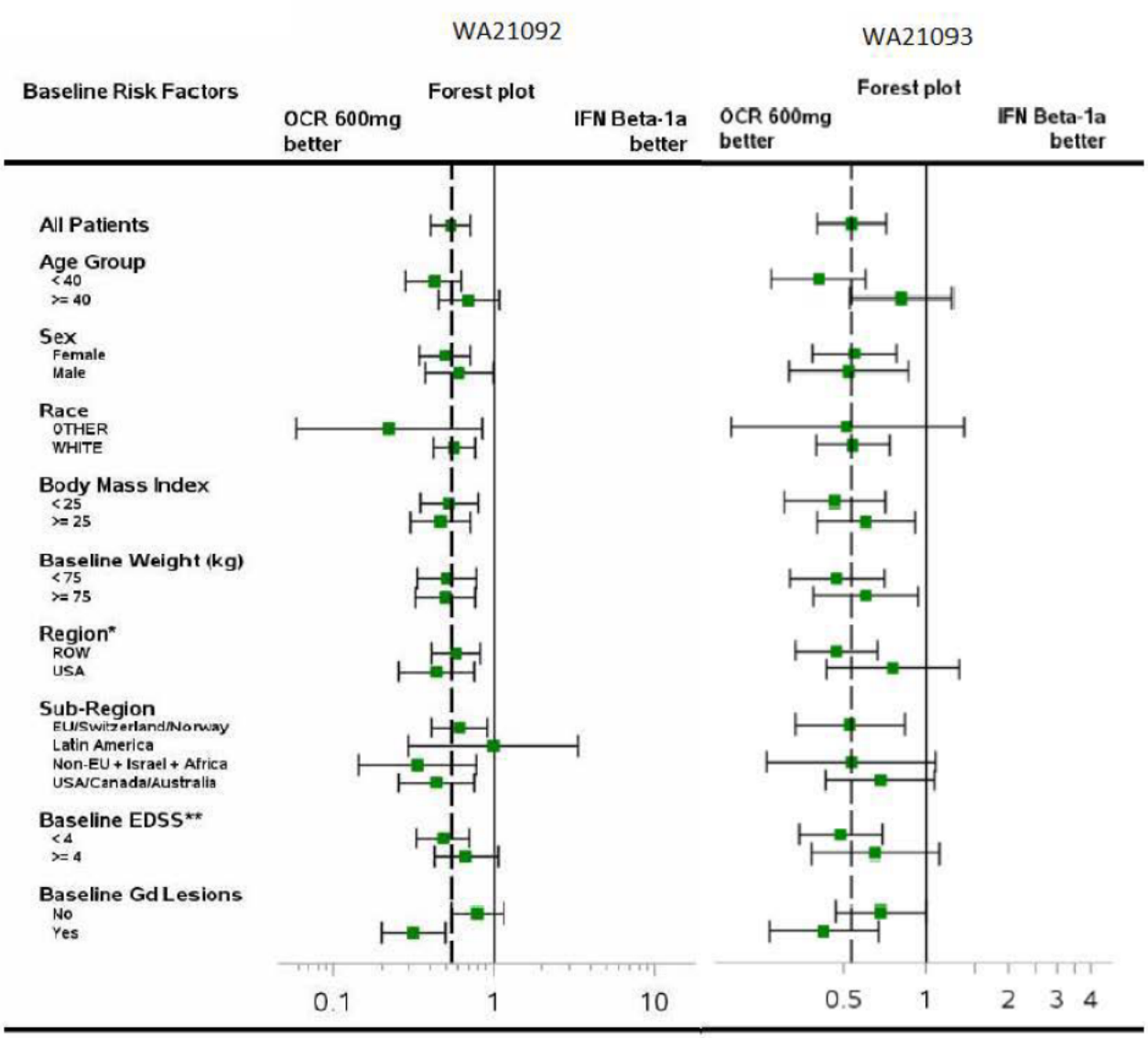
[29] Number needed to treat estimated by CDTL

[30] Csr-wa21092.pdf, pages 116 and 910 of 6491; csr-wa21093.pdf, pages 147 and 935 of 6798. Applicant's analysis assumed patients who dropped out for an outcome reason had a relapse.

[31] Csr-wa21092.pdf, pages 148 and 996 of 6491; csr-wa21093.pdf, pages 147 and 1022 of 6798

[32] Csr-wa21093.pdf, pages 147 and 989 of 6491; csr-wa21093.pdf, pages 146 and 1015 of 6798

Figure 2 ARR in Subpopulations in Trials WA21092 and WA21093[33]



[33] Adapted from Figure 4, csr-wa21092.pdf, page 115 of 6491 and csr-wa21093.pdf, page 114 of 6798

Table 7 Rate Ratios for the Annualized Relapse Rate in RMS Trials

Rate Ratios for ARR in Two RMS Trials Ocrelizumab to Rebif		
	WA21092	**WA21093**
Age Group		
< 40	0.423	0.403
≥ 40	0.692	0.808
Sex		
Female	0.498	0.547
Male	0.607	0.520
Region		
Non-US	0.579	0.470
US	0.435	0.754
Baseline EDSS Score		
< 4	0.480	0.485
≥ 4	0.669	0.652
Baseline BMI		
< 25	0.527	0.463
≥ 25	0.463	0.602

Significant Review Issues in RMS Trial Design, Conduct, or Analysis

Compared to those in previous MS trials, the protocols for the two RMS trials included significant refinements to the processes for determining when relapse and disability progression events occurred. These procedures did nothing to reduce the extent of any unblinding but did *limit the effects of any unblinding of patients or treating physicians* on clinical outcomes. There were monthly telephone interviews with patients between scheduled visits that are likely to have decreased the number of unreported events. An electronic system collected EDSS scores directly from raters and limited their access to previous EDSS scores. The primary analyses used a true intent-to-treat analysis on all randomized patients.[34] A data-driven computer algorithm defined relapse events in a manner that relied less on the clinical judgment of treating physicians than the methods in many other RMS trials.

In his clinical review, Dr. Rodichok identifies a number of uncertainties related to the design, conduct, and analysis of the two clinical trials.

There is likely to have been **unblinding of patients and treating physicians**. The side effects of Rebif are quite common and, when present, specific to the treatment. Infusion reactions in patients assigned to ocrelizumab are also informative. In addition, there is

[34] Csr-wa21092.pdf, Statistical Analysis Plan, page 4968 of 6491.

evidence that some patients in MS trials discuss methods of unblinding.[35] Despite the refinements in the process to determine relapse events mentioned above, patients and treating physicians, who may have been unblinded by side effects, still made the most significant decisions required to determine if a relapse event occurred. Blinding the EDSS raters does not reduce the chances that knowledge of treatment group by patients and treating physicians affects the clinical outcomes.

The **dropout rates** were as low as 10% and as high as 23% in the 4 arms of the 2 trials. In each trial, there were more dropouts in the Rebif group (6% and 9% for trial 21092 and 21093, respectively; see Table 2). The ratio of the dropout rate to the absolute difference in the proportion of patients free of relapse at 96 weeks in the 4 arms of the trials ranged from approximately 1.8 to 0.8. These ratios indicate that the information lost because of dropout introduces a moderate amount of uncertainty about the trial results. In other words, unknown events that would have occurred in patients who dropped out could have produced a moderate change in the results. There is more uncertainty in the Rebif arms of the trial because of the higher dropout rates. The difference between treatment arms indicates the dropout may have been due, in some degree, to decisions informed by knowledge of treatment arm or post randomization events.

Efficacy Conclusion for the RMS Indication

In agreement with Drs. Rodichok and Yan, this review concludes that, despite concerns about dropout and bias due to treatment-disclosing side effects, evidence from two adequate and well-controlled trials supports the conclusion that ocrelizumab reduced the annualized relapse rate in patients with relapsing multiple sclerosis compared to Rebif. Ocrelizumab also reduced the proportion of patients who experienced episodes of disability progression lasting 12 weeks or longer, a secondary outcome.

Efficacy in Primary Progressive Multiple Sclerosis

The evidence to support the safety and efficacy of PPMS comes from a single trial, WA25046. The application refers to the results of the two trials in RMS as confirmatory evidence. This review describes the trial and the results as the applicant reported them.

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[35] Wall Street Journal, July 29, 2014, www.wsj.com/articles/researchers-fret-as-social-media-lift-veil-on-drug-trials-1406687404 and MS website for patients, www.thisisms.com/forum/introductions-f20/topic19069.html#p185386.

A discussion of uncertainties in the trial and the relatedness of the applicant's confirmatory evidence follow the description of the results.

PPMS Trial: Design

PPMS Trial WA25046 is a 2:1 randomized, event-driven, double-blind, double-dummy, parallel-group, placebo-controlled Phase III trial with a planned sample size 630 patients, 420 treated with ocrelizumab, 210 with placebo.

The date of the first version of the statistical analysis plan is December 20, 2013, [36] a year after randomization of the last patient on December 27, 2012, and 6 months after Version D of the protocol, dated June 15, 2012, came into effect.

The sample size determination assumed the two-year progression rate among PPMS patients receiving ocrelizumab is 30% compared with 43% among patients receiving placebo. A two-group test of equal exponential survival with exponential dropout defined the sample size for the time to CDP. With a 2:1 randomization ratio and a one-year accrual period with a 3.5 year maximum treatment period, the sample size of 630 patients would provide approximately 80% power allowing for a dropout rate of 20% over 2 years. For adequate power, there must be 253 disability events to detect the planned treatment difference.

The trial was to end 120 weeks after randomization of the last patient unless 253 disability progression events had not occurred. In that case, follow-up was to continue until 253 or more events would occur.

The primary outcome event is confirmed disability progression (CDP), an event defined by a computer algorithm using changes from baseline in the EDSS score to determine the start of the event and confirm the continuation of the event for 12 more weeks.[37] One exception is that if the patient drops out of the study after the initial worsening in EDSS and before the event duration is confirmed to continue at least 84 days, then the statistical analysis imputes a CDP. In her review, Dr. Yan comments that this imputation is not usual in MS trials.[38] For instance, the two ocrelizumab RMS trial analyses did not use imputation in the primary analysis. Blinded raters determined

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[36] csr-wa25046.pdf, page 5300 of 5131.

[37] "Disability progression is defined as an increase of ≥ 1.0 point from the baseline EDSS when the baseline score is 5.5 or less, and ≥ 0.5 when the baseline score is more than 5.5, that is not attributable to another etiology (e.g., fever, concurrent illness, or concomitant medication)." csr-wa25046.pdf, page 5164 of 5131.

[38] Dr. Yan's review page 53 of 55.

EDSS scores every three months and at unscheduled visits for patients with symptoms suggestive of MS worsening.

Selection criteria used McDonald criteria from 2005 to include patients with a year of disability progression since onset and two of a) brain MRI T2 lesions, or b) MRI spinal cord lesions, or c) CSF oligoclonal band. They excluded patients with a history of relapsing MS.[39]

PPMS Trial: Results

PPMS Trial: Study Population

The PPMS trial WA25046 randomized 732 patients, 244 to placebo, 488 to ocrelizumab, in 95 weeks between March 3, 2011, and December 27, 2012. The number of patients randomized is 102 patients more than the 630-patient sample size that the protocol specifies. The clinical cut-off date (CCOD) for the trial is July 24, 2015, which is 134 weeks after the trial randomized the last patient. The protocol specifies that the CCOD is 120 weeks after randomization of the last patient, which is April 16, 2015, unless 253 CDP events had not occurred. CCOD is 4 years and 143 days after randomization of the first patient. Database lock occurred on September 18, 2015, 56 days after the CCOD.[40]

Baseline Characteristics. Table 8, below, shows that randomization evenly balanced all the baseline characteristics among PPMS patients in Trial WA25046 **except** the mean number of gadolinium enhancing lesions (0.6 versus 1.2). Table 8 also highlights **differences in disease characteristics** between the RMS and PPMS populations. In PPMS, the proportion of women is 50% instead of 66%. In general, 6 years after disease onset, PPMS patients *compared to RMS patients* are 10 years older and have twice the EDSS score, half as many enhancing lesions on MRI, 50% less MRI T2 lesion volume, and twice the rate of progression after disease onset (0.7 EDSS points per year compared to 0.3 EDSS points per year). Compared to RMS patients, the T2 lesion count is similar, but the PPMS lesion volume is less and the baseline EDSS score is two full points greater. These differences are consistent with reports in the medical literature.

One quarter of the PPMS patients had prior treatment with drugs directed at MS. The trial randomized 75% of the patients outside the United States.

[39] csr-wa25046.pdf, page 4994 of 8131.
[40] csr-wa25046.pdf, page 81 of 8131.

Table 8 PPMS Trial WA25046 Baseline Characteristics Compared with RMS Trials

Baseline Characteristics PPMS Trial WA25046 Compared to Baseline RMS Trials 20192 and 20193						
Baseline Characteristic	Trial WA25046 - PPMS		Trial WA21092 - RMS		Trial WA21093 - RMS	
	Placebo	Ocrelizumab	Rebif	Ocrelizumab	Rebif	Ocrelizumab
N	244	488	411	410	418	417
Age (Years)	44.4	44.7	36.9	37.1	37.4	37.2
% Age less than 45 PPMS, 40-RMS	48%	47%	59%	59%	57.7	60.4
Proportion Female	50.8%	48.6%	66%	66%	67%	65%
Weight (kg)	72.81	72.46	75.9	74.6	75.0	75.8
BMI	25.03	24.84	26.4	25.9	26.3	26.4
Mean Years Since MS Onset	6.14	6.66	6.25	6.74	6.68	6.72
Mean Years Since MS diagnosis	2.75	2.85	3.71	3.82	4.13	4.15
Prior MS treatment	12.3%	11.3%	29.0%	26.6%	25.12%	27.34%
Proportion with GdE Lesions[41]	24.7%	27.5%	38.1%	42.5%	41.4%	39.0%
Mean Enhancing lesions at baseline	0.6	1.21	1.87	1.69	1.95	1.82
Volume of T2 lesions (cm^3)	6.17	7.31	9.74	10.84	10.61	10.73
Baseline mean T2 lesion count[42]	48.2	48.7	51.11	51.17	50.97	49.30
EDSS Mean	4.73	4.74	2.75	2.86	2.84	2.78
EDSS Max	6.5	7	6	6	6	6
EDSS Median	4.5	4.5	2.5	2.5	3.0	2.5
EDSS progression per year[43]	0.770	0.712	0.440	0.371	0.426	0.414
Proportion from US Centers	13.9%	13.7%	25.5%	25.6%	27.3%	26.9%
Different RMS and PPMS						
Different Placebo and Ocrelizumab						

Dr. Rodichok points out that there is an imbalance in the mean number of gadolinium-enhancing lesions at baseline in the PPMS trial with nearly 50% fewer in the placebo group (darker red highlighting in Table 8, above). If ocrelizumab is more effective when there is acute inflammation and if gadolinium-enhancing lesions indicate inflammation, then this imbalance introduces a bias that favors ocrelizumab.

This review notes that the mean number of T2 lesions at baseline in PPMS is very similar to that in RMS. However, the baseline EDSS is much higher in PPMS than RMS (4.7 versus 2.8), consistent with differences between PPMS and RMS observed in pathology studies--the lesions in PPMS cause more disability. The lower mean number of gadolinium enhancing lesions is also consistent with pathological differences between the diseases. See below 4(d) Relatedness: the medical literature

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[41] Csr-wa25046 page 91 of 8131, csr-wa21092 page 103, csr-was21093 page 102.
[42] Dr. Rodichok's review page 74 of 194, page 104 of 194, and page 148 of 194.
[43] Calculated by CDTL: (mean EDSS at baseline)/(mean years since onset of PPMS)

Study Completion. In WA25046, the dropout rate at 120 weeks was 29% in the placebo group and 18% in the ocrelizumab group. In the ocrelizumab group, 6 patients dropped out before they received any treatment compared to 1 placebo patient. By the time of the clinical cut-off date, 34% of the placebo and 21% of the ocrelizumab patients dropped out.

Table 9 Completion Rate in PPMS Trial

Completion Rate at Week 120 in PPMS Trial WA25046[44]		
	Placebo	**Ocrelizumab**
Subjects Randomized	244	488
Dropped Out	70	86
Completed week 120	174	402
Completion Rate[45]	71%	82%
Dropout Rate[45]	29%	18%
Difference in completion rate[45]	11%	
Completion Rate at Cut-Off Date		
Completed at cut-off date	162	387
Completion Rate[45] at cut-off date	66%	79%
Dropout Rate[45]	34%	21%
Difference in completion rate[45]	13 %	

PPMS Trial: Primary outcome

Table 10, below, summarizes the sponsor's primary clinical efficacy results for PPMS trial WA21046. The results show a statistically significant reduction in the time to first confirmed disability progression event (CDP). For a CDP event to occur, there first had to be an increase above baseline at any scheduled or unscheduled EDSS: an initial disease progression event (IDP). An IDP event becomes a CDP event if an EDSS rating more that 83 days later confirms a sustained increase in the EDSS without any interim non-confirming EDSS ratings. An IDP event also becomes a confirmed event if there are no subsequent EDSS ratings. The applicant defines these events as imputed CDP events. In her review, Dr. Yan writes "i*n a pre-specified sensitivity analysis based on the un-imputed events, it was reported by the sponsor and confirmed by the reviewer that the treatment difference was reduced with a hazard ratio of 0.82 and a p-value of 0.1477."*[46]. She

[44] Csr-WA25046.pdf, page 82 of 8131.
[45] Calculated by CDTL.
[46] Dr. Yan's review, page 36 of 50

also notes that "*a 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).*"

Table 10 Primary Outcome for PPMS Trial WA25046 -- 12-Week Disability Progression

Primary Outcome for PPMS Trial[47] Disability Progression Confirmed at 12-Weeks With Imputation		
Trial	**Placebo**	**Ocrelizumab**
ITT--Patients Randomized (n)	244	488
Patients With Confirmed Disability Event (%)	96 (39.3%)	160 (32.9%)
Kaplan Meier Estimate of CDP Rate at 120 weeks (%)	33.98%	30.23%
Hazard Ratio	0.76*	
95% confidence interval	(0.59, 0.98)	
p-value	0.0321[48]	

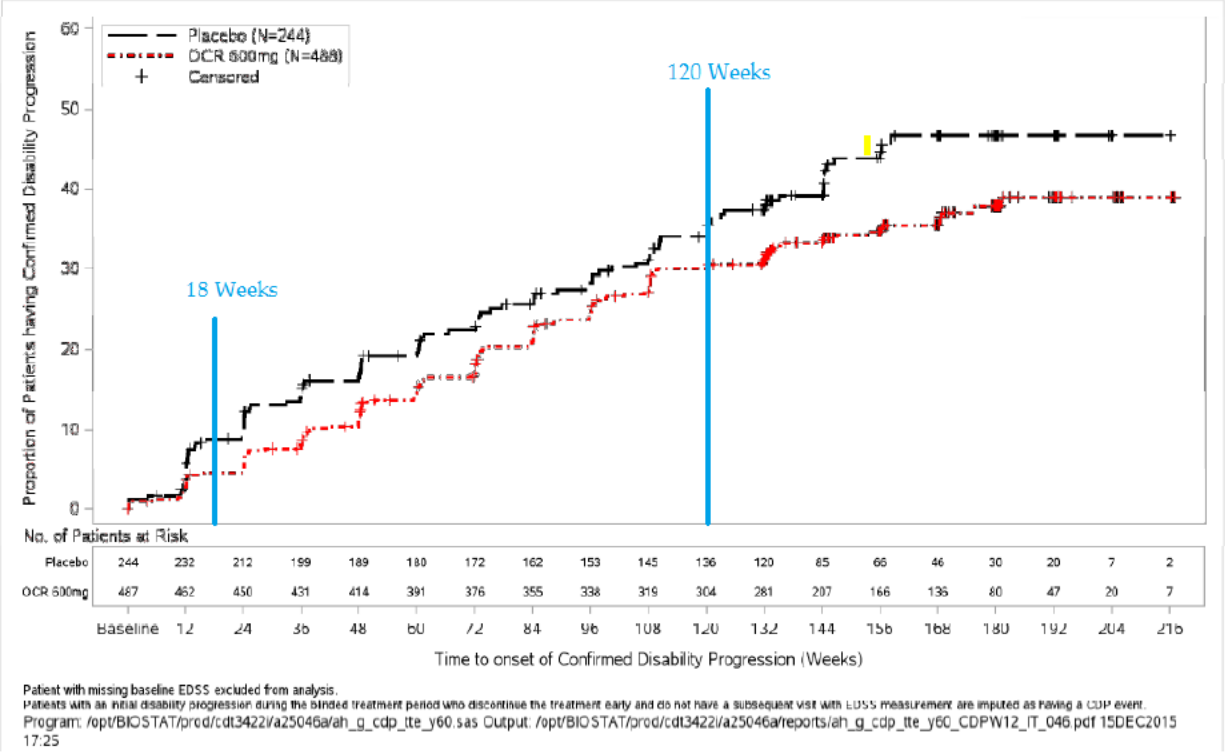
* Stratified by Geographical Region (US vs. ROW) and Age (<= 45, >45 years). Stratified Cox regression analysis produces the hazard ratios. The analysis excludes patients with missing baseline EDSS and imputes a CDP event in patients with an initial disability progression during the blinded treatment period who discontinued the treatment early and do not have a subsequent visit with EDSS measurement.

Figure 3, below, shows the Kaplan-Meier plot of disability progression from baseline to 216 weeks. This review added the vertical blue lines to emphasize the 120-week time point (minimum follow-up expected of all patients) and the 18-week time point (after completion of all 12-week EDSS ratings).

[47] Csr-WA25046, page 98 of 8131.

[48] This analysis imputes 9 and 12 CDP events in the ocrelizumab and placebo groups, respectively. (Dr. Rodichok's review, Table 124, page 153). Without imputation, the hazard rate would be 0.82 and the p-value 0.1477 (Dr. Yan's review, Table 18, page 37 of 50).

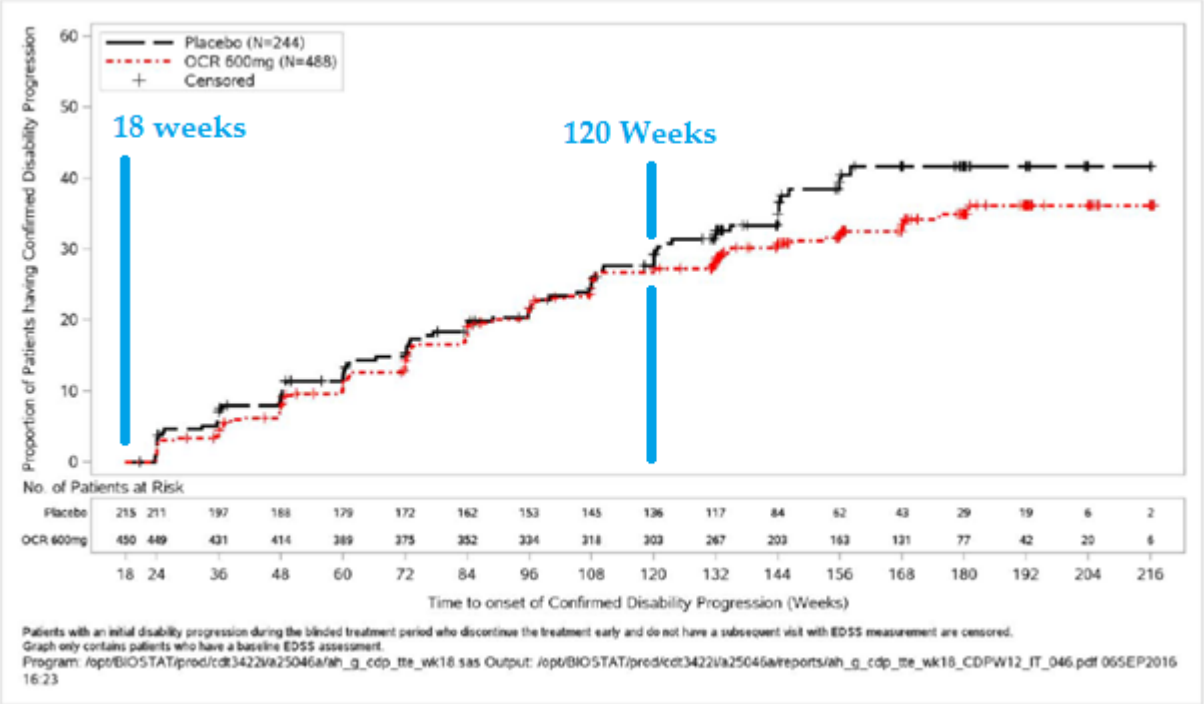
Figure 3 Kaplan-Meier Plot of Time to 12-Week CDP in PPMS Trial WA25046[49]



Unlike the Kaplan-Meier curve for both of the RMS trials (see Figure 1, above) where the curves for the two treatments diverged continuously over time, the curves for ocrelizumab and placebo do not diverge for 120 weeks after the first scheduled visit. In the prescribing information for FDA-approved drugs, it is unusual for the curves not to diverge for disability progression. The applicant provided Kaplan-Meier curves beginning with all the patients at risk after 18 weeks (the first scheduled EDSS examination was at 12 weeks). See Figure 4 below. The reason the curves fail to separate after 18 weeks of treatment is not apparent. Dr. Yan states that the low hazard ratio [in favor of ocrelizumab] after Week 120 is probably due to the imputed CDP of 6 patients in the placebo group versus one patient in the OCR group after week 120.[50] It appears that the major effect of ocrelizumab may be to reduce the rate of CDP events during the first 18 weeks of treatment. There may be other explanations, but this unusual feature of the primary outcome increases uncertainty about the results of the trial. For whatever reason, it appears the ocrelizumab had no effect on the rate of disability progression for two years after the scheduled EDSS rating at 3 months.

[49] Csr-wa25046.pdf, page 99 of 8131
[50] Dr. Yan's review, page 44 of 55

Figure 4 Kaplan-Meier Curve Starting After First Scheduled Visit (18 Weeks) Using Imputed Values[51]



PPMS Trial: Secondary Outcomes

Table 11, below, presents the results of pre-specified secondary analyses in the hierarchical order from the statistical analysis plan.

[51] Seq 0042 Response - 8Sept2016 (4).pdf, p. 56 of 108

Table 11 PPMS Trial 25046 Secondary Outcomes

PPMS Secondary Outcomes for Trial WA25046 at 120 Weeks[52]						
Hierarchy of Ten Secondary Outcomes 120-week double-blind epoch	Placebo	Ocrelizumab 600	p-value (Applicant)	p-value[53] (Dr. Yan)	Rate Ratio (Ocr/Placebo)[54]	Absolute Difference (NNT)
1. % With Disability progression lasting 24 weeks[55]	32.7%	28.3%	.0365		0.86	4.4%(23)
2. Relative Reduction in Timed 25-Foot Walk (T25FWT)	55.1	38.9	.0404		0.69	
Dr. Yan's T25FWT analysis without imputation Dr. Yan's MMRM analysis				0.0528* or 0.0783**		
3. Change in Total Volume of T2 Lesion Ratio to Baseline[56]	7.426	-3.366	0.0001	na	-1.45	
4. Percent Change Total Brain Volume	-1.093	-0.902	.0206	na	0.82	
5. Change in SF-36 (Physical Component)	-1.108	-0.731	0.6034	na	0.66	

* without carrying forward the baseline value.
**using MMRM method specified in penultimate SAP
Not significant

The application does not explain the clinical significance of the effect of ocrelizumab on the timed 25-foot walk test (T25FWT) at 120 weeks. Dr. Rodichok notes that the percent improvement over placebo is less than the 20% that DNP typically considers a clinically relevant improvement in walking speed.[57] Dr. Yan[58] notes that the applicant submitted a substantive change to the statistical analysis plan (SAP) for the T25FWT and the T2-lesion volume on September 4, 2015, just prior to locking database 14 days later on September 18, 2015. This was the second change to the planned analysis for the T25FWT. The applicant made the change after reviewing post-randomization data in the PPMS trial and the two RMS trials. The new method added imputation for missing values. The final analysis method is complex and this review finds no clear clinical

[52] Data extracted from clinical-overview.pdf for WA25046, page 72 of 144
[53] Dr. Yan's review page 45 of 55.
[54] Calculated by CDTL
[55] Unlike the same outcome in RMS, analysis imputed a confirmed disability progression if the patient dropped out after an initial increase in the EDSS that indicated the start of a progression event.
[56] The table quotes the applicant's analysis. Dr. Rodichok calculated the change in cubic centimeters. Ocrelizumab decreased mean T2 lesion volume by 0.393 cc's. The volume increased by .788 cc's in the placebo group. The clinical significance is unknown.
[57] Page 173 of 194.
[58] Dr. Yan's statistical review, page 44 of 55.

interpretation. In the study report, *the applicant uses imputed values and reports a p-value of 0.0404 from an analysis of "estimates (back-transformed) based on mixed-effect model of repeated measures (MMRM) using unstructured covariance matrix: log(Post-BL/BL) = log(BL 25-FTW) + Geographical Region (US vs. ROW) + Age (<=45, > 45 years) + Week + Treatment + Treatment*Week (repeated values over Week) + log (BL 25-FTW)*Week. P-value from a ranked ANCOVA on Percent Change from Baseline adjusting for rank of BL 25-Foot Timed Walk (25-FTW), Geographical Region (US vs ROW) and Age (<=45, > 45 years); missing observations imputed with LOCF."*[59] At 120 weeks, 29% and 19% of patients had missing T25FWT results for placebo and ocrelizumab groups, respectively.

In regard to the T25FWT imputation, Dr. Yan states "a total of 20 patients (5 in the placebo group and 15 in the ocrelizumab group) did not have any post-baseline assessment scores and their baseline score was carried forward (specified in the revised SAP) in the rank ANOVA analysis. Given that about 70% of the patients in both groups had an increase in T25FW walking time, assigning a 0 change to 5 patients in the placebo group and 15 patients in the ocrelizumab group gave ocrelizumab a benefit in the analysis of treatment difference. [She] performed the same analysis without carrying forward the baseline value (i.e., patients without post-baseline scores were excluded) and a p-value of **0.0528** was obtained."[60]

Dr. Yan used the MMRM method[61] of analysis to obtain the same adjusted geometric mean; however, the p-value is **0.0783**

Dr. Yan's results for the T25FWT ranged from p=0.0528 to p=0.0783. This means that all the secondary outcomes, except 24-week disability progression, achieved only nominal statistical significance because of the pre-specified hierarchy. Dr. Rodichok comments that the percent improvement over placebo is less than the 20% that the Division typically considers a clinically relevant improvement in walking speed.[62]

PPMS Trial: Exploratory Outcomes

The protocol for Trial 25046 lists 19 possible exploratory outcomes.[63] See Table 13, below. The table does not provide p-values because of the hierarchical analysis--a prior secondary analysis did not achieve a p-value less than 0.05. In addition, the high dropout rate makes interpretation questionable. For many exploratory outcomes, there

[59] csrwa25046.pdf page 1186 of 8131.
[60] Dr. Yan's review, page 45 of 55.
[61] Mixed effect Model Repeat Measurement (MMRM)
[62] Rodichok review, page 172 of 194.
[63] csr-wa25046.pdf, page 5045

is missing data in patients who completed the trial. Dr. Rodichok's review[64] notes that at the end of the trial there is no clinically or statistically significant difference in the EDSS scores at the end of the trial by treatment group or in the EDSS change from baseline. See Table 12, below.

Table 12 PPMS Trial Mean of Last EDSS Score and Mean Change from Baseline

Trial WA25046 PPMS Mean of Last EDSS Score and Mean EDSS Change from Baseline[65]								
	Treatment	N	Mean	p-value	Std Dev	Min	Max	Median
Last EDSS Score	Ocrelizumab	482	5.02	0.3128	1.50	1	8	5.5
	Placebo	243	5.14		1.53	1.5	8.5	5.5
EDSS change from Baseline[66]	Ocrelizumab	481	0.307	0.0737	0.98	-4.25	3	0
	Placebo	243	0.449		1.06	-2.5	4.25	0.5

Table 13 List of Exploratory Outcomes in PPMS Trial WA25046

Exploratory Outcomes[67] PPMS Trial WA25046	
1.	% relapse-free
2.	Δ[68] T2 hyperintense lesion volume
3.	ARR for all[69] relapses
4.	ARR requiring IV steroid
5.	ARR of severe relapses
6.	% change in brain volume
7.	Δ timed 25-foot walk
8.	Δ 9-hole peg test
9.	Δ MFIS[70]
10.	Δ depression symptoms
11.	Δ Karnofsky Scale
12.	% change cortical gray matter volume
13.	% change white matter volume
14.	% with 24-week CDP
15.	% with 12-week CDI
16.	Disability improvement duration
17.	% improved, stable, or worsened

[64] Rodichok review, page 174 of 194.
[65] Adapted from Dr. Rodichok's review, Table 142, page 174/194
[66] Several baseline EDSS scores were missing. The screening EDSS score is used instead.
[67] csr-wa21092.pdf, page 4965 of 6491
[68] Δ = change in
[69] confirmed and unconfirmed
[70] Modified Fatigue Impact Scale

Exploratory Outcomes[67] PPMS Trial WA25046
18. Δ EDSS (see Table 12, above)
19. Δ Mental Component of SF-36

12-Week Confirmed Disability Progression in Patient Subgroups

See Figure 5, below. The applicant reports interaction tests for subsets defined by the presence of T1 Gd-enhancing lesions (interaction HR: 0.60 [CI: 0.33, 1.11], p = 0.1041) and sex (interaction HR: 1.45 [CI: 0.85, 2.47], p = 0.1676).[71] **Dr. Yan's analysis showed no treatment benefit for ocrelizumab, numerically or statistically, for female patients (hazard ratio 0.944).**[72] Of 124 placebo-treated females, 44 (35.5%) had CDP events compared to 236 ocrelizumab treated females with 85 (36.0%) CDP events.

The applicant identified baseline number of gadolinium-enhancing lesions and male sex as predictors of a favorable response to ocrelizumab in multivariate analysis testing for interaction.[73]

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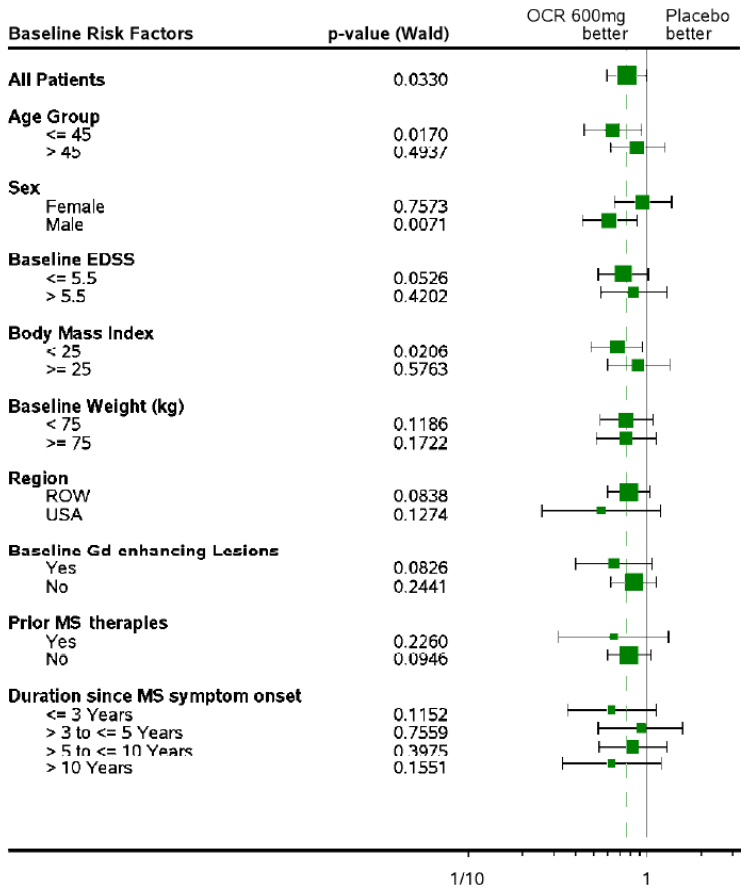
[71] csr25046.pdf, page 106 of 8131.
[72] Dr. Yan's review, Table 28, page 50 of 55. The applicant reports the hazard ratio for women to be 0.94 (0.66, 1.36), with p-value 0.7568
[73] PPMS csr-wa25046.pdf, page 103 of 8131

Figure 5 PPMS Trial Forest Plot for Subgroups: Time to 12-week CDP Event[74]



Significant Review Issues in Clinical Trial Design, Conduct, or Analysis

Credibility of a trial's results can be lost in small increments. Initially, the top line results of trial WA25046 led to expectations that the trial results were robust. As review proceeded, the review team became aware of problems with the results, the trial conduct, and the protocol that significantly diminished the review team's confidence in the results of the trial. Table 14, below, enumerates the more significant of these weaknesses.

[74] Adapted from csr-wa25046.pdf, Figure 4, page 104 of 8131.

Table 14 Concerns with Design, Conduct, and Data Quality for the PPMS Trial

Concerns with Design, Conduct, and Data Quality the of PPMS Trial	
Concern	**Discussion**
Imputation of primary outcome events	The imputation used in the PPMS trial, but not in the RMS trials, increased the number of confirmed outcome events by 21, 8% of the 256 CDP events used in the pre-specified primary analysis. **Without imputation, the p-value for the primary outcome changes from 0.032 to 0.148**
No treatment benefit for female patients	35.5% of women in the placebo group had CDP events compared to 36.0% of women in the ocrelizumab group. In the trial, there is no benefit of treatment with ocrelizumab in women, numerically or statistically.[75] This unusual finding is the result of pre-specified secondary analysis. If this result is real, it provides additional evidence that the effect of ocrelizumab on disability progression is significantly different in PPMS than in RMS. If not real, the result adds to uncertainty because of inconsistent results between important subgroups.
Lack of treatment effect after 18 weeks as seen in Kaplan-Meier curve of primary outcome	The Kaplan-Meier curves for confirmed disability progression are remarkably different in the RMS and PPMS trials. In the PPMS trial, the rate of progression is the same from 18 to 120 weeks, or longer, suggesting that any effect of ocrelizumab is limited to the first 18 weeks of treatment. In RMS, the treatment effect increases throughout the treatment period in both trials.
High rate of dropout and missing outcomes	The treatment group difference between the proportions of patients who had confirmed disability progression events is 4% to 7%. At the conclusion of the trial, the dropout rates are 34% and 21%, **5-fold and 3-fold greater than the 7% treatment effect for placebo and ocrelizumab**, respectively.[76] *With this many potential missing outcome events, there can be little confidence in the accuracy of the estimate of ocrelizumab's effect on disability progression.* The same ratios in the RMS studies for the relapse rate are 1-fold to 2-fold, and for CDP are 2-fold to 4.5-fold.
Determination of Baseline Primary Outcome Measure of Baseline after Recorded Time of Randomization and Infusion	In 29% of patients, investigators reported the baseline EDSS after infusion of the study drug and in 67% after randomization.[77] This represents an unusually extensive failure of investigators to follow fundamental principles of clinical research. It may be indicative of poor compliance with the protocol in other ways that are not as obvious.

Without changing the protocol, the applicant increased the sample size in the PPMS trial by 102 patients from 630 to 732. The trial results would be negative if the analysis uses the first 630 patients (p=0.087). If investigators had no information on the relative event rate at the time of the change, then it is unlikely that this change introduced significant bias. However, data-driven unplanned increases in sample size can bias trial

[75] Dr. Yan's review, Section 4.1, page 49 of 53.
[76] See Table 9 and Table 10 in this review.
[77] \\CDSESUB1\evsprod\BLA761053\0066, Response to Information Request November 4, 2016, Tables 2 and 3, page 8 of 27. Calculated by CDTL ((410+83)/732=67% for randomization, 141/732= 19% for infusion).

results. Essentially, the investigators changed to an adaptive design that is not in the protocol. The FDA Guidance on Adaptive Design states that adaptive designs have the "potential to increase the chance of erroneous positive conclusions and of positive study results that are difficult to interpret." Even if blinding is effective, some information, such as aggregated event rate, can bias decisions. There are other concerns about the increase in sample size; namely exposure of patients to risk without appropriate oversight. A review of the trial by the (b) (4)[78] identified the over-enrollment a critical problem because "in the case of over-enrollment, subjects are exposed to unnecessary burden and risks."

The (b) (4) identified 18 problems; 6 major, and one critical (the over-enrollment mentioned above). Other problems included the quality system, conduct and management (over-enrollment, vendor management, *primary endpoint*), data management (design and requirements of electronic data capture), and monitoring and auditing. The inspection team concludes that the PPMS trial "was not conducted fully in line with the requirements of the applicable European directives, guidelines and national legislation."

Review by Office of Scientific Integrity

Cara Alfaro, Pharm.D., Clinical Analyst, Good Clinical Practice Assessment Branch, Division of Clinical Compliance Evaluation, Office of Scientific Investigations, provided the Clinical Inspection Summary (CIS). Her team leader is Susan Thompson, M.D. The Branch Chief is Kassa Ayalew, M.D. For the PPMS trial, the CIS identifies problems at 2 of 4 clinical sites inspected. At one site, investigators did not record EDSS assessments into the computer tablet at the time they performed the assessments for 13 out 19 subjects, as the protocol specified. There were no source documents available to verify data integrity. Dr. Yan performed an analysis that excluded the patients from this site. The hazard ratio increased to 0.769 and the p-value increased from 0.032 to 0.454. At another site, two patients received the incorrect drug for single infusions. Dr. Yan found a minor change in the p-value (increased to 0.384) when she excluded these patients from the primary analysis.

Structured evaluation of evidence in the application to support the PPMS indication

The task for this secondary review is to consolidate the reviews from the different disciplines and make recommendations for approval and labeling. The clinical evidence supporting the PPMS indication presents a significant challenge because the clinical and statistical reviewers have identified weaknesses in the evidence the

[78] csr-wa25046.pdf, page 7019 -62 of 8131.

applicant has provided to support a claim that ocrelizumab slows disability progression in patients with PPMS. In addition, the primary clinical reviewer does not accept the applicant's rationale for using the two RMS trials to confirm the PPMS trial results. This review makes a determination about the effectiveness of ocrelizumab for PPMS using the criteria outlined in an **FDA guidance document** regarding clinical evidence of effectiveness.[79]

Section II-B of the guidance describes the importance of independent substantiation in the scientific basis for the legal standard.

> "The usual requirement for more than one adequate and well-controlled investigation reflects the need for **independent** substantiation of experimental results. A single clinical experimental finding of efficacy, unsupported by other **independent** evidence, has not usually been considered adequate scientific support for a conclusion of effectiveness."

A single trial requires independent evidence to support a conclusion of effectiveness.

The following statements from section II-A in that guidance describe situations where evidence from a single trial may be sufficient for approval:

> "Nevertheless, FDA has been flexible within the limits imposed by the congressional scheme, broadly interpreting the statutory requirements to the extent possible where the data on a particular drug were convincing. In some cases, *FDA has relied on pertinent information from other adequate and well-controlled studies of a drug, such as studies of other doses and regimens, of other dosage forms, in other stages of disease, in other populations, and of different endpoints, to support* ***a single adequate and well-controlled study*** *demonstrating effectiveness of a new use.* In these cases, although there is only one study of the exact new use, there are, in fact, multiple studies supporting the new use, and expert judgment could conclude that the studies together represent substantial evidence of effectiveness.
>
> "In other cases, FDA has relied on only a single adequate and well-controlled efficacy study to support approval — generally only in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit…"
>
> **"Whether related studies are capable of substantiating a single study of a new use is a matter of judgment and depends on the quality and outcomes of the studies and the degree of relatedness to the new use."**[80]

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[79] Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products, 1999, pages 3, 4, and 8.

[80] Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products, 1999, page 11.

The following discussion will use standards of evidence described in 21 CFR 314.126(a) and the Clinical Evidence Guideline quoted above to address whether there is evidence that meets FDA standards for safety and effectiveness. As shown in Figure 6, below, this review addresses four questions to determine whether the PPMS Trial WA25046 provides sufficient evidence for FDA approval without confirmatory evidence and, if not, whether the two RMS trials provide sufficient confirmatory evidence.

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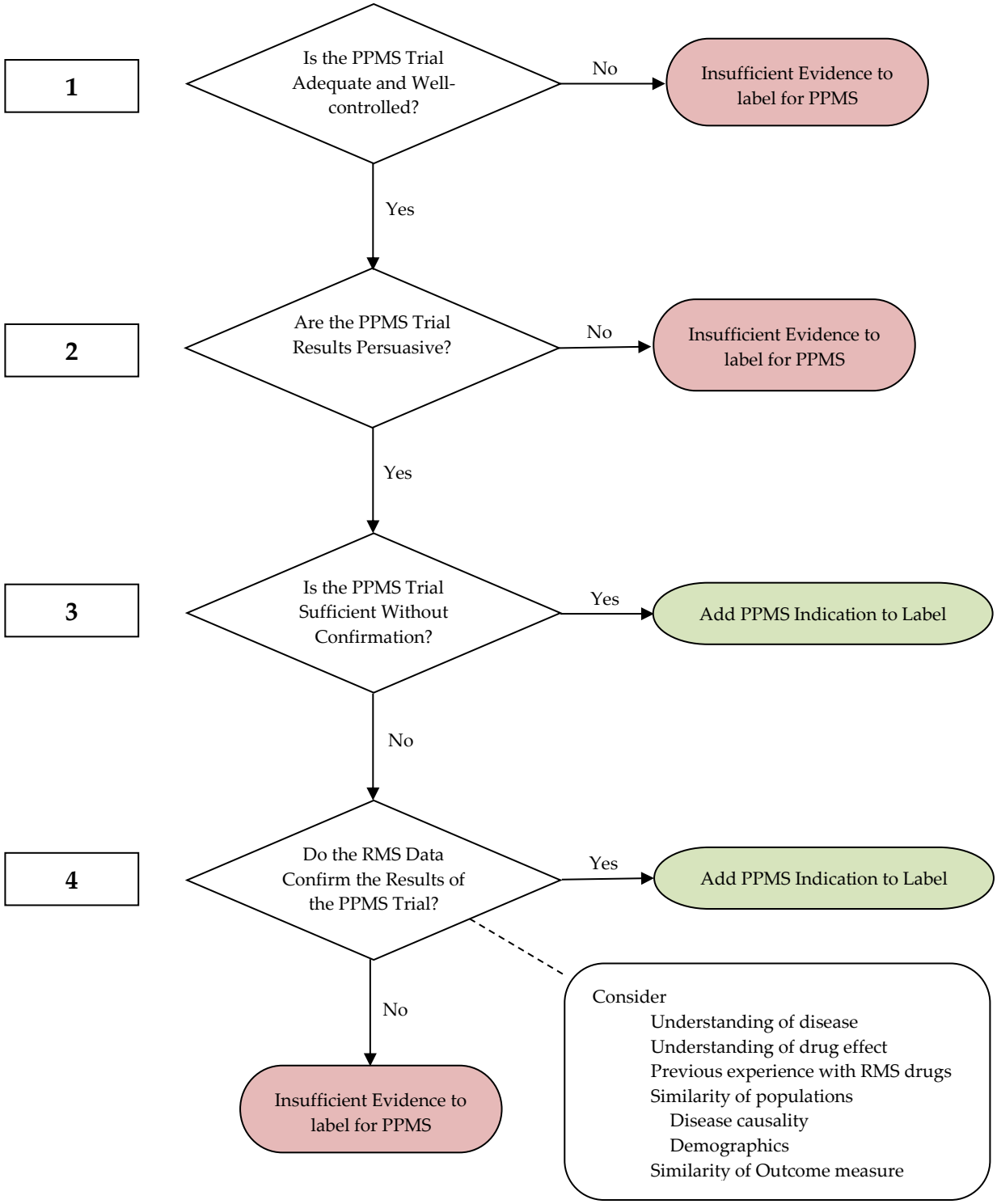
Figure 6 Algorithm to Evaluate Evidence Submitted to Support the PPMS Indication[81]



[81] See 21 CFR 314.126(a) and Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug andBiological Products.

This review agrees with the conclusions of the clinical and statistical reviews that the evidence in the application to support an effect on progression of disability is weak and with the clinical review that the PPMS trial results lack confirmation. The following paragraphs follow the outline of the algorithm in Figure 6, above, and document the effort the review team has made to use maximum available flexibility to identify sufficient confirmatory evidence to support the PPMS claims.

1-Is the PPMS trial adequate and well-controlled?

Dr. Rodichok agrees that it is adequate and well-controlled. Dr. Yan does not address this issue directly.

Control of bias. The trial protocol did not adequately control bias.

Dr. Yan identified possible bias because the protocol-specified primary analysis imputes "confirmed" disability events if, after an initial EDSS score signaled the start of a possible event, there is no confirming EDSS score 12 weeks later because the patient dropped out of the trial early. After removing this potential source of bias, *an analysis without imputation shows an increase in the p-value from 0.0321 to 0.1477.*[82] The analysis without imputation is the preferred analysis for CDP in MS trials and is the method used in the companion trials of ocrelizumab for RMS.

Conclusion: the PPMS trial is not well controlled.

Adequacy. Despite the questionable off-protocol 102-patient increase in the sample size, the PPMS trial results are sensitive to small changes in the number of outcome events as shown by the analysis without imputation above. Some unusual features of the trial results may be due, in part, to a small treatment effect and a high and unbalanced loss of primary outcome data. Some of these features include a lack of apparent treatment effect in women and in all patients for two years after the first scheduled visit. The number of patients with missing possible outcomes exceeded the absolute difference observed in the trial (maximum of 7.1%[83] absolute difference in Kaplan-Meier estimate and minimum dropout rate of 20%[84]).For these reasons, the trial does not contain a sufficient quantum of evidence to have confidence that the results are accurate. One could possibly explain these unusual results by simple chance, but that same argument would apply to the primary outcome as well. An adequate trial would not be likely to have these uncertainties.

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[82] Dr. Yan's review, pages 43 and 52.
[83] See Table 10 in this summary review on page 30.
[84] See Table 9 in this summary review on page 29.

To some, it may appear that there is a strong trend because the 0.1477 p-value without imputation is close to 0.05. The p-value for this study accounts only for variability due to the random assignment to treatment and the imputation. It does not address the uncertainty introduced by the poor control of bias, failure to follow the protocol, a significant loss of outcome data (dropout), and post-randomization changes in design described above. A p-value that accounts for all the uncertainties inherent in the protocol and the conduct of the trial would be greater than 0.1477.

This review concludes that *it would be reasonable to decide that the WA25046 trial is not adequate or well-controlled*.

2-Are the PPMS trial results persuasive?

Dr. Rodichok lacks confidence in the results of the trial because they are not statistically significant without imputation of primary outcome events. Also, the absolute reduction in the proportion of patients who experience these events is less than 5%, and because over 30% of patients experience progression events after two years of treatment with ocrelizumab.[85]

Dr. Yan notes that the use of imputation weakens the evidence of a reduction in disability progression in the PPMS trial. The two RMS trials did not use imputation, which is the usual method in MS trials.

In addition, two aspects of the PPMS trial results raise significant questions about the effectiveness of ocrelizumab for PPMS.

1. There is no apparent treatment benefit numerically or statistically among female patients (hazard ratio 0.944).[86]
2. In the applicant's primary analysis, the Kaplan-Meier curves show that confirmed disability events occurred at essentially the same rate in both arms of the PPMS trial for a period of 102 weeks (2 years) from Week 18 to Week 120.[87]

The conclusion of this review is that the PPMS Trial WA25046 does not provide persuasive evidence of effectiveness.

3 - Does the PPMS trial provide sufficient evidence by itself?

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[85] Dr. Rodichok's review, page 18 of 194.
[86] See Dr. Yan's review, page 49 of 53 and Figure 5 page 35 of this review.
[87] See Figure 3 on page 30 and Figure 4 on page 31 in this review.

Dr. Rodichok concludes for the reasons described in items 1 and 2, above, that the trial requires independent confirmation.

The conclusion of this review is that *the PPMS trial is not a single multicenter study of excellent design that provides highly reliable and statistically strong evidence of an important clinical benefit* as described in the Guidance on Clinical Evidence quoted above.

4 - Can the RMS trial results confirm the results of the PPMS trial (is the degree of relatedness between the two diseases sufficient)?

Given that the ocrelizumab application does not provide evidence from two adequate and well-controlled trials to support the effectiveness of ocrelizumab, other sources of confirmatory evidence might suffice. The FDA Guidance quoted above gives examples of **flexibility** in the type of evidence needed to support a single adequate and well-controlled study demonstrating effectiveness of a new use. It is important to note that this flexibility presupposes evidence from an adequate and well-controlled trial that demonstrates effectiveness in the new indication *--a supposition that is questionable for the single PPMS trial that is the subject of this review*.

Even if the PPMS trial is adequate and well controlled, the clinical evidence guideline requires a sufficient degree of relatedness to justify the use of evidence from adequate and well-controlled trials for different indications. Given the weakness of the evidence from the PPMS trial to support the effectiveness of ocrelizumab, *it is reasonable to require a high degree of relatedness between disability progression events in the confirmatory RMS trials and those in the PPMS trial.*

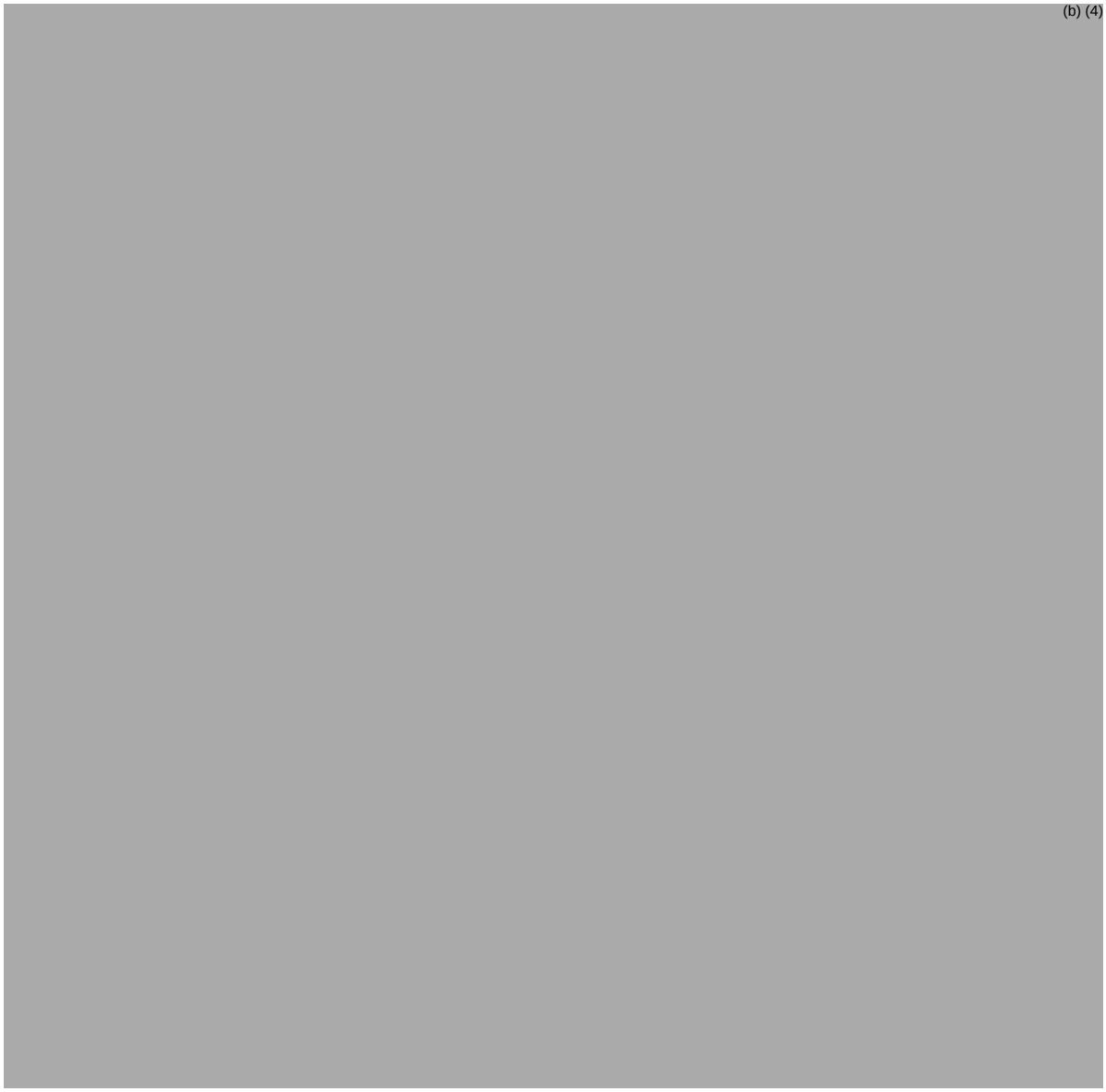
Below, under 5 subheadings, are different perspectives on the degree of relatedness for disability progression events.

After full review of the clinical trial results from the RMS and PPMS studies, the conclusion is that there is not sufficient independent evidence that progression in RMS relates to disability progression in PPMS to an extent that it can confirm the weak evidence of effectiveness in PPMS Trial 25046.

4(a) Relatedness: regulatory background for this application

In meetings with the applicant, FDA has agreed to consider whether a drug's effect on progression in RMS trials would be sufficient to confirm progression in other forms of MS. At an End-of-Phase 2 meeting in 2008, the applicant and FDA discussed the

relationship between relapsing and progressive MS.[88] Brackets, bold, and underlining added by this review.



From the minutes of the pre-BLA meeting held February 4, 2016:[89]

> Question 1: Does the Agency agree that the outcomes from the single pivotal Phase III Study WA25046 in patients with primary progressive MS with supportive evidence from related Studies WA21092 and WA21093 in the RMS patient population provides sufficient clinical evidence to support the review of the BLA for patients with primary progressive MS?

[88] Russell Katz, MD. Meeting Minutes December 5, 2008. Signed February 10, 2009

[89] February 4, 2016, Pre-BLA Meeting Minutes issued 2-26-2016

> FDA Preliminary Response to Question 1: In principle, yes, the PPMS study and the RMS studies appear appropriate for mutual support, but recognize that this is a preliminary assessment and a formal filing decision for the PPMS indication can only be made after receipt of the application. Also, note that the adequacy of the clinical data from study WA25046 in PPMS and studies WA21092 and WA21093 in RMS to support an indication for PPMS will be determined following **full review of the clinical trial results from these studies.**

Conclusion: it is appropriate to review the degree of relatedness between progression in RMS and PPMS to determine the adequacy of the clinical data from the RMS trials to support the PPMS indication.

4(b) Relatedness: the applicant's evidence and rationale

The following is the applicant's summary of the rationale for using the RMS data to confirm the PPMS results contained in the clinical overview document (this review adds the underlining and brackets):

> "Taken together, the above RMS and PPMS [clinical trial] results show that B cells play a role in the pathogenesis across the spectrum of MS, and that targeting CD20+ B cells with ocrelizumab can have a similar effect on common clinical and subclinical markers of disease progression in these related diseases. The significant reduction in 12-week [confirmed disability progression] CDP compared to the active comparator interferon beta-1a, in not only the pre-specified pooled population of Studies WA21092 and WA21093 but also consistently in both individual studies provides strong evidence of an effect of ocrelizumab on MS disability progression. Consistent results were seen in 24-week CDP. Demonstrating durability of effect with this endpoint is a more stable measure of disability and, therefore, further confirms ocrelizumab's impact in delaying disability progression. This reduction in CDP combined with the effect of ocrelizumab compared with interferon-beta-1a on other clinical and subclinical markers of disease progression in the RMS Studies WA21092 and WA21093 are supportive of and substantiate the efficacy results of ocrelizumab compared with placebo seen in the PPMS Study WA25046."[90]

The first sentence of the applicant's rationale appears to be an attempt to establish the degree of relatedness between the affect of ocrelizumab on CDP events in RMS to its effect (if any) on CDP events in PPSM. The sentence concludes that B-cells play a role in the pathogenesis across the spectrum of MS **because** of similar results in the PPMS and RMS trials. For this conclusion to be valid, the results of the PPMS trial must be valid. If the results are valid, then there is no need for confirmation. If the PPMS trial results are valid, then it would reasonable to conclude that ocrelizumab treatment appears to

[90] Page 84 of 144 in clinical-overview.pdf, Section 4.2.7.3, "Summary of the RMS Data Supporting the PPMS Results"

have an effect on CDP events in both RMS and PPMS. However, while still assuming the PPMS trial is valid, there is still not enough information to conclude what the mechanism of the effect is, and, most importantly, not enough information to conclude that the mechanism is the same in both RMS and PPMS. Without convincing evidence that there is a similar mechanism in play, the RMS trial results do not have a sufficient degree of relatedness.

There is another problem with the applicant's rationale. The purpose of the rationale is to establish a relationship between the CDP events in RMS and PPMS that will allow the RMS trial results to confirm the unconfirmed results of the PPMS trial. However, the applicant's rationale assumes that the results of the PPMS trial are valid. If they are valid there is no need to confirm them. The logic is circular. To conclude that there is a sufficiently strong relationship between PPMS and RMS to enable using the RMS data to confirm the PPMS data, there must be evidence independent of the PPMS trial.

If, independent of the PPMS trial, there were convincing evidence that the mechanism of disability progression in RMS had the same pathological mechanism as disability progression in PPMS, then the RMS trials could provide independent supporting evidence of the effect of ocrelizumab on disability progression. The relationship would have to be very strong because of the weak results of the PPMS trial.

As an example of relatedness, the Guidance on Clinical Evidence mentions that DNP has approved drugs for one form of epilepsy using as evidence positive results from one single adequate and well-controlled trial confirmed by evidence from trials in other forms of epilepsy. Though not described in the Guidance, the degree of relatedness is substantial because the drug reduces neuronal excitability and neuronal excitability is the cause of seizures in the different forms. The cause of disability progression in PPMS and RMS is not as clear. Neither is the mechanism by which ocrelizumab reduces disability progression in RMS. The degree of relatedness of disability in RMS to PPMS is much less than for the incidence of seizures in different forms of epilepsy.

The applicant's clinical overview does refer to medical literature to support the relatedness of the CDP outcomes in PPMS and RMS:

> "For the past two decades, MS was clinically subcategorized into four phenotypic disease patterns distinguished by the occurrence and timing of relapses relative to disease onset and disability progression (Lublin and Reingold 1996). However, more recently, it has been proposed that PPMS is not a separate entity but rather a part of the spectrum of progressive disease (Ontaneda and Fox 2015). Therefore, certain outcome

> measures of clinical and subclinical progression are relevant and meaningful in both RMS and PPMS."[91]

The Ontaneda and Fox review does not provide convincing support for the applicant's claim that disability progression in PPMS and RMS are closely related. The review, comparing progressive MS (PMS), PPMS and SPMS, states, "MS may be seen as a spectrum with an intense focal inflammatory component in RRMS and more neurodegenerative features with concomitant chronic inflammation and axon loss in [progressive MS] PMS."[92] However, the review reiterates that **the pathogenesis at the two ends of the spectrum, RMS and PMS, is different**.[93] Inflammation and focal demyelination with breakdown of the blood-brain barrier are RMS features while widespread degeneration of the white and grey matter with resultant atrophy with less focal disruption of the blood brain barrier are PMS features. The review notes that significant progress with treatment for RRMS has occurred because the target is inflammation but that progress in the treatment of progressing MS has not occurred because of the *incomplete understanding of the different pathogenesis.*

The applicant's rationale for using RMS trial results to confirm the PPMS trial results is not convincing because there is evidence that the pathogenesis of disability progression differs in the two forms of MS.

4(c) Relatedness: the primary clinical reviewer

Dr. Rodichok has considered the applicant's claim that the effect on of disability progression is the same in both trials. He concludes that the evidence from the RMS trials does not relate sufficiently to the findings in the PPMS trial to confirm the PPMS results. His reason is that clinical evidence from the RMS and PPMS trials shows significant differences in the patient population, the clinical course of the disease, and the progression events themselves.

He found that in the PPMS trial, confirmed disability progression (CDP) events occurred more frequently (33-40% versus 9-13%) and, on average, CDP events lasted 100 days longer in the PPMS trial than in the RMS trial. The proportion of CDP events that lasted until the last EDSS evaluation is higher in the PPMS trial even though the PPMS trial lasted longer (31-43% versus 5-9%). The relative reduction in CDP events in the RMS trial was higher than in the PPMS trial (33.1% versus 16.3%) despite the

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[91] Section 4.2.7, page 81 of 144, clinicaloverview.pdf
[92] Ontaneda D, Fox RJ. Progressive multiple sclerosis. Curr Opin Neurol 2015;28:237-243, page 238.
[93] Reflecting the lack of knowledge about the pathology of the different clinical syndromes of MS, some publications describe similarities between PPMS and SPMS, other describe differences.

presence of an active comparator in the RMS trial. A time to event analysis showed a more favorable hazard ratio in the RMS trial than in the PPMS population (0.60 versus 0.76, with p-values 0.0006 and 0.0321).

Dr. Rodichok concludes that although they have the same name and a similar definition, the CDP events are not the same in the two trials, and these differences do not support the assertion that evidence of a reduction in periods of disability in the RMS population can support a reduction in disability in PPMS patients. *Therefore, a comparison of the CDP primary endpoint in PPMS patients to the CDP endpoint in RMS patients would not be a valid assessment of the same endpoint across trials.*

In his review, Dr. Rodichok notes that the RMS and PPMS populations differ significantly in their demographic and baseline disease characteristics: an older age at onset, fewer gadolinium-enhancing lesions at baseline, a reduced T2 lesion volume, and a more balanced male-female distribution in the PPMS trial patients compared to the RMS trial patients.

"More importantly, the frequency and duration of the periods of disability in the PPMS population differ substantially from those in the RMS population. These data do not adequately support that RMS is sufficiently related to PPMS to allow the use of data from the RMS studies to support the results of the study in patients with PPMS. Therefore there remains significant uncertainty as to whether treatment with OCR is effective for the treatment of PPMS."[94]

Dr. Rodichok's concerns about relatedness are compelling because he bases them on evidence from the trials in the application. Evidence found in the trials supports the extent of the difference between disability progression in PPMS and RMS in medical literature reports (see 4d, below).

4(d) Relatedness: the medical literature

Dr. Rodichok is not alone in his doubts about the likelihood that MS treatments that slow disability events in relapsing MS will slow disability progression in progressive forms of MS. Experts are not in full agreement. Underlying the controversy is a lack of understanding of both the cause of the disability progression and the mechanism by which effective treatments produce effects in the MS population. Approved treatments, however specific their binding to drug targets, have widespread effects on multiple potential mechanisms.

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[94] Dr. Rodichok's review, page 17 of 194.

A multiple sclerosis reference[95] reviews the clinical and pathological characteristics of RMS and PPMS. Table 15, below, summarizes the differences.

Table 15 Degree of Relatedness of RMS to PPMS

Degree of Relatedness Differences between RMS and PPMS[95]		
	PPMS	**RMS**
Usual Clinical presentation	Continuous accumulation of neurological deficit from onset	Relapses and remissions
Initial symptoms	Motor symptoms with spastic paraparesis	Visual or sensory symptoms
Onset age	Significantly later than RMS	Earlier than PPMS
Sex	50-50 female-male	60-40 female-male
MRI	Fewer focal MRI lesions, less gadolinium enhancement, fewer new lesions over time compared to RRMS and SPMS.	More focal MRI lesions, more gadolinium enhancement, more new lesions over time compared to PPMS.
Pathology	Fewer white matter lesions; lesions are less inflammatory; cortical demyelination is characteristic; greater capacity for remyelination	More white matter lesions; lesions are more inflammatory; cortical demyelination not characteristic; less capacity for remyelination;
Mechanism of axonal loss	**A mild but diffuse and chronic inflammatory process**	**Acute focal inflammatory demyelination**

The comparison of baseline clinical and MRI characteristics in the PPMS and RMS trials in Table 8, page 17, confirms the clinical and MRI differences listed in Table 15, above.

The concluding paragraph in the section on the characteristics of PPMS in the same reference:[95]

> Whether these differences indicate that PPMS is a distinct clinical entity or just one end of the disease spectrum of MS has been a source of debate. The important question with regard to therapeutics is whether there is a fundamental difference in the mechanism underlying neurological deficit in a predominantly progressive disease compared with relapsing disease. The pathological substrate of irreversible neurological deficit is considered to be axonal loss. ***In RRMS, the mechanism of axonal loss appears to be related to acute focal inflammatory demyelination, whereas in PPMS axonal loss is associated with a mild but diffuse and chronic inflammatory process and this process in the spinal cord has been directly correlated with disability.***[95]

[95] Zhaleh Khaleeli and Alan J. Thompson, "Chapter 52: Treatment for patients with primary progressive multiple sclerosis," in *Multiple Sclerosis Therapeutics, Fourth Edition*, edited by Jeffrey A. Cohen and Richard A. Rudick, MD, Cambridge University Press, 2011, pages 604-606.

The final sentence in the paragraph quoted above summarizes credible evidence that the mechanisms causing disability progression may be different in RMS and PPMS. This suggests that the relationship between disability progression in RMS and disability progression is not sufficient for the RMS trial results to confirm the PPMS trial results.

4(e) Relatedness: Other clinical trials in PPMS

Clinical trials in PPMS provide convincing evidence that a treatment effect on disability in RMS trials cannot be relied on to support a treatment effect on disability in PPMS.

(b) (4)

In a different context, but perhaps still applicable to the (b) (4) counterexample, the Guidance on Clinical Evidence states:

> "A single favorable study among several similar attempts that failed to support a finding of effectiveness would not constitute persuasive support for a product use unless there were a strong argument for discounting the outcomes in the studies that failed to show effectiveness."[97]

(b) (4)

[97] Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products, 1999, page 6

4(f) Relatedness: Conclusion

The degree of relatedness of disability progression in RMS to that in PPMS is low. Clinical trials with other drugs, the differences in disability progressing in the ocrelizumab RMS and PPMS trials, the weakness of the applicant's rationale, pathological differences listed in Table 15, above, and the unknown drug and disease mechanisms all support Dr. Rodichok's conclusion that *the results from the RMS trials are not sufficient to confirm the results of the PPMS trial.*

Adequacy of confirmatory evidence for PPMS trial WA25046

Dr. Rodichok and Dr. Yan agree that the evidence to support an effect on disability progression in PPMS from trial WA25046 is weak. Therefore, strong confirmatory evidence is required to meet FDA standards of evidence. The ocrelizumab trials in RMS do not provide that evidence.

Efficacy Conclusion for the PPMS MS Indication

In his **clinical review**,[98] Dr. Rodichok presents his conclusions about the PPMS indication and PPMS Trial WA27046. In summary,

- The trial is adequate and well-controlled
- The results of the trial are not statistically persuasive
- The clinical efficacy shown by the primary results are apparent in only 5% of patients who took ocrelizumab
- Trial data show that RMS is not closely enough related to PPMS to justify using the results in the RMS trials to confirm the PPMS trial results.

Despite his concerns about the adequacy of the evidence, Dr. Rodichok recommends approval for PPMS because of the relative safety and unmet need for a treatment of PPMS.

On page 54 of her **statistical review**, Dr. Yan concludes that:

- "Study WA25046 provided data that were indicative of efficacy in the treatment of ocrelizumab in delaying the disability progression in patients with PPMS."
- "The evidence of the effectiveness was weakened by the failure of the study to withstand an important sensitivity analysis on un-imputed data, which is commonly used as the standard primary data for disability progression endpoint."

[98] Dr. Rodichok's review, page 16 of 194.

Dr. Yan does not offer a recommendation for or against approval of ocrelizumab to treat PPMS.

For PPMS, this review agrees with Dr. Rodichok that the evidence is not convincing that ocrelizumab is effective and with Dr. Yan that the evidence of effectiveness is weak, particularly in women. The safety reviewers, Drs. Boehm and Yasuda, are concerned about the unusual imbalance in cases of breast cancer observed in the ocrelizumab trials (6 ocrelizumab compared to 0 placebo). See Table 20, below. For women the risk benefit ratio is of concern because the observed risk of breast cancer is not offset by any observed beneficial effect in women.

7. Safety

Gerald Boehm, MD, performed the primary safety review. The safety team leader was Dr. Sally Yasuda. They both recommend approval if efficacy is demonstrated and the benefits outweigh the risks. A summary of the DRISK assessment of the need for a Risk Evaluation and Mitigation Strategy is at the end of this section, below.

Dr. Boehm reports that ocrelizumab is associated with infusion related reactions (IRRs), infections, malignancies including breast cancer, and depression. He cautions that these adverse reactions have potential for more serious outcomes after the drug is approved for marketing and patients may have fewer clinical evaluations than in the clinical trial setting. He recommends warnings in the labeling and a Medication Guide to mitigate potentially serious outcomes of these adverse reactions.

In her 45-page review, Dr. Yasuda focuses on the four safety findings emphasized by Dr. Boehm: IRR, infection, malignancy, and depression.

1. IRRs occurred in 35% of patients in MS trials despite the requirement for prophylactic pretreatment. The IRRs occurred most frequently after the first dose but continued to occur with subsequent infusions. Most of the IRRs were mild and occurred during the infusion period. Some occurred after the patient had left the clinic.
2. Non-serious infections occurred more often with ocrelizumab than with placebo or active comparator, but serious infections were less frequent with ocrelizumab. Opportunistic infections were not identified in MS patients treated with ocrelizumab.
3. Malignancies occurred three times as often with ocrelizumab than with placebo or active comparator. Six patients taking ocrelizumab developed breast cancer versus none in the control groups.
4. Depression suicidal, suicide attempt, and suicidal ideation occurred only in ocrelizumab patients and none in placebo in the PPMS trial, but depression alone occurred less frequently in ocrelizumab-treated patients than placebo in the PPMS. Rebif, the active control in the two RMS trials, is associated with depression. Depression events occurred more frequently with ocrelizumab than with Rebif in those trials (8% vs 7%).

Dr. Yasuda shares Dr. Boehm's concern that there is the potential for more serious outcomes outside of clinical trials after the drug approval when there may be less monitoring and much longer exposures to the drug. She recommends warnings in the labeling and a Medication Guide for patients to mitigate potentially serious outcomes

Quality of Safety Data

In his review, Dr. Boehm states that the safety data appeared to be reliable and consistent. He sent approximately 12 Information Requests for additional safety information. The applicant responded quickly the requests.

Exposure

Studies of all indications exposed 5,406 patients to ocrelizumab at doses ranging from 20 to 2000 mg given in courses of one or two infusions every 24 weeks. Indications included rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosis, lupus nephritis, and non-Hodgkin's lymphoma.

Table 16 summarizes the duration of exposure in all MS trials. Exposure within the MS development program exceeded ICH guidelines.

Table 16 Duration of Exposure to Ocrelizumab in MS Clinical Trials[99]

Duration of Exposure to Ocrelizumab in MS Trials				
Duration of Exposure	More than **23 weeks**	More than **47 weeks**	More than **71 weeks**	More than **95 weeks**
Number of Patients	1880	1640	1457	1388

Deaths

Dr. Boehm states that 11 deaths occurred in MS trials: 8 in patients treated with ocrelizumab, 2 with Rebif, and 1 with placebo. The causes of death for the 8 ocrelizumab patients were *suicide, metastatic pancreatic cancer, aspiration pneumonia, pneumonia, pulmonary embolism, sepsis without obvious source leading to multi-organ failure, sudden death, and a fall.* Dr. Boehm determined that there was no obvious relation to ocrelizumab except for the cases of pneumonia and sepsis where ocrelizumab may have increased susceptibility to infection.

[99] Table 3, page 27 of 162, Dr. Boehm, primary safety review.

The applicant reported 45 deaths among 2,926 ocrelizumab-treated patient in RA trials (1.5%). The overall death rate was 3.4-fold higher in RA than MS. Eight of the deaths were unlikely to be related to ocrelizumab because of low exposure or lack of recent exposure. For the remaining 37 deaths, the reported causes were: pneumonia (7), sepsis/septic shock (6), respiratory failure (3), lung cancer (3), sudden death/ death (3), myocardial infarction (2), brain edema, breast cancer, carbon monoxide poisoning, disseminated intravascular coagulation, gastric cancer, gastrointestinal carcinoma, gastrointestinal hemorrhage, ischemic cerebral infarction, multi-organ failure, pulmonary embolism, ruptured cerebral aneurysm, toxicity to various agents, and traffic accident.

18 deaths occurred in patients taking ocrelizumab in trials of SLE and NHL.

Overall, Dr. Yasuda concludes that "few deaths occurred in the MS controlled trials and it is difficult to determine the relationship between ocrelizumab and those deaths. Deaths in the RA trials were due to serious infections and sepsis, in many cases confounded by concomitant use of immunosuppressant drugs."[100]

Serious adverse events (SAEs)

Dr. Boehm found that in the ocrelizumab MS trials, any given SAE occurred in no more than 1% of exposed patients. The most common SAEs in MS trials were infections (urinary tract, pneumonia, appendicitis), fractures, seizures, MS relapse, infusion related reactions, cholelithiasis or cholecystitis, breast cancer, suicide attempt, pancreatitis, and back pain.[101] No SAEs indicated serious drug toxicity. There was no aplastic anemia, pancytopenia, rhabdomyolysis, Stevens Johnson Syndrome, toxic epidermal necrolysis, liver failure, or renal failure.

In the trials for other indications, the serious adverse event rates were higher. The significance of these rates is difficult to determine because the other indications were diseases that had an intrinsically higher baseline adverse event rate and frequent concomitant use of other drugs with high adverse event rates.

Table 17 and Table 18, below, present the serious adverse events rates in the ocrelizumab and control groups for the three largest trials in the application. Table 19 summarizes all serious adverse events that occurred in five or more patients by body system category in the MS trials. Of note, the placebo-controlled trial in PPMS reports

[100] Page 15 of 45 in Dr. Yasuda's review.
[101] Page 48 of 162 and following.

SAEs in 20% of patients compared to 7% in the RMS trials. Considering the similarities in baseline demographics, this may indicate differences in safety reporting procedures.

Table 17 Adverse Events in RMS Trials WA21092 and WA 21093

Serious Adverse Events in RMS Trials WA21092 and WA21093[102]			
	Rebif	**Ocrelizumab**	**Difference**
Number of Subjects	826	825	
Any SAE	8.7%	6.9%	1.8%
Discontinuations	6.2%	3.5%	2.7%
All Adverse Events	83%	83%	0%

Table 18 Adverse Events in PPMS Trial WA25046

Serious Adverse Events in PPMS Trials WA25046[103]			
	Placebo	**Ocrelizumab**	**Difference**
Number of Subjects	239	486	
Any SAE	22.2%%	20.4%	1.8%
Discontinuations	3.3%	4.1%	0.8%
All Adverse Events	90%	95%	5%

[102] Dr. Yasuda's review. .
[103] Trial 201 Clinical Study Report. Table 154. Page 845 of 1641.

Table 19 SAEs Reported by at least 5 patients, All MS Trials

Serious Adverse Events Reported by at least 5 patients, All MS Trials[104]	
MedDRA System Organ Class MedDRA Preferred Term	Ocrelizumab in MS Trials 2147 Patients 4,485PatientYears
Total with at least 1 SAE	**10.8%**
Infections and Infestations	**3.0%**
Urinary tract infection	0.7%
Pneumonia	0.4%
Appendicitis	0.3%
Nervous System Disorders	**1.6%**
Seizure	0.4%
Multiple sclerosis relapse	0.4%
Injury, Poisoning, and Procedural Complications	**1.5%**
Fractures	0.6%
Infusion related reaction	0.3%
Gastrointestinal Disorders	**1.1%**
Pancreatitis	0.2%
Neoplasms Benign, Malignant, and Unspecified	**0.8%**
Breast cancer	0.3%
Psychiatric Disorders	**0.7%**
Suicide attempt	**0.3%**
General Disorders and Administration Site Conditions	**0.6%**
Musculoskeletal and Connective Tissue Disorders	**0.6%**
Back pain	**0.3%**
Hepatobiliary disorders	**0.5%**
Cholecystitis or Cholelithiasis	**0.4%**
Cardiac Disorders	**0.4%**
Reproductive System and Breast Disorders	**0.4%**
Respiratory, Thoracic, and Mediastinal Disorders	**0.3%**
Blood and Lymphatic System Disorders	**0.3%**
Renal and Urinary Disorders	**0.3%**
Metabolism and Nutrition Disorders	**0.2%**

[104] Dr. Boehm's review, page 49 of 162.

Safety issues of concern

The safety reviews identified six safety issues of concern:

1. Infusion-related reactions
2. Infections
3. Malignancies
4. Depression/Suicide
5. Cholecystitis and Cholelithiasis
6. Pancreatitis

This review describes each of these issues of concern under italicized headings below.

--Infusion Related Reactions (IRRs)

Ocrelizumab is associated with IRRs. In MS trials, the protocols required premedication to minimize the number and severity of IRRs. All patients in MS trials received methylprednisolone 100 mg IV, 30 to 60 minutes prior to each infusion of study drug. The protocol recommended pretreatment with oral analgesic medications and an oral antihistamine.

In the RMS trials WA21092 and WA 21093, IRRs occurred in 34% of ocrelizumab-treated and 10% of Rebif-treated patients. In the PPMS trial WA 25046, 40% of ocrelizumab and 26% of placebo patients experienced IRRs. 62% to 82% of infusion reactions occurred during the infusion or before the patient left the clinic. Less than 1% were serious in MS controlled trials in PPMS and RMS. See Figure 7, below. Note that Drs. Boehm and Yasuda attribute some of the higher risk of IRRs in the PPMS trials to the increased duration of exposure (96 versus 120 weeks). Dr. Yasuda did not find that there is substantial evidence of any difference in IRRs between the 600mg single infusion course and the 300mg x 2 split infusion regimen.

Symptoms of IRRs included pruritus (30%), rash (30%), throat irritation (24%), flushing (16%), urticaria (9%), and oropharyngeal pain (8%). Symptoms of the 7 serious IRRs in controlled trials included bronchospasm, life-threatening hypotension with severe throat irritation, hyperthermia, and fever.

Figure 7 Infusion-related Reactions in RMS and PPMS Trials

Infusion-related Reactions in RMS and PPMS Trials[105]				
	RMS Controlled Trials		PPMS Controlled Trial	
	Rebif	**Ocrelizumab**	**Placebo**	**Ocrelizumab**
Patients (n)	826	825	239	486
Serious IRRs	0.1%	0.1%	0	1%
Discontinuations	0	1.3%	0.4%	0.4%
Any IRR	9.7%	34.3%	25.5%	39.9%

--*Malignancies*

Dr Yasuda notes a 2.5-fold increase in the number of patients treated with ocrelizumab compared to Rebif and a 2.9-fold increase compared to placebo. Breast cancer in the three main MS trials occurred in 6 patients treated with ocrelizumab compared to no cases in the control groups (Rebif or placebo). Table 20, below, summarizes the incidence of malignancies in MS trials.

Table 20 Malignancies in MS Trials

Malignancies in MS Trials[106]					
	All MS Trials	**RMS Controlled Trials**		**PPMS Controlled Trial**	
	Ocrelizumab	*Rebif*	*Ocrelizumab*	*Placebo*	*Ocrelizumab*
Number of patients	2279	826	825	239	486
Females	1398		541		240
All malignancies	1.0% (23)	0.2% (2)	0.5% (4)	0.8% (2)	2.8% (11)
Breast Cancer	0.6% (8)	0	0.3% (2)	0	1.6% (4)

The 23 malignancies in patients treated with ocrelizumab in all trials are (one case each unless noted are:

1. Breast cancer (8)
2. Malignant melanoma (2)
3. Adenocarcinoma of colon
4. Anaplastic large cell lymphoma
5. Endometrial cancer

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[105] Dr. Yasuda's review, page 20 of 45.
[106] Dr. Yasuda's review, page 27 of 45.

6. Malignant fibrous histiocytoma
7. Pancreatic carcinoma
8. Papillary thyroid cancer
9. Renal Cancer
10. Keratoacanthoma

DNP consulted the Division of Oncology Products (DOP1, Dr. Gwynn Ison), the Division of Hematology products (DHP, Dr. Bindu Kanapuru), and the Division of Epidemiology (DPI1) to assist with the evaluation of the malignancies associated with ocrelizumab. In their reviews, Drs. Ison and Kanapuru recommend evaluating cancer risk using all malignancy types. Dr. Ison recommends further evaluation of newly diagnosed malignancies. Dr. Kanapuru comments that the imbalance of breast cancer cases is concerning and recommends longer follow-up to characterize the association further. Both consultants question the applicant's comparisons to outside databases. Dr. Kanapuru cites a publication concluding that MS patients have a decreased overall risk of cancer but notes an increased risk for breast cancer in women with MS treated with immunosuppressive therapy. Drs. Ison and Kanapuru recommended describing the findings in labeling. Drs. Boehm and Yasuda agree with the consultants that the label for ocrelizumab should list the risk of malignancy as a Warning and that there should be a requirement to study the incidence of cancer if the drug is approved.

-- 4. Depression and Suicide

Dr. Boehm states that serious depression and suicide attempts occurred only in ocrelizumab patients and not in comparator patients in the MS controlled trials. Although depression adverse events occurred less frequently in ocrelizumab-treated patients than placebo in the PPMS controlled trial, they occurred slightly more frequently than with Rebif (8% vs 7%) in the two RMS trials. Therefore, because Rebif labeling has a warning about depression and suicide, Drs. Boehm and Yasuda agree that there should be a similar warning for ocrelizumab.

Again, there are consistently more events reported in the PPMS ocrelizumab trial. One possible explanation is more diligent AE reporting in the PPMS trial than in the RMS trials.

Depression-Related And Psychiatric Adverse Events in MS Trials[107]					
	All MS Trials	**RMS Controlled Trials**		**PPMS Controlled Trial**	
	Ocrelizumab	*Rebif*	*Ocrelizumab*	*Placebo*	*Ocrelizumab*
N	2147	826	825	239	486
Serious adverse events	0.7%a	0.8%	0.5%	0	0.8%
Completed suicide		0.1%	0.1%		
Depression		0	0.2%		
Depression suicidal		0.2%	0	0	0.2%
Suicidal ideation		0.1%	0	0	0.2%
Suicide attempt		0	0.1%	0	0.4%
All adverse events	15.5%	17.4%	18.1%	24.7	18.3%
Depression	6.4%	6.5%	7.8%	12.6%	9.7%

--5. Cholecystitis and Cholelithiasis

Drs. Boehm and Yasuda noted an imbalance in SAEs related to gall bladder disease (0.2% for Rebif and 0.7% for ocrelizumab in the RMS trials; 0.4% for placebo and 0.6% for ocrelizumab in the PPMS trial). They agreed that these events did not warrant mention in the ocrelizumab label because there was no corresponding imbalance in the rheumatoid arthritis trials.

--6. Pancreatitis

Drs. Boehm and Yasuda consider it significant the pancreatitis occurred in 5 ocrelizumab treated patients and none in the comparator subjects in controlled trials. Even though three of the patients with pancreatitis had known risk factors and there is no clear relationship to ocrelizumab, they agree that there should be postmarketing surveillance.

[107] Dr. Yasuda's review, page 33 of 45.

Common adverse events

Table 21 and Table 22, below, list adverse events that occurred in more than 5% of patients and more often in those treated with ocrelizumab

Table 21 Most Common Adverse Events in RMS Trials

Most Common Adverse Events in RMS Trials (WA21092 and WA21093) Events Occurring in At Least 5% of Patients and More Often with Ocrelizumab			
Body System or Organ Class	**Adverse Event**	**Rebif n = 826**	**Ocrelizumab n = 825**
Infections and Infestations	*Upper Respiratory Tract Infections*	29%	36%
	Urinary Tract Infections	14%	14%
	Herpes Infections	4%	6%
	Gastroenteritis	4%	6%
Injury, Poisoning, and Procedural Complications	*Infusion-related reactions*	10%	34%
Musculoskeletal and Connective Tissue Disorders	*Back pain*	4%	6%
	Pain in extremity	4%	5%
Gastrointestinal Disorders	*Abdominal pain*	4%	5%
Psychiatric Disorders	*Depression*	7%	8%
	Insomnia	5%	6%

Table 22 Most Common Adverse Events in the PPMS Trial

Most Common Adverse Events in the PPMS Trial (WA25046) Events Occurring in At Least 5% of Patients and More Often with Ocrelizumab			
Body System or Organ Class	**Adverse Event**	**Placebo n = 239**	**Ocrelizumab n = 486**
Infections and Infestations	*Upper Respiratory Tract Infection*	37%	39%
	Influenza	9%	12%
	Bronchitis	5%	7%
Injury, Poisoning, and Procedural Complications	*Infusion related reactions*	26%	40%
Psychiatric Disorders	*Insomnia*	5%	6%
Respiratory, Thoracic, and Mediastinal Disorders	*Cough*	3%	6%
Vascular Disorders	*Hypertension*	4%	5%

Need for Risk Evaluation and Mitigation Strategy (REMS) after Approval

The applicant did not submit a REMS but did submit a Risk Management Plan (RMP) that proposes post-marketing safety studies to further assess long term safety data. The Division of Risk Management assessed whether a REMS is necessary to ensure the safety and efficacy of ocrelizumab if it is approved and marketed. The DRISK review team was reviewer Laura Zendel, PharmD, BCPS; team leader Jamie Wilkins Parker, PharmD; and Division Director Cynthia LaCivita, PharmD. The team recommends that

a REMS is not necessary to ensure the benefits outweigh the risks of infusion related reactions, infections, and malignancy because:

a) Healthcare providers who treat RMS and PPMS are typically specialists and are familiar with the risk of infusion related reactions and infection with similar therapies and the importance of patient monitoring.
b) Including infusion related reactions as a warning with recommendations for pretreatment will be used to communicate and mitigate this risk.
c) Labeling infections as a warning would highlight the need for awareness of the potential for infections.
d) Labeling malignancies as a warning would highlight the need for awareness of the potential risk.

The review agrees that a REMS would not be necessary if ocrelizumab is approved.

8. Advisory Committee Meeting

There are no plans for an advisory committee meeting.

9. Pediatrics

The applicant has submitted an approved initial pediatric study plan to begin when there is enough information from results in adult trials.

10. Other Relevant Regulatory Issues

There are no other relevant regulatory issues.

11. Labeling

Labeling is under negotiation at the time of this review.

12. Postmarketing Recommendations

Postmarketing Requirements (PMRs) and Commitments (PMCs)

PMR's are currently under discussion.

13. Recommended Comments to the Applicant

None.

APPEARS THIS WAY ON ORIGINAL

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/s/

JOHN R MARLER
11/28/2016

Safety Team Leader Review

Date	October 25, 2016
From	Sally Usdin Yasuda
Subject	Safety Team Leader Review
NDA/BLA # Supplement#	BLA 761053
Applicant	Genentech
Date of Submission	April 28, 2016
PDUFA Goal Date	December 28, 2016
Proprietary Name / Non-Proprietary Name	Ocrevus/Ocrelizumab
Dosage form(s) / Strength(s)	Solution for intravenous infusion, 300 mg/10 ml
Applicant Proposed Indication(s)/Population(s)	Treatment of patients with relapsing forms of multiple sclerosis (RMS) and treatment of patients with primary progressive multiple sclerosis (PPMS)
Recommendation on Regulatory Action	If efficacy is demonstrated and the benefits of ocrelizumab outweigh the risks for either RMS or PPMS, then I recommend that approval for either RMS or PPMS include labeling language addressing adverse reactions of concern.
Recommended Indication(s)/Population(s) (if applicable)	

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Ocrelizumab is proposed to be used for treatment of patients with relapsing forms of multiple sclerosis (RMS) and treatment of patients with primary progressive multiple sclerosis (PPMS). This review evaluates the safety of ocrelizumab. If efficacy is demonstrated and the benefits of ocrelizumab outweigh the risks in either RMS or PPMS, then I recommend that approval be accompanied by labeling language including warnings and a medication guide to mitigate the risks.

This document reviews the risk profile of ocrelizumab. I summarize the findings of Dr. Jerry Boehm. Ocrelizumab is associated with infusion related reactions (IRRs), infections, malignancies including breast cancer, and depression. These adverse reactions have potential for more serious outcomes in the postmarketing period in which patients are monitored less frequently than in the clinical trial setting. Warnings in the labeling and a Medication Guide for patients may mitigate potentially serious outcomes of these adverse reactions. A recommendation regarding approvability can only be made based on a consideration of benefit and risk. I will provide an assessment of the risk, and recommendations for labeling in an effort to mitigate the risk if efficacy is demonstrated and it is determined that the benefits outweigh the risk such that ocrelizumab would be approved for either indication.

Risk:

Ocrelizumab is associated with IRRs that occurred in 35% of patients in the all MS trials pool, even in the setting of pretreatment that was required in the clinical trials. The IRRs occurred most frequently after the first dose but continued to occur with subsequent infusions. Most of the infusion reactions were mild and occurred during the infusion period, although some also occurred within 24 hours of the infusion but after the patient had left the clinic. Infections were commonly reported in the MS trials overall (54%) and in the controlled trials where they occurred more commonly with ocrelizumab than with comparator, although SAEs due to infections occurred less frequently with ocrelizumab than with comparator. Opportunistic infections were not identified in MS patients treated with ocrelizumab. Ocrelizumab was associated with malignancies in the MS trials, with an approximate 3 fold increase for ocrelizumab vs comparator in the controlled trials. In particular there was an imbalance in the controlled trials for breast cancer associated with ocrelizumab use (with 6 cases in women exposed to ocrelizumab vs none in comparator). There were 8 cases (8/1,398 females, 0.6%) in the all MS trials (Pool B). One case of breast cancer in a (Japanese) male occurred in a Rheumatoid Arthritis Trial, an unexpected occurrence given the background rate of breast cancer in Japanese men. SAEs of depression suicidal, suicide attempt, and suicidal ideation occurred only in ocrelizumab patients and none in placebo for PPMS. Depression TEAEs occurred less frequently in ocrelizumab-treated patients than placebo in the PPMS controlled trial, but in the RMS controlled trials (Pool A) they occurred slightly more frequently than interferon (8% vs 7%) than in interferon beta-1a that has a Warning for Depression and Suicide. There is uncertainty regarding potential for more serious outcomes in the postmarketing period in which patients are monitored less frequently than in the clinical trial setting. Warnings in the labeling and a Medication Guide for patients may mitigate potentially serious outcomes of these adverse reactions.

Paragraph #5: Analysis and Recommendation with Respect to Safety:

If ocrelizumab is approved, I recommend labeling that includes Warnings for IRRs, infections, malignancies, and depression/suicide, and guidance for pre-treatment to mitigate the risk of infusion reactions. I recommend a Medication Guide to describe these risks and symptoms of concern. I recommend enhanced pharmacovigilance postmarketing for events of serious infections, including opportunistic infections, with a focus on PML and Hepatitis B reactivation; cholecystitis/cholelithiasis; and pancreatitis. I recommend the following postmarketing requirements:

- Long-term observational postmarketing requirement to characterize safety with emphasis on the risk of malignancies and infections.
- Pregnancy registry.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Please refer to Dr. Rodichok's review of clinical efficacy.	
Current Treatment Options	• Please refer to Dr. Rodichok's review of clinical efficacy.	
Benefit	• Please refer to Dr. Rodichok's review of clinical efficacy.	
Risk	Safety database The safety database for ocrelizumab includes two Phase 3 interferon beta-1a controlled clinical trials in adults in RMS (WA21092 and WA20193) and their open label extensions, a Phase 2 dose finding trial in RMS (WA21493), and	Given the established relationship between *other* anti-CD20 monoclonal antibodies and IRRs including fatal infusion reactions that

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	one placebo-controlled trial in PPMS (WA25046), as well as supportive data primarily from controlled and open label studies in Rheumatoid Arthritis and more limited supportive data from studies in patients with Systemic Lupus Erythematosus (S), Lupus Nephritis (LN), and Non-Hodgkin's Lymphoma (NHL). Drug exposure is adequate, was at or above the proposed doses, and the demographics of clinical trial subjects reflects the intended population for use. Safety concerns • The most common AEs in the pooled RMS Phase 3 controlled phases (at least 5% and at least as frequent as interferon beta-1a) were: Upper respiratory tract infections (URI, 36%), Infusion related reactions (IRRs, 34%), Urinary tract infections (UTI, 14%), Depression (8%), Herpes infections (6%), Gastroenteritis (6%), Back pain (6%), and Insomnia (6%). The most common AEs in the PPMS controlled phase (at least 5% and at least 2% greater than placebo) were: IRRs (40%), URI (39%), Influenza (12%), Bronchitis (7%), and Cough (6%). • Eight deaths (0.4%, 0.18/100 PY) occurred in ocrelizumab-treated subjects in controlled and open label MS studies (Pool B): 1 of suicide in a patient with no signs or symptoms of depression prior to the event but with felony charges 2 days prior to the event, 1 of metastatic pancreatic cancer diagnosed approximately 51 months after beginning ocrelizumab, 1 of aspiration pneumonia in a patient with a history of dysphagia, 1 of pneumonia reported as desquamative pneumonia with associate bacterial component in a translated autopsy report for which a role for ocrelizumab cannot be ruled out, 1 of pulmonary embolism approximately10 months after the last dose of ocrelizumab, 1 due to systemic inflammatory response syndrome (SIRS) for which a role for ocrelizumab cannot be ruled out, 1 sudden death more than 1 year after the last dose, 1 due to injury (fall from great height) more than 1 year after last dose.	mostly occurred with the first infusion of those drugs, the Sponsor required premedication to prevent/mitigate IRRs in the ocrelizumab trials. Whether more serious IRRs would occur in the absence of pretreatment with ocrelizumab is unknown. Labeling including IRRs as a Warning with recommendations for pre-treatment could mitigate the potential risk. Ocrelizumab is associated with a risk of infections, and uncertainty exists in whether outcomes of infections would be more serious in an unmonitored outpatient setting. Labeling infections as a Warning would highlight the need for awareness of the potential for infections and may mitigate the risk for serious outcomes. Ocrelizumab is associated with an increased risk of malignancies, particularly breast cancer in males and in females. Labeling malignancies as a Warning would highlight the need for awareness of the potential. This may be particularly important in the outpatient setting in which patients may be seen less frequently than in the clinical trials. Malignancies should be further characterized in the postmarketing setting. There is an imbalance in SAEs with terms related to depression and suicide in RMS and PPMS controlled trials for ocrelizumab vs comparator and because TEAEs related to depression in RMS controlled trials were

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	There were too few deaths during controlled phases of the MS trials to support conclusions about relative mortality risks. Forty-five deaths (1.5%, 0.61/100 PY) occurred in All RA Trials (Pool E). The 37 deaths that occurred during treatment or within 1 year of the last dose included 7 pneumonia (6/7 had received other immunosuppressants), 6 sepsis/septic shock (4/6 had received corticosteroids and methotrexate), 3 respiratory failure, 3 lung cancer, 3 sudden death/death, 2 myocardial infarction, and 1 each of brain edema, breast cancer, carbon monoxide poisoning, disseminated intravascular coagulation, gastric cancer, gastrointestinal carcinoma, gastrointestinal hemorrhage, ischemic cerebral infarction, multi-organ failure, pulmonary embolism, ruptured cerebral aneurysm, toxicity to various agents, and traffic accident. Although the mortality rate for ocrelizumab and placebo were comparable in the controlled trials, the ocrelizumab groups had an increased number of infection/sepsis related deaths (5) compared to placebo (0). • Ocrelizumab is associated with IRRs. All patients in MS trials were pretreated with methylprednisolone prior to each infusion; pre-treatment with oral analgesic/antipyretic and an oral antihistamine was recommended. TEAEs of IRRs occurred in 35% in All MS Trials (Pool B), and approximately 2 to 3 times more frequently than comparator in controlled trials. There were few discontinuations or SAEs of IRRs (1% or fewer). IRRs occurred most frequently with the first dose but continued to occur with subsequent doses. Most (60-80%) occurred during the infusion but 18% to 38% occurred within 24 hours of the infusion but after leaving the clinic in RMS and PPMS controlled trials. No deaths were attributed to IRRs in ocrelizumab treated MS patients. The most common symptoms of IRRs related to ocrelizumab were pruritus, rash,	similar for ocrelizumab compared to interferon that has a Warning for Depression and Suicide. A Warning for ocrelizumab may help mitigate the risk. Five SAEs of pancreatitis occurred in ocrelizumab patients in controlled MS trials, 3 of them in patients with risk factors, and none in comparator patients. The relationship between the risk for pancreatitis and use of ocrelizumab is unknown. Postmarketing reports should be monitored for additional cases. There was an imbalance in AEs related to cholecystitis/cholelithiasis. Given that a similar imbalance was not seen in the RA trials, that these events are not mentioned in labeling for the approved antiCD20 monoclonal antibodies, and that these events are expected in the background, inclusion of these events in labeling is not recommended at this time. Reports of these events in the post marketing period should be monitored. Because the risk of adverse outcomes in pregnancy has not been characterized, and because ocrelizumab will be used in women of childbearing potential, a pregnancy registry should be considered as

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	throat irritation, flushing, urticaria, and oropharyngeal pain in RMS with similar IRRs in PPMS that also reported pyrexia commonly. 73% of IRRs were mild in Pool B. Antihistamines were the most commonly administered treatments for IRRs. In MS controlled trials, ocrelizumab patients pretreated with oral antihistamine and methylprednisolone generally had a least a 2-fold lower incidence in IRRs compared with pretreatment with methylprednisolone alone. Potential for more serious reactions in the absence of pre-treatment is unknown. • Infections were commonly reported in the MS trials overall (54%) and in the controlled trials. There was a slightly greater risk of infections with ocrelizumab compared to interferon in RMS Pool A and compared to placebo in the controlled phase of the PPMS trial. In controlled trials, infection SAEs occurred less frequently in ocrelizumab treated patients than in comparator patients. Infections resulted in few discontinuations. The most common infections and greater than interferon in RMS controlled trials were upper respiratory tract infections, herpes infections, lower respiratory tract infections, and gastroenteritis. The most common infections and greater than placebo in the PPMS controlled trial were upper respiratory tract infections, influenza, lower respiratory tract infections, and bronchitis; herpes infections also occurred at a rate greater than placebo. Opportunistic infections were not identified in MS patients treated with ocrelizumab. The greatest risk for infections was following the first dose in the controlled RMS trials. Whether outcomes of infections would be more serious in an unmonitored outpatient setting or in patients at greater risk for infections is unknown. • An increase in malignancies is observed for ocrelizumab compared to interferon in Pool A (2.5 fold increase) and compared to placebo in the placebo in the PPMS controlled trials (2.9 fold increase). In particular, there is an imbalance in breast cancer in the controlled trials in which 2 cases (0.3% of females) occurred in ocrelizumab vs none in interferon beta-1a in RMS Pool A and 4 cases (1.6% of females) occurred in the PPMS controlled trial in ocrelizumab vs none in placebo, all occurring	a postmarketing requirement.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	after at least 1 year of treatment with ocrelizumab, with 8 cases (8/1,398 females, 0.6%) in the all MS trials (Pool B). In the all RA trial pool, 7 patients were diagnosed with breast cancers: 6 females (6/2,341 females, 0.3%) and 1 male (1/585 males; 0.2%), an unexpected event given the background incidence of male breast cancer. • There was no imbalance in SAEs or TEAEs in the *Psychiatric disorders* SOC overall in the controlled trials in RMS or PPMS. However, SAEs of depression suicidal, suicide attempt, and suicidal ideation occurred only in ocrelizumab patients and none in placebo for PPMS. Depression TEAEs occurred less frequently in ocrelizumab-treated patients than placebo in the PPMS controlled trial, but in the RMS controlled trials (Pool A) they occurred slightly more frequently than in interferon beta-1a (8% vs 7%) that has a Warning for Depression and Suicide. Because interferon beta-1a labeling has a warning for depression and suicide, I recommend considering a warning for ocrelizumab. <u>Safety in the post-market setting</u> The risk for serious outcomes of adverse events including infections and malignancies in the postmarketing period when patients are likely to be observed less frequently than in clinical trials is unknown. <u>Other uncertainties</u> • SAEs of pancreatitis occurred in 5 ocrelizumab treated patients and none in the comparator subjects in controlled trials. Three of the patients with pancreatitis had known risk factors. A clear relationship to ocrelizumab is not present at this time. • Cholecystitis/cholelithiasis occurred more frequently with ocrelizumab but the significance of this finding is not clear. • The risk of adverse outcomes in pregnancy has not been characterized.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• Product labeling with Warnings and a Medication Guide regarding the risks of IRRs, infections, malignancies, and depression/suicide may mitigate the risks of serious outcomes of these events. A post-marketing requirement for an observational safety study will help to evaluate the main safety risks of ocrelizumab in the post-marketing setting.	Warnings and a Medication Guide with information regarding the main safety risks may help mitigate serious outcomes of these risks in the post-marketing setting. A post-marketing requirement for an observational safety study will help to evaluate the main safety risks of ocrelizumab in the post-marketing setting.

2. Background

This memorandum summarizes the primary concerns from the safety review, conducted by Dr. Gerard Boehm, of the ocrelizumab BLA 761053 and provides my conclusions and recommendations regarding the safety findings and management of the risks. I also discuss the reviews from Dr. Gwynn Ison (Division of Oncology Products 1), Dr. Bindu Kanapuru (Division of Hematology Products), and Dr. Elisa Braver (Office of Pharmacovigilance and Epidemiology) regarding malignancies.

- *The product information and the applicant's proposals*

Ocrelizumab is a recombinant humanized monoclonal IgG1 antibody that, according to the sponsor, selectively depletes CD20-expressing B cells[1,2,3]. The sponsor states the capacity of B-cell reconstitution and pre-existing humoral immunity are preserved and that innate immunity and total T cell numbers are not affected. The Sponsor proposes that the therapeutic clinical effects in MS involve immunomodulation through reduction in number and function of B cells. The proposed indications for ocrelizumab are treatment of patients with relapsing forms of multiple sclerosis (RMS) and treatment of patients with primary progressive multiple sclerosis (PPMS). The proposed dose for either indication is 600 mg as an initial dose (given as two 300 mg intravenous infusions separated by 2 weeks) followed by 600 mg administered by intravenous (IV) infusion every 6 months.

As Dr. Boehm notes, the Sponsor included as events of special interest adverse events associated with the class of anti-CD20 monoclonal antibodies: serious infections, malignancies, and infusion related reactions (IRRs).

Rituxan is an anti-CD20 monoclonal antibody approved for treatment of patients with Non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), and Rheumatoid Arthritis (RA) in combination with methotrexate, and Wegners's Granulomatosis and microscopyic Polyangitis. Adverse reactions in Warnings and Precautions of the Rituxan labeling include Infusion Reactions, Severe Mucocutaneous Reactions, Hepatitis B Virus Reactivation, Progressive Multifocal Leukoencephalopathy (PML), Infections, Cardiovascular (discontinue for serious or life-threatening arrhythmias, noting in section 6 that patients with RA are at increased risk for cardiovascular events compared with the general population). [4]

Ocrelizumab is not approved for any other indication in the United States. The sponsor evaluated ocrelizumab for treatment of rheumatoid arthritis (RA), systemic lupus

[1] Daclizumab, in comparison, is thought to modulate IL-2-mediated activity of T cell signaling by binding to the CD25 subunit of the high affinity IL-2 receptor on T cells.
[2] The Sponsor used CD 19+ B cells as a marker for CD20 because the presence of ocrelizumab interferes with the assay for CD20.
[3] According to Boross and Leusen, CD20 is a general B cell marker of which the exact biological function is unknown. Boross P, Leusen JHW. Am J Cancer Res 2012: 2(6):676-690.
[4] The Rituxan labeling also includes severe renal toxicity after Rituxan administration patients with NHL who experience tumor lysis syndrome and in patients with NHL administered concomitant cisplatin therapy. It also includes bowel obstruction and perforation in patients receiving Rituxan in combination with chemotherapy.

erythematosus (SLN), lupus nephritis (LN), and non-Hodgkin's lymphoma (NHL). According to the Clinical Overview (p. 21), the development program for RA was stopped based on safety (increased incidence of serious and opportunistic infections compared with comparator) and efficacy. The development program for lupus was terminated early (b) (4) because of an increased incidence of serious and opportunistic infections in the ocrelizumab LN study.

- *Therapeutic context*

Multiple sclerosis (MS) is a chronic, autoimmune and neurodegenerative disorder of the central nervous system that affects approximately 2.5 million individuals worldwide. According to the Sponsor, MS typically begins between the ages of 20-40 years with women affected twice as often as men. However, according to the Sponsor, PPMS, accounting for approximately 10% of all cases, has a mean age of onset of approximately 40 years and there is no gender difference. Dr. Boehm provides a list of the products already approved for use in patients with relapsing forms of multiple sclerosis in the United States. The available products have a variety of safety issues. Please refer to his review (page 18-19) for a summary of important safety issues for the approved products. There are no treatments approved for PPMS.

- *Regulatory background and marketing history*

Please refer to Dr. Larry Rodichok's review.

3. Product Quality

Please refer to the CMC review.

4. Nonclinical Pharmacology/Toxicology

Please refer to the nonclinical reviews. In the nonclinical overview the sponsor contends that drug-related effects were consistent with the expected pharmacologic depletion of B cells. The sponsor notes adverse events in the pre-and postnatal cynomolgus monkey study in which glomerulopathy or lymphoplasmacytic inflammation in the kidney were evident in neonates, and that there was evidence of opportunistic infections leading to moribundity in 2 neonates.

5. Clinical Pharmacology

Please refer to the Clinical Pharmacology review. The following information regarding pharmacokinetics and pharmacodynamics is from of the Clinical Overview provided by the applicant and reflects the findings most relevant to safety.

- Terminal elimination half-life is 26 days.
- B cell depletion in blood was complete and sustained on average for 6 months after first drug administration, although up to 5% of patients showed repletion greater than

lower limit of normal (LLN) or baseline (whichever was lower) at least at 1 time point between infusions; repletion occurred less frequently in patients with higher exposures.

- Median time to repletion (Phase 2 study WA21493) was 72 weeks after the last infusion. Ninety percent of all patients had B cells repleted to the LLN or baseline (whichever was lower) by approximately 2.5 years after last infusion.
- In RA studies, the majority of patients demonstrated depletion of B cells within 7 days from the infusion.[5]

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Please refer to Dr. Larry Rodichok's review of efficacy.

8. Safety

8.1 Safety Review Approach

The following pools were agreed upon by the Sponsor and the Division during pre-BLA meetings for the analysis of ocrelizumab clinical safety:

Pool A: *Phase 3 RMS Controlled Trials* (controlled phase of WA21092 and WA20193)
Pool B: *MS all Exposure* (RMS Pool B, PPMS trial WA25046, and Phase 2 dose finding trial WA21493[6])
Pool C: *Phase 3 RMS All Exposure* (controlled and open label phases of WA21092 and WA21093)
PPMS trial WA25046 (Phase 3 PPMS controlled trial)
Pool D: *Phase 2 and 3 RA Controlled Trials* (7 placebo controlled studies)
Pool E: *RA All Exposure* (9 RA studies including controlled, open label extension, and safety follow-up periods).

	Description	Trials Included	Number exposed to ocrelizumab	Number exposed to IFN B1-a	Number exposed to Placebo
Pool A	*Phase 3 RMS Controlled Trials*	Controlled phase of WA21092 and WA20193	825	826	-
Pool B	*MS all Exposure*	RMS Pool A PPMS trial WA25046	2147	-	-

[5] In RMS, the nadir occurred by week 2. Please refer to p. 35 of this memo.
[6] Only the first dose of this study was controlled. The Sponsor included WA21493 in this pool for the adverse events, but not for the evaluation of laboratory data.

		Phase 2 dose finding trial WA21493			
Pool C	*Phase 3 RMS All Exposure*	controlled and open label phases of WA21092 and WA21093	1448	-	-
PPMS	Phase 3 PPMS Controlled Trial	WA25046	486	-	239
Pool D	*Phase 2 and 3 RA Controlled Trials*	7 placebo controlled studies	2133: 1186 (400 mg) 947 (1000 mg)	-	981
Pool E	*RA All Exposure*	9 RA studies including controlled, open label extension, and safety follow-up periods	2926	-	-

I note that Pool B is used as the combined MS pool throughout Dr. Boehm's review and throughout my memo. The findings in the All RMS pool (Pool C, a subset of Pool B) are consistent with those reported in RMS Controlled Trials (Pool A) and similar to those reported in All MS trials (Pool B). I agree with Dr. Boehm that the Pool C data do not appear to provide additional useful information.

The primary data in Dr. Boehm's review and in this memo are from the MS trials. Supportive safety data include primarily Pools D and E for the RA studies, as well as studies in SLN, LN, and NHL

In RMS studies WA21092 and WA21093 subjects were given intravenous infusions of ocrelizumab 600 mg (given as two 300 mg infusions on Days 1 and 15 of the first 24-week dose and as a single infusion of 600 mg on Day 1 of each 24 week dose thereafter) or interferon beta-1a 44 μg given subcutaneously three times a week, for 96 weeks, after which all eligible patients could enter the open label extension (OLE). Patients who withdrew prematurely from the controlled period, or who withdrew from the OLE or did not enter the OLE were entered into the safety follow-up (SFU) that lasted at least 48 weeks, and longer until B cell repletion occurred. B cell repletion was defined as return to baseline or lower limit of normal (LLN, 80 cells/uL), whichever was lower.

In the RMS Phase 2 dose finding study WA21493 (double-blind, randomized, placebo controlled and interferon controlled, parallel group study) ocrelizumab subjects were randomized to receive study drug every 24 weeks in a double blind phase: either 2000 mg for 1 dose, 600 mg for 1 dose, placebo for 1 dose, or IFN for 1 dose, followed by 72-week unblinded phase with 3 doses of 600 mg each in each treatment arm After completion of the controlled period, patient initially entered a treatment-free SFU period. The OLE was subsequently introduced, but there was a variable treatment-free period before restarting ocrelizumab.

In PPMS Study 25046 ocrelizumab was given as two 300 mg IV infusions separated by 14 days, at a scheduled interval of every 24 weeks through at least 120 weeks, and compared to

placebo. That was followed by an OLE. Patients who completed or withdrew prematurely from double-blind treatment were encouraged to enter a SFU period.

Study drug was administered on an outpatient basis, in a hospital or clinic environment under close supervision with immediate availability of full resuscitation facilities. Patients remained under observation for at least 1 hour after the completion of each infusion.

Patients could not have received a live vaccine within 6 weeks prior to randomization, and immunization with any live or live-attenuated vaccine was not recommended within 6 weeks prior to first dosing, during study drug treatment and for as long as the patient was B-cell depleted.

Patients could not have had previous treatment with Ampyra[7], B-cell targeted therapies (e.g. rituximab), previous treatment with alemtuzumab, anti-CD4, cladribine, cyclophosphamide, mitoxantrone, total body irradiation, or bone marrow transplantation, or treatment with cyclophosphamide, azathioprine, mycophenolate mofetil [MMF], cyclosporine, methotrexate, within 24 months prior to screening, natalizumab within 24 months prior to screening (and if ever treated with natalizumab, duration could only have been less than 1 year), fingolimod within 24 weeks prior to screening[8]. These limitations should be considered if ocrelizumab is approved.

8.2 Review of the Safety Database

Adequacy of the drug exposure experience (i.e., the safety database)

A total of 5406 patients (5214 patient years) were exposed to ocrelizumab across all indications. I show exposure in the Phase 3 MS trials in the table below.

Exposure in Phase 3 MS Trials in the ISS

Phase 3 Controlled MS trials (Pool A)	All MS pool (Pool B)[9]	All RMS pool (Pool C)	Phase 3 Controlled PPMS Trial
825 patients	2147 patients	1448 patients	486 patients
1448 PY[9]	4485 PY	2305 PY	1447 PY[10]

The RA development program evaluated doses ranging from 20 mg to 2000 mg.

[7] In the RMS phase 3 trials
[8] In PPMS Study 25046, any previous treatment with natalizumab, or fingolimod was excluded; treatment with beta-interferons, glatiramer acetate, IVIG, plasmapheresis, or other immunomodulatory therapies within 12 weeks prior to randomization were excluded.
[9] Exposure in MS trials increased to 2,279 patients and 5711 PYs at the time of the 90 day safety update because of patients who started/continued OLE ocrelizumab treatment.
[10] From Summary of clinical Safety, p. 89

The table below, from Dr. Boehm's review, shows duration of exposure in the All MS pool (Pool B) through the 90 Day Safety Update. The exposure, including exposure at relevant doses in the MS population, exceeds ICH guidelines of 1500 patients total, 300-600 patients for 6 months, and 100 patients for 1 year.

Duration of Exposure in MS trials, through the 90 Day Safety Update

Number of patients exposed to Ocrelizumab, MS All Exposure (Pool B):			
>23 weeks	>47 weeks	>71 weeks	>95 weeks
N=2,104	N=2,063	N=1,719	N=1,502

Dr. Boehm notes that the mean number of ocrelizumab doses for the overall MS population was 4.7 (median 5) and the mean cumulative dose was 2,825 mg (median 3,000mg, range 9-8,220 mg).

For all MS trials, the median age was 40 years (range 18 - 58 years), 62% of patients were female and 92% were white. Differences in the RMS and PPMS populations included gender (66% of ocrelizumab patients were female in the RMS trials, compared to 49% in the PPMS trial), mean age (37.2 years in the RMS trials compared to 44.6 years in the PPMS trial), race (90% of ocrelizumab patients in the RMS trials were White compared to 93% in the PPMS trial) and region (26% of ocrelizumab patients were from the USA in the RMS trials compared to 13% in the PPMS trial).

8.3 Adequacy of Applicant's Clinical Safety Assessments

Dr. Boehm notes that the Sponsor included all AEs recorded through the entire observation period and did not exclude events occurring after stopping treatment. Because of the 26 day half-life and the persistent effect on B cell depletion, it seems appropriate that a minimum observation period would be 24 weeks. However, in the all MS Pool B (excluding Phase 2), I note that only 146 patients entered the SFU, with 121 of those patients observed for 24-96 weeks after the last infusion.[11]

Dr. Boehm describes the adequacy of the safety assessments in detail. He considered the safety data provided by Genentech reliable and consistent. He noted that the presentations were occasionally limited and accessing certain information in the application was difficult, but that the Sponsor was responsive and quickly addressed deficiencies in response to Information Requests. Dr. Boehm notes that he was able to replicate the Sponsor's analyses. He noted that the Sponsor used common definitions of AE, SAEs, and TEAEs and that the coding process for verbatim AE terms was adequate and should allow for accurate estimates of event risks. Serious MS relapses were included as AEs.

[11] ISS Table 78.

8.4 Safety Results

Dr. Boehm has identified a number of important safety concerns that occurred in the clinical trials to a greater extent in subjects receiving ocrelizumab than comparator. These include IRRs, infections, malignancies, and SAEs related to depression and suicide. Some adverse reactions (IRRs and infections) occurred most frequently with the first dose although a risk persisted throughout the trials.

In this section I first discuss the deaths in the database. Then I provide a general overview of the safety results regarding SAEs and discontinuations. Next I discuss safety issues of concern and then other serious adverse events, incorporating information from SAEs, Discontinuations, TEAEs, and labs, as appropriate. That is followed by a summary of TEAEs. I finish Section 8.4 with a summary of the other issues discussed in Dr. Boehm's safety review (including laboratory values, vital signs and electrocardiograms and immunogenicity).

Deaths

Dr. Boehm notes that deaths were infrequently reported in the MS trials. Eight deaths (8/2,149; 0.37%) occurred in ocrelizumab-treated patients in the MS trials overall compared to 45/2,926 (1.5%) in the RA trials overall. The mortality rate for ocrelizumab in the MS trials overall was 0.18 per 100 PY compared to 0.61 per 100 PY in the RA trials overall. I show mortality risks in the controlled trials in the table below and discuss individual cases below. I agree with Dr. Boehm that there were too few deaths during controlled phases of the MS trials to support conclusions about relative mortality risks.

	Mortality risk (# deaths/number of subjects in trial)	
	Ocrelizumab	**Control**
RMS	1/825 (0.12%)	2/826 (0.24%) IFN-beta-1a)
PPMS	4/486 (0.8%)	1/239 (0.4%) (placebo)
RRMS Phase 2 Dose Finding Study WA21493	3/110 (2.7%)	0/54 (IFN-beta-1a) 0/54 (placebo)
RA trials (controlled phases)	13/2133 (0.6%)	2/981 (0.2%)

In the RMS controlled phase (Pool A) the one death (WA21093-234069-1936964) was due to *suicide* in a patient with no previous relevant medical history but a recent felony charge. I agree with Dr. Boehm there is no obvious link.

In the PPMS controlled trial the placebo death was following a traffic accident. The causes of death in ocrelizumab patients were as follows:

Subject WA25046-208392-21404 died of *metastatic pancreatic cancer* with which she was diagnosed approximately 3 years and 4 months of treatment with ocrelizumab. I agree with Dr. Boehm there is no obvious link, but that a possible contribution of ocrelizumab cannot be excluded.

Subject WA25046-208690-26307 with a history of dysphagia developed fever and productive cough and hospitalized for pneumonia that worsened, with chest X-ray showing infiltrates in 2/3 of the left lung and the right upper lung; reported cause of death was respiratory failure with severe probable *aspiration pneumonia*. I agree this is likely related to the patient's dysphagia.

Subject WA25046-208367-3032 was a nonsmoker who died of "*desquamative pneumonia* with associated bacterial component" according to the translated autopsy report that developed approximately 1 month after the 2nd dose (IRR occurred with the first dose). I agree with Dr. Boehm that ocrelizumab could have contributed.

Subject WA25046-208159-44002 died of *pulmonary embolism* approximately 10 months after discontinuation of ocrelizumab. I agree with Dr. Boehm that there is no obvious link between ocrelizumab and the event and the long interval between the last dose and death suggests a low likelihood that ocrelizumab contributed.

Three deaths occurred in MS dose finding study WA21493; 2 occurred more than 1 year after the final dose of ocrelizumab (WA21493-140977-2301 due to unknown cause; WA21493-141-24-5303 subsequent to fall from great height). Subject WA21493-140942-1515 died due to *systemic inflammatory response syndrome (SIRS), disseminated intravascular coagulation, and multiorgan failure* that began approximately 12 weeks after the first cycle (ocrelizumab 1000 mg) with a narrative that Dr. Boehm believes describes sepsis without obvious source resulting in multiorgan failure. I agree with Dr. Boehm that ocrelizumab could have contributed to the event through increased susceptibility to infection or contribution to the inflammatory response.

The 45 deaths in the RA program included 3 that occurred at least 350 days after having only a single dose (including 1 case of "B-cell lymphoma") and 5 that occurred at least 1 year after the last dose and I agree with Dr. Boehm that the likelihood of an association between ocrelizumab and the deaths is remote. For the remaining 37 deaths, the reported causes, as noted by Dr. Boehm, were pneumonia (7), sepsis/septic shock (6), respiratory failure (3)[12], lung cancer (3, patients with history of cigarette smoking), other cancers (1 each of breast cancer, gastric cancer, gastrointestinal carcinoma after approximately 1 year, 6 months, and 3 years of treatment, respectively), sudden death/death (3), myocardial infarction (2), brain edema, carbon monoxide poisoning (after accidental house fire/cardiac arrest), disseminated intravascular coagulation (subsequent to pneumonia and SIRS 556 days after last ocrelizumab; 1 month after etanercept), ischemic cerebral infarction in a patient with a history of atrial fibrillation, multi-organ failure, pulmonary embolism, ruptured cerebral aneurysm, toxicity to

[12] WA20495-110578-50703 with pneumonia/sepsis, WA20494-119481-23802 presumed due to pulmonary embolus complicated by pneumonia.

various agents, and traffic accident (single dose, no details). Of note, 4/6 sepsis cases had received corticosteroids and methotrexate and 6/7 pneumonia cases cases had also received other immunosuppressants including corticosteroids, methotrexate[13], adalimumab[14], tolizumab1[5], or abatacept[15]. Dr. Boehm notes that although the mortality rate for ocrelizumab and placebo were comparable in the controlled trials, the ocrelizumab groups had an increased number of infection/sepsis related deaths (5) compared to placebo (0).

Deaths in trials of other indications, as reported by Dr. Boehm, were due to similar causes as those in the MS and RA trials.

In summary, few deaths occurred in the MS controlled trials and it is difficult to determine the relationship between ocrelizumab and those deaths. Deaths in the RA trials included deaths due to serious infections and sepsis, in many cases confounded by concomitant use of immunosuppressant drugs.

SAEs and Discontinuations and TEAEs overall

Overall, there was not an imbalance in SAEs in the controlled trials although some specific SAEs did occur more frequently on ocrelizumab than comparator as discussed below. Discontinuations and TEAEs overall in the PPMS controlled trial occurred slightly more frequently than placebo. TEAEs overall in the RMS controlled trials occurred at the same frequency as interferon beta-1a and discontinuations occurred less frequently. I show these results in the table below.

Patients with SAEs, Discontinuations, or TEAEs in MS Trials

	All MS Trials (Pool B)	RMS Controlled Trials (Pool A)		PPMS Controlled Trial	
	Ocrelizumab n=2147	IFN beta-1a n=826	Ocrelizumab n=825	Placebo N=239	OCR N=486
All SAEs	10.8%	8.7%	6.9%	22.2%	20.4%
Discontinuations [a]	3.2%	6.2%	3.5%	3.3%	4.1%
TEAEs[b]	80%	83%	83%	90%	95%

[a] Withdrawal from treatment because of AEs
[b] Patients with at least 1 AE

Serious adverse events (SAEs)

Dr. Boehm notes that in the ocrelizumab MS trials, no single SAE was reported by at least 1% of exposed patients. The most commonly reported SAEs in all MS trials (Pool B) were infections (3%), fractures (0.6%), seizures (0.4%), MS relapse (0.4%), infusion related reactions (0.3%), cholelithiasis/cholecystitis (0.4%), breast cancer (0.3%), suicide attempt (0.3%), pancreatitis (0.2%), and back pain (0.3%). Dr. Boehm identified 1 SAE of immune thrombocytopenic purpura (**WA21493-141003-4354**) that occurred more than 1 year after the last dose of ocrelizumab and I

[13] Boxed warning for malignant lymphoma and for opportunistic infections.
[14] Boxed warning for serious infections and malignancy.
[15] Warning for infections.

agree with Dr. Boehm that the role of ocrelizumab in this case is not clear. He identified 1 case of agranulocytosis (WA25046-208244-47506) that occurred 14 months after the first ocrelizumab dose; the patient was treated with antibiotics and filgrastim and her neutrophil count improved. She continued to receive ocrelizumab and completed the controlled phase approximately 19 months after the event resolved. I agree with Dr. Boehm that the role of ocrelizumab in this event is not clear and I agree that lack of recurrence while continuing in the trial seems reassuring.

As Dr. Boehm notes, individual SAEs generally occurred too infrequently in the controlled phases of MS trials to allow for robust comparisons of risk by treatment, but SAEs reported more frequently with ocrelizumab than control included fractures, breast cancer, and cholelithiasis/cholecystitis in the RMS trials, and IRRs, pneumonia, breast cancer, pancreatitis, cholelithiasis/cholecystitis, and back pain in the PPMS trial.

In MS dose finding trial WA21493 Controlled phase 3.7% (2/54) of placebo patients reported SAEs compared to 1.8% (1/55) of ocrelizumab 600 mg patients and 3.6% (2/55) of ocrelizumab 1000 mg patients, and 3.7% (2/54) of interferon beta-1a patients. Dr. Boehm notes that the SAEs reported for ocrelizumab were abdominal pain upper (600 mg), systemic inflammatory response syndrome, and anxiety (both 1000 mg).

Dr. Boehm notes that there were no SAEs of aplastic anemia, pancytopenia, rhabdomyolysis, Stevens Johnson Syndrome, Toxic Epidermal Necrolysis, liver failure, or renal failure in MS trials[16]. There do not appear to be cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). SAEs of pancreatitis are discussed in Dr. Boehm's review and under Submission Specific Issues in my memo.

In All RA Trials (pool E) SAEs the reported rate of SAEs was 14.4 per 100 patient years. Those occurring at the highest rate were infections (3.8 per 100 patient years). In RA Controlled Trials (Pool D), the SAEs with the highest rate and greater in either ocrelizumab dose group than placebo were infections. Infections appeared to be dose related overall and included urinary tract infections and pneumonia among those with the highest rates. Other SAEs reported at a greater rate for ocrelizumab than placebo included IRRs.

Discontinuations

In RMS controlled trials, the risk for discontinuation for AEs was higher among interferon beta-1a patients than ocrelizumab patients as shown in the table above. The most common AE leading to discontinuation among ocrelizumab patients in Pool A or Pool B was *infusion related reactions* (1.3% in ocrelizumab vs 0 in interferon beta-1a.). In PPMS in the SOC Neoplasm Benign, Malignant and Unspecified, 1 placebo patient (0.4%) discontinued compared to 7 ocrelizumab patients (1.4%) and the AEs leading to treatment discontinuation in more than 1 patient in that pool and greater than placebo were breast cancer and infusion related reactions. Discontinuations in MS dose finding trial WA21493 occurred with frequencies similar to those in the other MS pools and were due to hypersensitivity, infusion related reactions, and anxiety.

[16] Dr. Boehm identifies SAEs of nephrotic syndrome and renal failure in WA20499-SLE and 1 SAE each of focal segmental glomerulosclerosis, renal failure, and renal infarct in OCR 1000 mg (but not in OCR 400 mg or placebo) in RA controlled trials.

According to the sponsor, the majority of patients who experienced AEs leading to discontinuation in Pool A discontinued following Dose 1, with the rate decreasing with each subsequent dose.

In RA trials, IRRs were the only AEs leading to discontinuation of more than 3 ocrelizumab patients. In RA controlled trials the frequencies of AEs leading to discontinuation were similar to those in the MS controlled trials.

Safety issues of concern in Dr. Boehm's review include:

- Infusion Related Reactions
- Infections
- Malignancies
- Depression/Suicide
- Cholecystitis and Cholelithiasis
- Pancreatitis

Genentech included adverse events associated with the class of anti-CD20 monoclonal antibodies as events of special interest for further analyses. These events included serious infections, malignancies, and infusion related reactions.

Submission Specific Safety Issues

Infusion Related Reactions (IRRs)

Ocrelizumab is associated with IRRs. Given the established relationship between *other* anti-CD20 monoclonal antibodies and IRRs including fatal infusion reactions that mostly occurred with the first infusion of those drugs, the Sponsor required premedication to prevent/mitigate IRRs in the ocrelizumab trials. All patients in MS trials received methylprednisolone 100 mg IV, 30 to 60 minutes prior to each ocrelizumab/placebo infusion. Pre-infusion treatment with oral analgesic/antipyretic (e.g. acetaminophen 1g) and an oral antihistamine (e.g. diphenhydramine 50 mg) was recommended but not mandated. TEAEs of IRRs occurred in 35% in All MS Trials (Pool B), in 34% of ocrelizumab and 10% of interferon beta-1a patients in Phase 3 Controlled RMS trials (Pool A), and in 40% of ocrelizumab and 26% of placebo patients in the PPMS controlled trial. There were few discontinuations or SAEs of IRRs (1% or fewer). IRRs occurred most frequently with the first dose but continued to occur with subsequent doses. Most (60-80%) occurred during the infusion but 18% to 38% occurred within 24 hours of the infusion but after leaving the clinic. The most common *symptoms of IRRs* related to ocrelizumab were pruritus, rash, throat irritation, flushing, urticaria, and oropharyngeal pain in RMS with similar IRRs in PPMS that also reported pyrexia commonly. No deaths were attributed to IRRs in ocrelizumab treated MS patients and most (73%) IRRs were mild in Pool B. Antihistamines were the most commonly administered treatments for IRRs. In MS controlled trials, ocrelizumab patients pretreated with oral antihistamine along with methylprednisolone generally had a least a 2-fold lower incidence in IRRs compared with pretreatment with methylprednisolone alone; addition of analgesics/antipyretics to oral antihistamines did not appear to have additional benefit. Potential for more serious reactions in the absence of pre-treatment is

unknown. I recommend labeling as a Warning and recommendations for pre-treatment to mitigate the risk of IRRs.

Dr. Boehm notes that given the established relationship between *other* anti-CD20 monoclonal antibodies and IRRs including fatal infusion reactions that mostly occurred with the first infusion, the Sponsor required premedication to prevent/mitigate IRRs in the ocrelizumab trials. He notes that all patients in MS trials received methylprednisolone 100 mg IV, 30 to 60 minutes prior to each ocrelizumab/placebo infusion. Pre-infusion treatment with oral analgesic/antipyretic (e.g. acetaminophen 1g) and an oral antihistamine (e.g. diphenhydramine 50 mg) was recommended but not mandated.[17]

SAEs, Discontinuations, and TEAEs of IRRs

	All MS Trials (Pool B)	RMS Controlled Trials (Pool A)		PPMS Controlled Trial	
	Ocrelizumab n=2147	IFN beta-1a n=826	Ocrelizumab n=825	Placebo N=239	OCR N=486
SAEs	0.3%	0.1%[c]	0.1%[c]	0	1%
Discontinuations[b]	1%	0	1.3%	0.4%	0.4%
TEAEs	34.2%[a]	9.7%	34.3%	25.5%	39.9%

[a]Derived by Dr. Boehm.
[b] Protocols required discontinuation for Grade 4 IRR that occurred during a previous infusion.
[c] From p. 1025 of ISS.

For MS trial WA21493, one patient discontinued for an IRR.

In All RA Trials (Pool E) IRRs led to discontinuation in 0.9% (25/2926) ocrelizumab patients. In RA controlled trials (Pool D), IRRs led to discontinuation in 1% (9/947) ocrelizumab 1000 mg patients, 0.l9% (11/1186) ocrelizumab 400 mg patients, and 0.1% (1/903) placebo patients.

IRR risk with dose and over time

Dr. Boehm shows that in RMS Controlled Trials (Pool A) IRRs were persistently more common in ocrelizumab patients than interferon patients over time through the 4th dose. He shows that IRRs occurred most frequently with the first dose (Day 1, the first of two 300 mg infusions) and then declined in frequency but continued to occur with subsequent doses (Day 15 on the second of the two 300 mg infusions and the subsequent single 600 mg infusions). Dr. Boehm also notes that the PPMS ocrelizumab patients similarly experienced IRRs most frequently following the first dose with decreases in frequency following subsequent doses (all infusions given as two 300 mg doses given 2 weeks apart, with that cycle repeated every 24 weeks). The data below, from Dose 1 for RMS and for PPMS, show the decrease in IRRs on Day 2 of Dose 1:

[17] These pre-treatment procedures were also in place for trials in other indications.

RMS Controlled phase (Pool A)		**300 mg Dose 1 Day 1**		**300 mg Dose 1 Day 2**	
	Treatment	OCR	IFN	OCR	IFN
	Risk of IRRs	27.52%	6.55%	4.71%	2%
PPMS Controlled Phase					
	Treatment	OCR	Placebo	OCR	Placebo
	Risk of IRRs	27.40%	12.10%	7.30%	6.00%

Although the risk for IRRs overall for patients on ocrelizumab was slightly greater for PPMS (almost 40%) compared to RMS (34%) in the controlled trials, Dr. Boehm notes that the PPMS trial was longer (120 weeks vs 96 weeks) and included more infusions as every dose was administered as split infusions in the PPMS trial.

The Sponsor proposes that both MS and PPMS patients could be dosed with a single 600 mg dose from Dose 2 onwards (rather than the split dosing for PPMS as in the clinical trial). Dr. Boehm points out that there is no empirical data to support the assumption that the split dosing regimen in PPMS does not confer a benefit in IRR risk as there is no direct comparison of the two regimens within the PPMS trial. Dr. Boehm provides the Sponsor's comparison of IRRs in RMS Dose 2, 3, and 4 (600 mg each) vs PPMS Dose 2, 3, and 4 (300 mg on Days 1 and 15 for each dose). Although cross-study comparisons have limitations, it does not appear that there was a substantial reduction in risk of IRRs, severity, or common symptoms on Day 1 of each cycle when given as a split (300 mg dose) compared to a 600 mg single dose. I show the risk of IRRs from those data:

	RMS Dose 2	**PPMS Dose 2**		**RMS Dose 3**	**PPMS Dose 3**		**RMS Dose 4**	**PPMS Dose 4**	
	Day 1	Day 1	Day 15	Day 1	Day 1	Day 15	Day 1	Day 1	Day 15
Regimen	600 mg	300 mg	300 mg	600 mg	300 mg	300 mg	600 mg	300 mg	300 mg
Pts with Infusions	779	465	449	759	452	437	732	439	430
Pts with IRRs	13.7%	11.6%	5.1%	9.6%	11.5%	5.0%	7.8%	6.6%	3.0%

I agree with Dr. Boehm that that there is no empirical data to support the assumption that the split dosing regimen in PPMS does not confer a benefit in IRR risk. However, I also do not find strong data to support a difference in the 2 doses with respect to infusion reactions, although the limitations of cross-study comparisons and the different populations of RMS and PPMS must be considered.

Timing of IRRs with respect to a given dose

Dr. Boehm notes that during the controlled phase of the RMS trials and the PPMS trials, the majority of patients experienced the IRR during the infusion (80.6% in RMS and 61.3% in PPMS). Eleven percent of RMS patients and 20% of PPMS patients with an IRR experienced the event after the infusion while still in the clinic, and 18% of RMS patients and 38% of PPMS patients with an IRR experienced the event within 24 hours of the infusion but after leaving the clinic.[18]

IRR symptoms and signs

In the controlled phase of the RMS trials (Pool A), Dr. Boehm notes the *symptoms of IRRs* reported by at least 5% of ocrelizumab patients with IRRs and more frequently compared to interferon beta-1a patients were pruritus (30%), rash (30%), throat irritation (24%), flushing (16%), urticaria (9%), and oropharyngeal pain (8%). He notes that similar IRRs at similar frequencies were reported for PPMS, although pyrexia was a common IRR (13%) in PPMS, but only 4% in RMS.

Dr. Boehm shows that in RMS *vital sign changes* were more common in the interferon beta-1a-treated patients than in the ocrelizumab patients except for hypertension which occurred with the same frequency in both (approximately 1.4%). He notes that the majority of the vital sign abnormalities in both RMS and PPMS were grade 1 or 2 severity, although there were several cases of Grade 3 vital sign abnormalities in the ocrelizumab groups for both RMS [6 AEs in 4 patients; hypotension (2), hypertension, bradycardia, tachycardia, pyrexia] and PPMS (3 AEs in 2 patients; hypotension, hypertension, pyrexia).

IRR Severity

Dr. Boehm notes that no deaths were attributed to IRRs in ocrelizumab treated MS patients. Dr. Boehm notes that in the MS trials almost all IRRs were graded 1-3 (73% were grade 1 in Pool B). Antihistamines were the most commonly administered treatments for IRRs; other treatments included corticosteroids, analgesics, and nonsteroidal anti-inflammatory medications. In RMS controlled trials (Pool A), 54% of patients with an IRR had an infusion modification, most with slowing or interruption of infusion. In the PPMS controlled trial, no patient with an IRR had their infusion slowed or discontinued; 2.6% had their infusion interrupted.

Dr. Boehm has summarized the 7 IRRs classified as SAEs for all MS trials (Pool B). Four occurred within 15 minutes to 2 hours after beginning the first infusion. IRRs in the subjects were bronchospasm (a grade 4 event; **subject WA221092-20753-1922844**), life-threatening hypotension (a grade 4 event in a patient who also had severe laryngeal/throat irritation/throat pain, stuffiness, and mild increase in temperature; **subject WA21493-140993-4051**), hyperthermia/ tachycardia/ hypertension/ nausea and hypotension/pruritus and vomiting (**subject WA25046-208367-30302**), and fever/rigors/tachycardia (**subject WA25046-208688-14402**). **Subject WA25046-207348-12602** developed hypotension, ectopic ventricular beats, paleness, intense asthenia, QT prolongation (*QTc 615 ms*) 1 hour after starting infusion on day 1191; the IRR resolved following morning although QT prolongation was noted again 3 months later and I do not believe it is clear as to which if any of these events might have had a contribution from ocrelizumab in this patient. **Subject WA25046-208444-37004** developed fever, flu-like syndrome (asthenia), and psychomotor retardation within 24 hours of completion of infusion on day 170 and no action was taken with ocrelizumab because of the IRR. Subject **WA25046-208787-32311** developed spasticity and was unable to move legs or get out of wheelchair within 24 hours of an infusion given after almost 3 years of treatment; the event was considered resolved approximately 11 days later.

[18] The same patient may have had more than 1 IRR.

IRRs leading to discontinuation in RMS controlled trials (Pool A) included rash, pruritus, and throat irritation, dyspnea, nasal congestion, and flushing. In the PPMS controlled trial IRRs leading to discontinuation were flushing, hyperhidrosis, and oropharyngeal pain.

Dr. Boehm notes that in RMS controlled trials (Pool A), ocrelizumab patients pretreated with oral antihistamine along with methylprednisolone had a least a 2-fold lower incidence in IRRs compared with pretreatment with methylprednisolone alone, except in Dose 1, infusion 2, and he notes that the addition of analgesics/antipyretics to oral antihistamines did not appear to have additional benefit. Similar findings were observed in the PPMS trial controlled phase.

I agree with Dr. Boehm that IRRs should be described in labeling in a Warnings and Precautions statement and guidance regarding pre-treatment and management of IRRs should be provided. Dr. Boehm notes that the Sponsor has proposed such language.

Infections

As Dr. Boehm notes, infections are a well-established adverse effect with anti-CD20 monoclonal antibodies, including opportunistic infections. In the MS controlled trials, a higher percentage of ocrelizumab patients experienced infections than comparator patients. These included upper respiratory tract infections, lower respiratory tract infections, and herpes related infections. In the RMS trials, a higher percentage of interferon patients experienced SAEs than ocrelizumab patients; in the PPMS trials a higher percentage of ocrelizumab patients experienced SAEs than placebo patients. There were no opportunistic infections identified in MS control trials. Two deaths in MS trials were due to infection, and as noted above, it is possible that ocrelizumab could have contributed. I agree with Dr. Boehm that infection risk should be described in the Warnings and Precautions section of labeling.

Infections were commonly reported in the MS trials overall and in the controlled trials. There was a slightly greater risk of infections with ocrelizumab compared to interferon in RMS Pool A and compared to placebo in the PPMS Pool. In controlled trials, infection SAEs occurred less frequently in ocrelizumab treated patients vs comparator patients. Infections resulted in few discontinuations. The most common infections and greater than interferon in RMS controlled trials were upper respiratory tract infections, herpes infections, lower respiratory tract infections, and gastroenteritis. The most common infections and greater than placebo in the PPMS controlled trial were upper respiratory tract infections, influenza, lower respiratory tract infections, and bronchitis; herpes infections also occurred at a rate greater than placebo. The greatest risk for infections was following the first dose in the controlled RMS trials.

The following table shows SAEs (occurring in at least 2 patients in the RMS Controlled Trials or PPMS Controlled Trials and more frequently than control and select SAEs of interest), Discontinuations, and TEAEs due Infections in the ISS[19]

	All MS Trials (Pool B)	RMS Controlled Trials (Pool A)	PPMS Controlled Trial

[19] In the 90 day safety update, 57% of MS patients had an infection. The rate of infections was 76/100 PY. Infection SAEs occurred in 4.7% of patients.

	Ocrelizumab n=2147	IFN beta-1a n=826	Ocrelizumab n=825	Placebo N=239	OCR N=486
SAEs of Infections [a]	3.0%	2.9%	1.3%	5.9%	6.2%
Urinary tract infections[d]	0.7%	0.4%	0.2%	2.1%	2.3%
Pneumonia[c]	0.4%	-	-	0.8%	1.4%
Appendicitis	0.3%			0	0.4%
Cellulitis	0.2%,[b]	0.1%	0.2%	0	0.4%
Bronchitis		-	-	0	0.4%
Biliary Sepsis		0	- 0.1%	-	-
Discontinuations	0.3%[e]	0	0.2%	1.3%	0.8%
TEAEs	54.4% (78 per 100 PY)	52.4%	58.4%	67.8%	69.8%

[a] SAEs in Pool B reflect those reported by at least 5 subjects.
[b] 5 additional cases were reported in the 90 day safety update.
[c] Includes pneumonia and bronchopneumonia
[d] Includes cystitis, urinary tract infection, and pyelonephritis
[e] Two additional events (acute hepatitis C, infection) were reported in the 90 day safety update

SAEs
The most commonly reported SAEs in MS Pool B were infections. None was considered to be an opportunistic infection.[20]

The SAE of biliary sepsis (**Subject WA21092-244362-1928501**) occurred in a patient with hepatomegaly and exacerbated chronic calculus approximately 4 months after beginning ocrelizumab; the patient was treated, the event resolved, and he completed the controlled phase of the trial and entered the open label phase with no additional SAES; the role of ocrelizumab in contributing to this event is unknown.

In addition to the SAEs shown in the table above, there was 1 SAE each (0.1% each) of device related infection, herpes simplex, and upper respiratory tract infarction compared to none in interferon beta-1a in RMS Controlled Trials (Pool A). There was 1 SAE each (0.2% each) of abscess limb, bursitis infective, diverticulitis, erysipelas, gastroenteritis, gastrointestinal infection, impetigo, infected dermal cyst, mastitis, neutropenic sepsis, peritonitis, post procedural cellulitis, viral infection, and viral pericarditis compared to none in placebo in the PPMS controlled trial.

No SAEs of infections were reported in the controlled phase of WA21493.

SAEs of Infections in all RA trials (Pool E) occurred in 3.8% of subjects. Those reported in at least 5 subjects were similar to the infections in the MS population: pneumonia (0.7%), urinary tract infection (0.3%), cellulitis (0.2%), sepsis (0.2%), gastroenteritis (0.2%), and herpes zoster,

[20] The Sponsor provided the approach to analyses of opportunistic infections as discussed on p. 113 of Dr. Boehm's review. I agree with Dr. Boehm that, although the Sponsor did not provide a report of the findings, the approach appears reasonable.

bronchitis, diverticulitis, appendicitis, bronchopneumonia, pneumonia bacterial, pyelonephritis, and septic shock each occurring in 0.1%). There were also 5 SAEs of pneumocystis Jirovecii pneumonia, 3 of which occurred in a controlled trial. Opportunistic infections were pneumocystis jiroveci pneumonia (5), herpes zoster (3), herpes zoster oticus, herpes zoster simplex, varicella zoster pneumonia, systemic candida, esophageal candidiasis, mycobacterium absessus infection, atypical pneumonia, and hepatitis B.

In RA controlled trials (pool D), SAEs of infections occurred in 4.4% of OCR 400 mg, 6.4% of OCR 1000 mg, and 3.4% of placebo subjects. Those occurring in at least 2 patients in any dose group and more frequently than placebo were bronchitis, urinary tract infection, pneumonia, appendicitis, bronchopneumonia, pneumocystis jiroveci pneumonia, pseudomembranous colitis, pulmonary tuberculosis, and septic shock.

SAEs of infections in other indications included the following: cytomegalovirus, pneumonia, pneumocystis jiroveci pneumonia, septic shock, upper respiratory tract infection, and urinary tract infection (and no SAEs in placebo) in WA20499-SLE; pneumonia and appendicitis in WA20500-LN.

Discontinuations

As shown in the table above, there were few discontinuations for infections, and there did not appear to be an imbalance in discontinuations due to infections between ocrelizumab and control in the MS trials. In RMS Pool A the infections leading to discontinuation were urinary tract infection and cellulitis. In the PPMS trial, infections leading to discontinuation of ocrelizumab were infectious colitis, pneumonia, urinary tract infection, and viral infection. There were no infections leading to discontinuation in MS dose finding trial WA21493. In all RA Trials (Pool E) the infections leading to discontinuation were (2 patients each) arthritis bacterial, herpes simplex, pulmonary TB, and upper respiratory tract infection. Events leading to discontinuation in LN study WA20500 were 1 event of herpes zoster in the ocrelizumab 1000 mg group and 1 case each of cryptococcal meningoencephalitis, suspected infection, and pneumocystis jiroveci in the ocrelizumab 400 group (and abscess limb in placebo).

TEAEs

Events in the Infections and Infestations SOC were the most commonly reported TEAEs. As shown in the table above, TEAEs in the Infections SOC occurred slightly more frequently ocrelizumab than for control in the RMS or PPMS controlled trials. The most common infections (≥5% in ocrelizumab and greater than interferon beta-1a) in RMS Pool A were upper respiratory tract infections (36% for OCR vs 29% for IFN beta-1a), herpes infections (6% for OCR vs 4% for IFN beta-1a), gastroenteritis (6% for OCR vs 4% for IFN beta 1a). Combined lower respiratory tract infections occurred in 8% for OCR vs 5% for IFN beta-1a. The most common infections (≥5% in ocrelizumab and greater than placebo) in the PPMS controlled trial were upper respiratory tract infection (39% for OCR vs 37% for placebo), influenza (12% for OCR vs 9% for placebo), and bronchitis (7% for OCR vs 5% for placebo). Lower respiratory tract infections occurred in 10% for OCR and 8% for placebo. In the PPMS trial, similar to the RMS trials, herpes infections also occurred and at a rate greater than placebo (4% for OCR vs 3% for placebo). Upper respiratory tract infection and influenza were also among the most common TEAEs in MS dose ranging trial WA21493 and occurred more

frequently than comparator. The most common TEAEs for all MS Trials (Pool B) reflected those in the controlled trials and occurred with similar frequencies as occurred in the controlled Phase 3 trials.

In all RA trials (Pool E) events in the Infections and Infestations SOC were the most common AEs and occurred at a rate of 74 per 100 PY. The most common were upper respiratory tract infection, (12 per 100 PY), nasopharyngitis (8 per 100 PY), urinary tract infection (7 per 100 PY),and bronchitis (6 per 100 PY). In Pool D infections occurred at a greater rate with OCR 400 mg (105 per 100 PY) and 1000 ng (113 per 100 PY) than placebo (98 per 100 PY)[21] ; Dr. Boehm shows that the most common and greater than placebo in either OCR dose group were acute sinusitis, oral herpes, and tooth abscess.

In lupus study WA20499, Infections and Infestations were also the most commonly reported TEAEs (30% for placebo, 73% for OCR 400 mg, and 50% for OCR 1000 mg). In LN Study WA20500 upper respiratory tract infection and urinary tract infection were among the most common TEAEs (at least 10% in any dose group and greater than placebo).

Severity and Timing of Infections
Dr. Boehm notes that the majority of infections in ocrelizumab treated patients were grade 1[22] or 2 (95% in RMS and 92% in PPMS controlled trials). He notes that there were more ocrelizumab patients with Grade 4 or 5 infections compared to interferon or placebo in the MS controlled trials, but the number was small (2 in RMS controlled trials and 10 in PPMS) and I agree these numbers cannot support definitive conclusions regarding risk. No fatal infections were reported during the controlled phase of RMS trials; 2 ocrelizumab patients experienced Grade 5 events (pneumonia, aspiration pneumonia) in the PPMS controlled trial.

Of note, in contrast to RA trials in which 16 events were identified that appeared to be opportunistic infections[23], opportunistic infections were not identified in MS patients treated with ocrelizumab. Dr. Boehm notes that RA patients are generally older than MS patients, with greater comorbid disease burden, and in the RA trials, exposed to combination immunosuppressive therapy including methotrexate (boxed warning for bone marrow suppression and potentially fatal opportunistic infections) and leflunomide (Warnings and Precautions for severe infections, pancytopenia, and agranulocytosis).

With respect to the risk of infections over time in the RMS controlled trials, the highest risk and greater difference of upper respiratory tract infections and of herpes infections compared to interferon was following the first dose. After that, the rates declined but remained slightly

[21] Table 84 of the ISS.
[22] According to p. 28 (Section 1.1.4.1) of the Summary of Clinical Safety, AEs were graded according to NCI CTCAE version 4.0. In that system, Grade 1 is mild (asymptomatic or mild symptoms; intervention not indicated); Grade 2 is moderate (minimal, local or noninvasive intervention indicated); Grade 3 is severe or medically significant but not immediately life-threatening; Grade 4 has life-threatening consequences with urgent intervention indicated; Grade 5 is death related to adverse event.
[23] Pneumocystis jiroveci pneumonia, herpes zoster, herpes zoster oticus, herpes simplex, varicella zoster pneumonia, systemic candida, esophageal candidiasis, mycobacterium abscessus infection, atypical pneumonia, and hepatitis B.

greater for upper respiratory tract infections and approximately 2x greater for herpes infections. Although infection rates were greatest with the first dose (for either ocrelizumab or placebo) in PPMS, Dr. Boehm notes that for PPMS the Sponsor did not find a consistent trend in infection rate over time.

Dr. Boehm notes that the Sponsor did not find an association between neutropenia and infections (in patients with Grade 2 or higher neutropenia). Levels of IgM decreased over the course of treatment. The rate of infection in patients with low levels of IgM in all MS Trials (Pool B) was similar to the rate in the overall in that Pool. The rate of serious infection in patients with low levels of IgM in Pool B was slightly higher than the rate overall in that Pool, although, as Dr. Boehm notes, the 95% confidence intervals overlapped.

Dr. Boehm notes that for overall infections in MS the following factors predicted risk of infection:

Increased risk	Decreased risk
Female sex[24]	Regions other than US/Canada/Australia
Higher BMI/weight	Previous steroid use
History of Cardiac disease	
History of previous infections	
Lower IgG at baseline	

Malignancies

An increase in malignancies is observed for ocrelizumab compared to interferon in Pool A (2.5 fold increase) and compared to Placebo in the placebo in the PPMS controlled trials (2.9 fold increase). In particular, there is an imbalance in breast cancer in the controlled trials in which 2 cases (0.3% of females) occurred in ocrelizumab vs none in interferon beta-1a in RMS Pool A and 4 cases (1.6% of females) occurred in the PPMS controlled trial in ocrelizumab vs none in placebo, all occurring after at least 1 year of treatment with ocrelizumab. Together in the MS controlled trials, the breast cancer risk in female ocrelizumab patients was 0.8% (6/781) vs 0/688 for female comparator patients. Overall there were 8 cases of breast cancer (8/1,398 females, 0.6%) in the all MS trials (Pool B).[25] In the all RA trial pool, 7 patients were diagnosed with breast cancers: 6 females (6/2,341 females, 0.3%). In that pool breast cancer occurred in 1 (Japanese) male (1/585 males; 0.2%), an unexpected event given the background incidence of male breast cancer in Japan as noted below. I agree with Dr. Boehm and with the consultants that the risk of malignancy should be included in labeling, as a Warning as suggested by Dr. Boehm, and followed-postmarketing as a PMR.

Dr. Boehm has identified an increase in malignancies for ocrelizumab compared to interferon in Pool A (2.5 fold increase) and compared to Placebo in the placebo in the PPMS controlled trials

[24] This was the case in RMS and PPMS, and was also the case for comparator in those trials. Please refer to Tables 33 (p. 125) and 36 (p. 129) of Dr. Boehm's review.
[25] An additional case of breast cancer was reported as a late breaking event after the cutoff date. A late breaking case of esophageal cancer and a case of basal cell carcinoma were also reported. There are not updated exposure data at the time of the review when the case was reported to calculate the risk.

(2.9 fold increase), with an imbalance in breast cancer in the controlled trials as shown in the table below.

	All MS Trials (Pool B) through the 90 Day Safety Update	RMS Controlled Trials (Pool A)		PPMS Controlled Trial	
	Ocrelizumab[b] n=2,279 (5,711 PY)	IFN beta-1a n=826	Ocrelizumab n=825	Placebo N=239	OCR N=486
Patients diagnosed with 1 or more malignancies	1.0% (n=23) 0.4/100 PY	0.2% (n=2) 0.14/100 PY	0.5% (n=4) 0.28/100 PY	0.8% (n=2)	2.8% (n=11)
Types of Malignancies					
Breast Cancer	0.6% (8 /1,398) females (0.23/100 PY)	n=0	0.3% (2/541 females)	n=0	1.6% (4/240 females)
Basal cell carcinoma	0.2% (n=5)[a]				N=3
- Adenocarcinoma of colon - Anaplastic large cell lymphoma - Endometrial cancer - Malignant fibrous histiocytoma - Malignant melanoma (2) - Pancreatic carcinoma, - Papillary thyroid cancer - Renal Caner - Keratoacanthoma	< 0.1% each (n=1 each, except for malignant melanoma)	Mantel cell lymphoma Squamous cell carcinoma	Malignant melanoma Renal cancer	Basal cell carcinoma Adenocarcin-oma of the cervix	Anaplastic large cell lymphoma Endometrial cancer Malignant fibrous histiocytoma Pancreatic carcinoma metastatic

[a] 5 patients; 1 patient had 3 basal cell carcinomas.
[b] Data shown are for the 90 day safety update, reflecting an increase from the ISS exposure of 2,147 patients in which 0.8% had malignancies (n=18; 0.4/100 PY), with breast cancer in 0.5% (n=7), and basal cell carcinoma in 0.1% (n=3).

Breast Cancer in MS trials
Dr. Boehm has further evaluated the breast cancer cases. Seven of the 8 cases (including the case in the 90 day safety update) had similar ages (41-54 y.o.); the other female was 28 y.o. The women were exposed to cumulative doses of 1800 mg to 4600 mg, except for the 28 y.o. female who had a cumulative dose of 600 mg. The durations between first ocrelizumab exposure and

breast cancer symptoms/diagnosis were 378 to 917 days. The women were from European countries and one from the US. Dr. Boehm notes a family history of breast cancer in 1 patient. I agree with Dr. Boehm that nothing in the narrative summaries would exclude a possible causal/contributory role of ocrelizumab in the breast cancer cases.

Other Malignancies in MS trials
Other than breast cancer, the malignancies were generally isolated cases and it is not possible to draw a conclusion between ocrelizumab exposure and a specific type of these malignancies, although a role for ocrelizumab cannot be ruled out.

Malignancies in other indications
In All RA trials (Pool E) ocrelizumab 3.2% of ocrelizumab patients (94/2926 patients) had one or more malignancies (1.28/100 PY). Dr. Boehm notes that these included 7 patients diagnosed with breast cancers. The *breast cancers* were in 6 females (6/2,341, 0.3%) and 1 male (1/585; 0.2%). The most frequently reported malignancies were basal cell carcinoma (0.9%), and malignant melanoma, prostate cancer and squamous cell cancer of the skin that each occurred in 0.2%. Please refer to Dr. Boehm's review for the complete list of malignancies that each occurred in 1 to 4 patients.

Dr. Boehm notes that the *male breast cance*r in the RA trials occurred in a 67 y.o. Japanese male previously treated with infliximab and was diagnosed with breast cancer 1 year after beginning ocrelizumab. He notes that this is an unexpected event given that there were 585 males exposed to ocrelizumab in RA trials, and the background incidence of male breast cancer in Japan is estimated to be 0.18/100,000 man years.

In the RA controlled trials, Dr. Boehm shows that the risk for malignancies was similar for the placebo (1%), ocrelizumab 400 mg (0.7%), and ocrelizumab 1000 mg (1.2%) groups and that the rates per 100 PY were also similar in these groups. He notes that 1 placebo patient and no ocrelizumab patients were diagnosed with breast cancer in the RA controlled trials.

Comparison of malignancy rates to rates in RA controlled trials and to external data sources

Dr. Boehm points out that the controlled phase data for the RA trials are not directly comparable to the data from the MS trials, due to the shorter trial duration. In MS trials 1,140 patients were exposed for at least 95 weeks (716 in RMS and 424 in PPMS controlled trials). In contrast, in the RA controlled trials, exposure for at least 96 weeks (672 days) was only in 104 patients. I agree this is important because the earliest breast cancer case in the controlled MS trials occurred after 393 days, and 4 of the 8 cases occurred beyond 96 weeks.

D. Boehm summarizes the comparison used by the Sponsor comparing the malignancy rate in all MS trials (Pool B) to comparators from the controlled phases of these trials and to 3 external data sources. The external sources were a (b) (4) report including malignancy rates compiled from placebo comparator groups in MS trials identified by searching published trials, to represent a rate for patients enrolled in MS trials but not exposed to investigational drugs; and population based epidemiologic data from a Danish MS registry and a Canadian MS registry. Dr. Boehm shows that the malignancy rates overall for ocrelizumab (0.425/100 PY in the ISS, prior to the 90 day safety update) were similar to the rates in the registries, but he shows an increased rate for

female breast cancer for ocrelizumab , although with overlapping confidence intervals, compared to the rates in the other registries as shown below, extracted from Dr. Boehm's review:

	Ocrelizumab Pool B	MS Trial Placebo[a]	MS Registry
Malignancies	0.425 (0.256-0.664)	0.50 (0.36-0.67)	0.67 (0.64-0.71)[b]
Breast cancer (female)	0.261 (0.105-0.538)	0.16 (0.06-0.32)	0.21 (0.18-0.23)[b] 0.14 (0.11-0.16)[c]

[a] (b) (4) report
[b]Danish registry
[c] Canadian registry

I note that the Sponsor considers these to be similar rates.

Consultant Reponses Regarding Malignancies

As Dr. Boehm notes, the Division of Neurology Products consulted the Division of Oncology Products 1 (DOP1, Dr. Gwynn Ison), the Division of Hematology products (DHP, Dr. Bindu Kanapuru), and the Division of Epidemiology 1 (DPI1) to assist in evaluating this issue.

Drs. Ison and Kanapuru thought that all malignancies should be considered in the evaluation of the cancer risk. Dr. Ison commented that a potential safety signal should not be ruled out at this time and recommended further evaluation on newly diagnosed malignancies. Dr. Kanapuru commented that the imbalance of breast cancer cases is concerning and that longer follow-up is recommended to further characterize the finding. Neither consultant found the comparisons to outside databases reassuring, and Dr. Kanapuru cited a publication concluding that MS patients have a decreased overall risk of cancer but that noted an increased risk for breast cancer in women with MS treated with immunosuppressive therapy. Drs Ison and Kanapuru recommended describing the findings in in labeling.

DEPI was consulted to evaluate two sources cited by the Sponsor which they claim found no additional risk of breast cancer with another anti-CD20 monoclonal antibody, Rituxan, and to evaluate the external data sources used as comparative data by the Sponsor to asses malignancy risk observed in the ocrelizumab MS controlled trials. Dr. Braver concluded that these comparisons cannot be interpreted due to limitations in their analyses, including the lack of control for potential confounding factors and the lack of traditional analyses on dose-response and time intervals between exposure and diagnosis. In an email dated September 12, 2016, following review of additional analyses, Dr. Braver noted that the overall malignancy rate, as well as breast cancer incidence, was higher in ocrelizumab patients at least 45 y.o. than those less than 45 y.o.

Psychiatric Disorders

There was no imbalance in SAEs or TEAEs in the *Psychiatric disorders* SOC overall in the controlled trials in RMS or PPMS. However, as Dr. Boehm shows on p. 121 of his review, there was an imbalance in SAEs of depression suicidal, suicide attempt, and suicidal ideation occurring only in ocrelizumab patients and none in placebo for PPMS. Depression TEAEs occurred less frequently in ocrelizumab-treated patients than placebo in the PPMS controlled trial, but occurred slightly more frequently than interferon (8% vs 7%) in the RMS Controlled Trials (Pool A).

Because interferon beta-1a labeling has a warning for depression and suicide, I agree with Dr. Boehm that a Warning for depression and suicide for ocrelizumab should be considered.

SAEs and TEAEs of Psychiatric Disorders in Ocrelizumab MS Trials

	All MS Trials (Pool B)	RMS Controlled Trials (Pool A)		PPMS Controlled Trial	
	Ocrelizumab n=2147	IFN beta-1a n=826	Ocrelizumab n=825	Placebo N=239	OCR N=486
SAEs	0.7%[a]	0.8%	0.5%	0	0.8%
Completed suicide		0.1%	0.1%		
Depression		0	0.2%		
Depression suicidal		0.2%	0	0	0.2%
Suicidal ideation		0.1%	0	0	0.2%
Suicide attempt		0	0.1%	0	0.4%
TEAEs	15.5%	17.4%	18.1%	24.7	18.3%
- Depression	6.4% [a]	6.5%	7.8%	12.6%	9.7%

[a] Other AEs included depressed mood (0.7%), suicide attempt (0.3%), suicidal ideation (0.18%), completed suicide (0.05%).

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Dr. Boehm describes the Sponsor's approach to identifying potential cases of DRESS and I agree with him that the approach seems reasonable. There were no cases of DRESS identified RA trials or in MS through the 90 Day safety update.

Anaphylactic Reactions

Dr. Boehm describes the Sponsor's approach to identifying potential cases of anaphylaxis. The Sponsor identified 4 potential cases in the ISS but determined that they did not represent anaphylaxis. These are summarized by Dr. Boehm, and I agree with him that these do not appear to be cases of anaphylaxis. He notes that no cases of anaphylaxis were identified in the 90 day safety update.

Autoimmune disorders

Dr. Boehm reviewed the Sponsor's approach to review of autoimmune AEs and believes that it would have likely captured autoimmune AEs in the development program. In the MS trials, Dr. Boehm notes that 12 patients (0.6%) with 13 potential autoimmune disorders were identified. The events included multiple sclerosis (n=8), autoimmune thyroiditis (n=2), immune thrombocytopenic purpura (n=1), autoimmune uveitis (n=1), and alopecia areata (n=1). Two additional events (ITP, autoimmune thyroiditis) were identified in the 90 day safety update. Given the few events that occurred, I agree with Dr. Boehm that there did not appear to be evidence to support an association between ocrelizumab and autoimmune AEs.

Other Serious adverse events

Cholelithiasis and Cholecystitis

Dr. Boehm identified an imbalance in SAEs coded to the preferred terms cholecystitis, cholecystitis acute, cholecystitis, chronic, and cholelithiasis. He notes that these events can occur commonly in females of the age group that make up the cases. He notes that similar imbalances were not observed in the RA controlled trials, and that the labeling for approved anti-CD20 monoclonal antibodies not does include language about such events. I agree with Dr. Boehm that the evidence does not support mentioning in labeling at this time, but that postmarketing reports should be monitored for these events.

Cholecystitis/Cholelithiasis SAEs and TEAEs occurred more commonly in ocrelizumab treated patients than in comparator subjects in MS controlled trials.

The following table shows SAEs and TEAEs due to Cholecystitis/Cholelithiasis in MS trials in the ISS.

	All MS Trials (Pool B)	RMS Controlled Trials (Pool A)		PPMS Controlled Trial	
	Ocrelizumab n=2147	IFN beta-1a n=826	Ocrelizumab n=825	Placebo N=239	OCR N=486
SAEs of Cholecystitis/Cholelithiasis [a]	0.4%	0.2%	0.7%	0.4%	0.6%
Discontinuations[c]	-	-	-	-	-
TEAEs	[b]	1%	1.6%	0.4%	1.2%

[a] Cholecystitis, Cholecystitis acute, Cholecystitis chronic, and Cholelithiasis. Nine SAEs (0.4%) were reported in the ISS with 2 additional cases reported in the 90 day safety update. -
[b] In the ISS (p. 1526): Cholelithiasis (12 patients, 0.6%), Cholecystitis (3 patients ,0.1%), Cholecystitis acute (0.1%), Cholecystitis Chronic (< 0.1%).
[c] I did not identify discontinuations due to Cholecystitis/Cholelithiasis in these trials in the ISS.

All 9 patients with these SAEs in the ISS were female with an average age of 43 (median 46 years, range 21-53 years), with an average duration of ocrelizumab treatment prior to the SAE of 360 days (median 376 days, range 116-602); 1 had a prior history of cholelithiasis/cholecystitis. 8 of the 9 underwent cholecystectomy for treatment of the SAE. The 2 additional patients with these SAEs in the 90 day safety update were 21 and 23 y.o. females, diagnosed on Study day 332 and 948 days after the first infusion, respectively; both underwent cholecystectomy and continued in the trial. An additional patient had a pancreatitis SAE attributed to cholelithiasis that was characterized as an AE. (An additional patient with biliary sepsis/chronic calculous cholecystitis was discussed under infections; biliary sepsis began approximately 1 month after starting ocrelizumab; he was treated with antibiotics, completed the controlled study and entered the open label phase with no additional AEs and the role for ocrelizumab is not clear in this event.)

Dr. Boehm finds no imbalance for Cholecystitis/Cholelithiasis SAEs or in TEAEs in the RA controlled trials (Pool D). He specifically notes that there were no SAEs of

Cholecystitis/Cholelithiasis reported in WA20500-LN and does not note Cholecystitis/Cholelithiasis among reported SAEs in trials for other indications.

Pancreatitis

SAEs of pancreatitis occurred in 5 ocrelizumab treated patients and none in the comparator subjects in controlled trials. Three of the patients with pancreatitis had known risk factors. I agree with Dr. Boehm that a clear relationship to ocrelizumab is not present at this time. I agree with him that postmarketing reports should be monitored for additional cases.

The following table shows SAEs of Pancreatitis in MS trials in the ISS.

	All MS Trials (Pool B)	RMS Controlled Trials (Pool A)		PPMS Controlled Trial	
	Ocrelizumab n=2147	IFN beta-1a n=826	Ocrelizumab n=825	Placebo N=239	OCR N=486
SAEs of Pancreatitis/Pancreatitis acute	0.2%	0%	0.1%	0%	0.4%

Dr. Boehm notes that cases of pancreatitis are concerning events in drug development programs. He has assessed the cases in the ocrelizumab development program as is routinely done to assess for relationship to experimental treatments.

Dr. Boehm identified 5 SAEs of pancreatitis in MS ocrelizumab patients. Two cases were noted in the presence of cholelithiasis (**WA25046-208392-21411** and **WA25046-208701-38002**) and 1 case was attributed to hypertriglyceridemia (**WA21092-207782-1923291**); cholelithiasis and hypertriglyceridemia are known risk factors for pancreatitis. Dr. Boehm notes that 2 cases did not have an identified cause (**WA21093-233905-1936451** and **WA21092-234569-1926571**).

There were 3 SAEs of pancreatitis in the RA trials (Pool E): Subject **WA20494-114672-45707** resolved with papillotomy and stone retrieval; Subject **WA20496-137401-15560** with a history of cholelithiasis and s/p cholecystectomy in whom pancreatitis resolved 4 days later after treatment with pain medication, H3 blocker and anti-nausea medication); and Subject **WA20496-137416-17042** who was treated with esomeprazole, hydrocortisone, promethazine, metoclopramide, and morphine and the event resolved 15 days later. Two patients in the OCR 1000 mg group (none in placebo or OCR 400 mg) had an AE of pancreatitis or acute pancreatitis in the controlled Phase of the RA trials.

In light of the presence of known risk factors in 3 of the 5 cases of pancreatitis in MS trials, I agree with Dr. Boehm that the divergent etiologies do not suggest a clear relationship to ocrelizumab and do not support labeling at this time. I agree with him that postmarketing reports should be monitored for additional cases.

Serious Skin Reactions

As previously noted Dr. Boehm identified no SAEs of Stevens Johnson Syndrome or Toxic Epidermal Necrolysis (including in the 90 day safety update) in the MS trials. There were no

SAEs in the Skin and Subcutaneous Tissue Disorders SOC attributable to ocrelizumab in the RA controlled trials. Overall in MS trials and RA trials, rash was the most common adverse event in the Skin and Subcutaneous Tissue Disorders SOC, occurring at a frequency of 3%. Although there did not appear to be a safety signal for serious skin reactions, there was one SAE of *bullous drug eruption* (*psoriatic spongiotic dermatitis with features of psoriasis*) in a controlled MS trial. I discuss that SAE below, followed by a summary of the TEAEs related to skin disorders.

Subject **WA21093-233958-1936676** developed a *bullous drug eruption* (*psoriatic spongiotic dermatitis with features of psoriasis*). The event occurred 57 days following the most recent infusion (approximately1.5 years after starting ocrelizumab). Ocrelizumab was permanently discontinued. A recurrence of blisters was observed approximately 2 months after discontinuation, and the event was considered resolved approximately 6.5 months after discontinuation.

TEAEs of *Skin and Subcutaneous Tissue Disorders* occurred in 13.6% [including *rash* (2.6%), *alopecia* (1.3%), *pruritus* (1.3%), and *eczema* (1.1%)] of ocrelizumab patients in all MS Trials (Pool B). In controlled trials of RMS (Pool A), TEAEs in this SOC occurred in 14% for OCR vs 13% for interferon, with *pruritus* being the most common (2% for OCR vs 0.7% for interferon). In the PPMS controlled trial TEAEs in this SOC occurred in 20% for OCR and 18% for placebo; these TEAEs included slight imbalance in *rash* (3% for OCR vs 2% for placebo). In MS dose finding study WA21493 *rash* occurred in 6% of OCR 600 mg, none in OCR 1000 mg, compared to 2% for interferon beta-1a and none in placebo. In All RA Trials (pool E) *rash* was the most common AE in this SOC, and in RA Controlled Trials (pool D) *contact dermatitis* was the most common AE in this SOC (with a relative risk at least 2x placebo).

Blood and Lymphatic System Disorders

As previously mentioned, Dr. Boehm identified no SAEs of aplastic anemia or pancytopenia in MS trials. In the PPMS controlled trial Dr. Boehm identified 1 case each (0.2% each) of agranulocytosis, febrile neutropenia, and microcytic anemia. Dr. Boehm describes the case of *agranulocytosis* in **Subject WA25046-208244-47506** who had baseline monocytes, erythrocytes, leukocytes, and platelet count within the normal ranges. Approximately 14 months after her first infusion, she was diagnosed with agranulocytosis with leukocyte count $0.52x10^9$/L, neutrophil count $0x10^9$/L, lymphocyte count $0.36x10^9$/L with temperature of 39° C, sore throat, and bilateral lower limb spasticity. She was treated with antibiotics and filgrastim. Her neutrophil count was in the normal range 5 days later and the event was considered resolved. She continued in the study and completed the controlled phase approximately 19 months later. I agree with Dr. Boehm that the role of ocrelizumab in this case is not clear, and that it is reassuring that the event did not recur while she remained in the study.

Dr. Boehm shows that SAEs of febrile neutropenia and granulocytopenia (1 case each in each dose group for OCR) neutropenia (1 case in OCR 400 mg) and 1 case each in OCR 1000 mg of agranulocytosis, cytopenia, leukopenia, and pancytopenia occurred in the RA controlled trials (and none in placebo). As noted previously, the RA patients were exposed to combined immunosuppressants (methotrexate or leflunomide), confounding these findings. Dr. Boehm also notes that SAEs of interest in Study WA20500-LN included 5 SAEs of neutropenia, 3 of agranulocytosis, and 2 of febrile neutropenia, and additional TEAEs of anemia, leukopenia,

and neutropenia that occurred in OCR-treated patients more frequently than in placebo treated patients. These subjects were also treated with other immunosuppressants.

Portal Vein Thrombosis and Splenic Vein Thrombosis

Dr. Boehm identifies 1 SAE of *splenic vein thrombosis* in **Subject WA21093-234088-1937266** that occurred 5 days after the most recent infusion, 1 year after starting ocrelizumab, in a 35 y.o. female taking norethindrone as an oral contraceptive. She was treated with heparin and warfarin and discharged on rivaroxaban and continued in the study. An SAE of *portal vein thrombosis* occurred in **Subject WA21092-206568-1920925**, a 49 y.o. female, 34 days after her most recent infusion and approximately 2.5 years after beginning ocrelizumab. She was treated with nadroparin, rivaroxaban, and warfarin. She was discontinued from the trial. I agree with Dr. Boehm that the role for ocrelizumab in these events is not clear.

Significant Adverse Events

Dr. Boehm notes that 5% of ocrelizumab patients in the ISS had dose interruptions for AEs, most commonly for IRR (n=20) and infections. [26] Dr. Boehm notes that 81% of MS patients had AEs that were mild or moderate in intensity (Grade 1 or 2). Fourteen percent had Grade 3 (severe) events including IRRs, 1.8% had Grade 4 (life threatening events, all but 1 - hyperamylasemia - reported as SAEs), and 0.4% (n=8) had Grade 5 (fatal) events.

Treatment Emergent Adverse Events and Adverse Reactions

The most commonly reported TEAEs in the MS trials (at least 5%) were infections, IRRs, headache, back pain, arthralgia, fatigue, and depression. In controlled trials in MS, TEAEs that occurred in at least 5% and greater than comparator were various infections, IRRs, depression, back pain, and insomnia in RMS, and IRRs, various infections, and cough in PPMS. Cholecystitis/cholelithiasis also occurred more frequently in ocrelizumab treated patients than comparator in both RMS and PPMS.

Dr. Boehm shows that the SOC with the most AEs in the RMS and PPMS controlled trials (and slightly greater than comparator in those studies) and the most AEs in the All MS Pool and the All RA pool was Infections and Infestations, as previously discussed, with TEAEs in that SOC occurring in 50-60% of ocrelizumab patients.

Dr. Boehm provides tables of the most common AEs (at least 2% and greater than comparator) for the RMS and PPMS controlled pools. The following information is extracted from those tables (and in addition I include AEs that were at least as great as IFN beta-1a because that is the active comparator).

The adverse events most commonly reported (at least 5% in ocrelizumab and at least as great as IFN beta-1a) in RMS controlled trials were:

Body System or Organ	Adverse Event	RMS Controlled Trials

[26] Dr. Boehm notes that the 90 day safety update included an additional 9 patients with AEs leading to dose interruptions, and that these AEs were similar to those reported in the ISS.

Class		(Pool A)	
		IFN beta-1a n=826	Ocrelizumab n=825
Infections and Infestations	Upper Respiratory Tract Infections[a]	29%	36%
	Urinary Tract Infections	14%	14%
	Herpes Infections[b]	4%	6%
	Gastroenteritis[c]	4%	6%
Injury, Poisoning, and Procedural Complications	Infusion related reactions	10%	34%
Musculoskeletal and Connective Tissue Disorders	Back pain	4%	6%
	Pain in extremity	4%	5%
Gastrointestinal Disorders	Abdominal pain[d]	4%	5%
Psychiatric Disorders	Depression	7%	8%
	Insomnia	5%	6%

[a] Includes upper respiratory tract infection, sinusitis, pharyngitis, nasopharyngitis, rhinitis, viral upper respiratory tract infection, laryngitis, tonsillitis, acute tonsillitis, acute sinusitis, tracheitis, pharyngitis streptococcal, chronic sinusitis, pharyngitis bacterial, pharyngotonsilitis, viral rhinitis, viral sinusitis, viral tonsillitis, viral pharyngitis
[b] Includes herpes simplex, herpes virus infection, herpes zoster, genital herpes, ophthalmic herpes simplex, oral herpes, varicella
[c] Includes enteritis, enteritis infectious, enterocolitis infectious, gastroenteritis, gastroenteritis viral , gastrointestinal infection, gastrointestinal viral infection
[d] Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, epigastric discomfort, gastrointestinal pain.

The adverse events most commonly reported (at least 5% in ocrelizumab and greater than placebo) in the PPMS controlled trial were:

Body System or Organ Class	Adverse Event	Placebo n=239 %	Ocrelizumab n=486 %
Infections and Infestations	Upper Respiratory Tract Infection[a]	37	39
	Influenza	9	12
	Bronchitis[b]	5	7
Injury, Poisoning, and Procedural Complications	Infusion related reactions	26	40
Psychiatric Disorders	Insomnia	5	6
Respiratory, Thoracic, and Mediastinal Disorders	Cough	3	6
Vascular Disorders	Hypertension	4	5

[a] Includes upper respiratory tract infection, sinusitis, pharyngitis, nasopharyngitis, rhinitis, viral upper respiratory tract infection, laryngitis, tonsillitis, acute tonsillitis, tracheitis, pharyngitis streptococcal, chronic sinusitis, pharyngotonsilitis
[b] Includes bronchitis, bronchitis viral, bronchitis chronic

Dr. Boehm shows TEAEs reported in at least 1% of patients in All MS Trials (Pool B). I have extracted those that were reported in at least 5% as shown in the table below. They are similar to those reported in the controlled trial pools, with the addition of headache and fatigue.

The adverse events most commonly reported (at least 5% in ocrelizumab) in the all MS pool were:

Body System or Organ Class	Adverse Event	Ocrelizumab n=2147 %
Infections and Infestations	Upper Respiratory Tract Infection	33
	Urinary tract infection	15
	Influenza	6
	Bronchitis	6
	Gastroenteritis	5
	Herpes infections	5
Injury, Poisoning, and Procedural Complications	Infusion related reactions	34
Nervous System Disorders	Headache	10
Musculoskeletal and Connective Tissue Disorders	Back pain	8
	Arthralgia	6
	Pain in extremity	5
General Disorders and Administration Site Conditions	Fatigue	7
Psychiatric Disorders	Depression	6

TEAEs in the dose finding MS trial WA21493 were generally similar in type and frequency to those in the RMS and PPMS controlled trials and in the all MS trials pool. The most common TEAEs in the controlled RA trials (Pool D) (and greater than comparator, excluding the AE of rheumatoid arthritis) were infusion related reactions, and the most common TEAEs (at least 5%, 146/2925) in the all RA trials (Pool E) were generally similar to those seen in the MS trials: Infections and Infestations (upper respiratory tract infection, nasopharyngitis, urinary tract infection, bronchitis, sinusitis, and influenza), IRRs, nausea and diarrhea, back pain, headache, cough, and hypertension. As previously noted, TEAEs in Study WA20500 - LN, unlike the other trials, included anemia, leukopenia, and neutropenia in at least 10% in an ocrelizumab treatment group and greater than placebo. I note that patients in this study had concomitant immunosuppressive therapy including cyclophosphamide, azathioprine, or mycophenolate mofetil.

Laboratory Findings

Please refer to Dr. Boehm's detailed review of laboratory findings.

Laboratory Findings in MS Trials
In RMS controlled trials Dr. Boehm finds that mean change from baseline did not strongly suggest ocrelizumab-related effects for the majority of tested analytes. He reports that lymphocytes decreased slightly in both interferon and ocrelizumab groups. He shows that ocrelizumab patients experienced mean increases in creatine kinase, noting that the majority were single occurrences, while patients in the interferon beta-1a group generally experienced mean decreases; I agree that the significance of these results is not clear. Dr. Boehm notes that there were no cases of rhabdomyolysis or myopathy AEs in ocrelizumab patients, and that myalgia AEs occurred more frequently in comparator patients compared to ocrelizumab patients in the RMS and PPMS trials.

In PPMS controlled trials, Dr. Boehm shows that ocrelizumab patients experienced mean decreases in lymphocytes starting at week 12 and that the decreases were greater than in placebo; the decreases remained steady through week 120. He notes that the change in creatine kinase observed in RMS was not observed in PPMS.

Dr. Boehm shows laboratory measures (hematology and chemistry) for which ocrelizumab patients more frequently had a lab abnormality compared to interferon beta-1a but shows that the risk differences for these abnormalities were low and notes that the abnormalities were generally not persistent.

Dr. Boehm shows that lab data from RMS controlled trials and the PPMS controlled trial did not suggest an increased risk of transaminase elevations with ocrelizumab. He notes that the Sponsor identified no cases in the MS trials of ocrelizumab patients with transaminases at least 3X ULN associated with increased total bilirubin (Hy's law cases).

In All MS trials, neutropenia occurred in 326 patients. Grade 1 neutropenia (< LLN – 1.5X 109/L) occurred in 210 patients. There was no association between neutropenia Grade 2 or higher and infections.

Dr. Boehm has reviewed laboratory related AEs. He identifies 1 ocrelizumab patient (**WA21092-205658-1920921**) in all MS trials (Pool B) who had slightly elevated ALT (and AST and GGT) at screening and fluctuating ALT throughout the controlled phase and who experienced an SAE under the SOC investigations that was *ALT elevated* (approximately 3x ULN, with total bilirubin 20 uM/L), with a CT showing diffuse parenchymal changes and with negative HIV and hepatitis tests; he continued in the study. The role of ocrelizumab in this case is not clear.

No AEs in the Investigations SOC led to discontinuation of ocrelizumab in an MS trial.

Dr. Boehm notes that in all MS trials (Pool B), laboratory AEs under the Investigations SOC were not commonly reported. Those AEs reported by at least 5 MS patients were blood creatine phosphokinase increased (1.1%), as well as ALT increased, GGT increased, liver function test abnormal, hepatic enzyme increased, transaminases increased, AST increased, blood immunoglobulin M decreased, and blood triglycerides increased, all at less than 1%. He

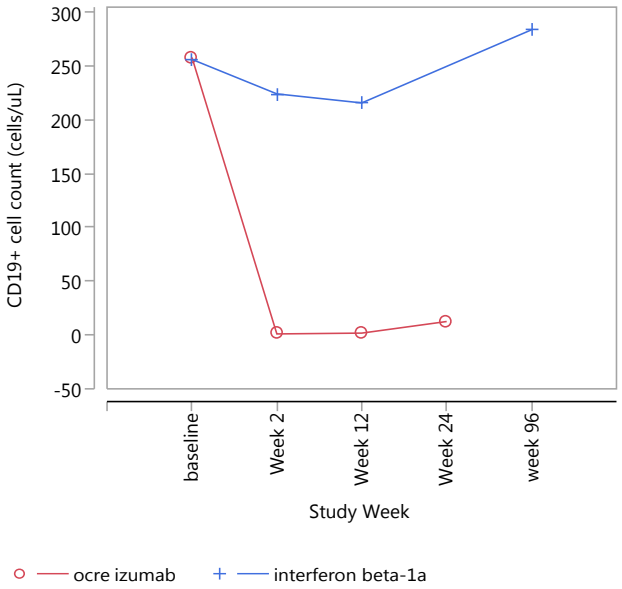
also reported amylase increased (0.5%) and lipase increased (0.4%). In the controlled RMS trials (Pool A) the only Investigations AE that occurred in at least 2 ocrelizumab patients and more frequently than interferon (interferon beta-1a 0.1%, ocrelizumab 0.2% for each) were blood glucose increased and blood triglycerides increased In the PPMS controlled trial, small differences between ocrelizumab and placebo (and frequencies of 1% or less for ocrelizumab) were observed in transaminase-related labs, amylase and lipase increased, blood testosterone decreased, white blood count decreased, eosinophil count increased, and WBC urine positive.

In the RA controlled trials (Pool D), Dr. Boehm notes that a higher percentage of ocrelizumab patients experienced decreases in neutrophil counts and in WBC counts compared with placebo (both in approximately 4% of ocrelizumab patients and 1-2% of placebo patients). He noted that other lab abnormalities were experienced by similar percentages of ocrelizumab and placebo patients, and notes that there did not appear to be differences in percentages of patients experiencing elevations of AST or ALT. He notes that the Sponsor identified no cases in the RA trials of ocrelizumab patients with transaminases/bilirubin in the Hy's law range.

Submission Specific Laboratory Results

Dr. Boehm identified decreases in CD19+ cell counts and in immunoglobulins in ocrelizumab-treated patients. I agree with him that these changes may be responsible for the increased risk for infection in ocrelizumab patients.

I show mean change from baseline in CD19+ cell count, as derived from Dr. Boehm's review, in the figure below for RMS controlled trials (Pool A) in which CD19+ cell counts in ocrelizumab treated patients fell to nadir levels by week 2 and remained at those low levels through week 24. Dr. Boehm notes that for the small number of patients (34) who entered the SFU after stopping ocrelizumab, the mean CD19+ cell count at SFU week 12 was 28.2, by week 24 was 127.2 (n=32), at week 48 was 173.7 (n=15) and at week 72 was 223.4 (n=5).



Dr. Boehm notes that the mean change results for CD19+ cell counts for the ocrelizumab group in the PPMS controlled trial were similar to those in the RMS trials, with minimal changes in placebo throughout the trial. CD19+ similarly increased slowly over time, although the recovery seemed slower, with counts at SFU week 36-96 fluctuating between 37-86.9.

Dr. Boehm notes that a small number of patients in RMS and PPMS trials repleted their cell counts before the next infusion (less than 5%).

Dr. Boehm shows decreases in mean CD3+, CD4+, and CD8+ T lymphocyte cell counts following the first infusion in RMS controlled trials (Pool A), with little change over subsequent infusions and he shows that declines in interferon patients were greater than those for interferon. He notes no notable changes in NK cells for ocrelizumab. I note a recent publication summarizing evidence of CD20+ Tcells in humans and suggesting that anti-CD20+ antibodies could directly affect T cells[27].

In RMS controlled Trials (Pool A), ocrelizumab patients experienced a mean 40% decline in IgM at week 96 that was not observed in interferon patients. At week 96, 91% of ocrelizumab patients experienced a decline in IgM of more than 20% from baseline, compared to 14% of interferon patients. At week 96, 17% of ocrelizumab patients had an IgM result below the lower limit of normal, compared to 0.8% of interferon patients. Declines in IgA and IgG were smaller (but also occurred more frequently in ocrelizumab patients than in interferon patients). Dr. Boehm notes that the declines in immunoglobulin levels in the PPMS trial were similar to the RMS results in patients exposed to ocrelizumab, with negligible changes in placebo patients.

I agree with Dr. Boehm that the effects on CD19+ cells and immunoglobulins are likely responsible for the increased risk for infection in ocrelizumab patients.

Vital Signs

Please refer to Dr. Boehm's review for details regarding vital signs findings. I agree with him that ocrelizumab did not appear to be associated with notable differential effects on vital signs compared to interferon and placebo.

Dr. Boehm notes that at the non-infusion visits, mean changes in vital signs were small and similar for the interferon and ocrelizumab groups in RMS controlled trials, and for placebo and ocrelizumab groups in PPMS Trials. For infusion visits, Dr. Boehm notes that in the RMS trials and in the PPMS trials, both ocrelizumab and comparator patients experienced small mean declines from baseline in systolic and diastolic blood pressure following infusions, and small mean increases from baseline in heart rate (approximately 8-9 bmp for ocrelizumab, and about 1 bpm higher than for comparator), greatest at approximately 3 hours.

[27] Colombe Agahozo M, Peferoen L, Baker D, Amor S. CD20 therapies in multiple sclerosis and experimental autoimmune encephalomyelitis – Targeting T or B cells? Multiple SclerosisandRelatedDisorders;2016:110–117.

Dr. Boehm shows that the percentages of patients meeting potentially clinically significant (PCS) vital sign criteria (high or low) were generally small and similar between the treatment groups in RMS controlled trials (Pool A). This was similarly true for the PPMS controlled trial. The differences occurred across the doses/infusion days.

Electrocardiograms (ECGs)

ECGs were performed at screening, baseline (prior to first infusion), study week 72, and at the withdrawal of treatment visit. I note that ECGs were not performed during infusions and Dr. Boehm notes that no systematic analysis of ECG intervals was undertaken. In RMS controlled trials (Pool A), Dr. Boehm notes that no ECG related AE was reported more than once for ocrelizumab patients. A variety of ECG related AEs (21) were reported in the All MS Trials Pool A (21) and in the PPMS trial (5). It is difficult to determine the role of ocrelizumab.

I note that the Rituximab label has Warning 5.7 regarding cardiac arrhythmias during infusions (although the label notes that patients with RA are at greater risk for cardiovascular events than the general population).

QT

ECG intervals were not systematically measured/ assessed in the ocrelizumab development program. Dr. Boehm notes that in all MS trials (Pool B) no patients had an AE of QT prolongation, although patient WA25046-207348-12602 had an IRR during which a QTc of 615 ms was reported as I have previously noted. The Sponsor has explained that rationale for the lack of necessity for a thorough QT study based on the biologic plausibility (large size, high target specificity, low-off target potential, and cardiac cells do not express CD20 antigen), literature review finding no relevant QT/QTc interval prolongations for 15 monoclonal antibodies or antibody-drug conjugates or cases indicative of drug-induced QT prolongation for 28 pre-identified monoclonal antibody drugs authorized in Europe, and nonclinical studies in monkeys that did not find evidence of QT prolongation.

Dr. Boehm believes that the Sponsor provided a reasonable justification for lack of a formal QT study with ocrelizumab, and I agree.

Immunogenicity

Dr. Boehm notes that development of anti-drug antibodies (ADA) occurred infrequently during MS trials and was similar for ocrelizumab (< 2%) and interferon (1%) or placebo (4%). One ocrelizumab patients in RMS and 1 in the PPMS controlled trials tested positive for neutralizing antibodies to ocrelizumab and neither experienced an IRR or hypersensitivity reactions.

Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Please refer to discussion of Malignancies.

Human Reproduction and Pregnancy

Please refer to Dr. Boehm's review for details. I believe it is difficult to attribute the few and disparate adverse events in pregnancy to ocrelizumab because of exposure that ended generally long before conception and concomitant exposure to known teratogens. The assessment of a causal relationship between ocrelizumab exposure and spontaneous abortions is difficult. I recommend a pregnancy registry as a postmarketing requirement.

The sponsor considered that an embryo/fetus was potentially transplacentally exposed to ocrelizumab if ocrelizumab was last administered less than 3 months before conception, during pregnancy, or exact exposure unknown. Although the Sponsor considered that no relevant transport of immunoglobulins including ocrelizumab through the placenta occurs in the 1st trimester, they considered exposure to occur even if ocrelizumab was administered before the 2nd trimester.

Despite mandatory contraception, Dr. Boehm notes that the sponsor identified 51 pregnancy related AEs (49 pregnancies in 35 women who received ocrelizumab); 26 of the AEs came from the MS trials.

The total of 49 pregnancies exposed to ocrelizumab in the entire safety database resulted in 24 live births (5 from MS trials).

Among the 24 live births, 15 were normal and full term (4 in MS trials and 11 in other indications) and 1 (non-MS) was normal with unknown gestational week. One (MS) live birth was *preterm*, with *benign nasopharyngeal neoplasm* (classified as a structural malformation), jaundice, respiratory distress (secondary to nasopharyngeal mass), and jaundice and low birth weight (possibly due to preterm delivery); the last ocrelizumab dose had been 6 months prior to conception. Two non-MS live births had structural malformations: **AER 606368** with *congenital positional feet contracture and limited hips abduction* in a mother who had taken methotrexate (a teratogen) up to 4 months prior to conception and last ocrelizumab 12.5 weeks prior to conception; **AER 1110613** with small right *renal cyst* in a mother who had stopped ocrelizumab 3 years prior to conception and in whom azathioprine (a teratogen) was stopped 6 weeks after conception. Four non-MS live births were pre-term; 2 of the 4 had abnormal findings: **AER 687303** with low birth weight with the last ocrelizumab dose 4 months before conception (and rabeprazole, prednisolone and teratogens mycophenolate and irbesartan stopped 18 days after conception); **AER 715989** was *small for gestational age*, APGAR score 9 at 10 minutes (normal) with *respiratory distress* requiring oxygen therapy for 4 days and experiencing *sepsis, hypertension, retinopathy of prematurity, hyperbilirubinemia, and neonatal anemia* with a mother whose pregnancy was complicated by gestational hypertension and pre-eclampsia and risk factors for prematurity and small for date babies, and concomitant teratogenic medications, with last ocrelizumab 10 months before conception. 1 non-MS live birth (**AER 6202950**) had *growth alteration* because of low birth weight.

Among the 25 ocrelizumab pregnancies not resulting in live births, there were 9 with elective terminations (7 in MS and 2 in other indications; none with embryo/fetal malformations). In non-MS indications, 11 had spontaneous or missed abortions, or fetal death and none had

evidence of embryo/fetal abnormalities (one was in a mother who died from pulmonary embolism). There were 4 pregnancies ongoing at the time of the data cut-off (but reported with normal babies at full term in the 90 day safety update[28]), and 1 with an outcome unknown due to loss to follow-up. In addition to those 25 cases, at the 90 day safety update there was a stillbirth at unknown gestational week.

Pediatrics and Assessment of Effects on Growth
Not evaluated in the pediatric population in this development program.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound
Dr. Boehm notes that the Sponsor's review of events suggestive of drug abuse (terms mapping to the SOC of Psychiatric Disorders and Nervous System Disorders) and additional terms related to abuse did not find evidence of ocrelizumab-related drug abuse, and the Sponsor's review of clinical cases did not identify any withdrawal event terms related to ocrelizumab.

Concerns identified through U.S. or foreign postmarket experience
Ocrelizumab is not yet marketed in the rest of the world.

Potential safety issues that could cause concern when considering how the drug may be used in the postmarket setting

I agree with Dr. Boehm that during the post-marketing experience cases of infections, including serious and opportunistic infections, would be expected because of the suppressive effects of ocrelizumab on the immune system. I agree that the Sponsor should monitor for postmarketing serious and opportunistic infections with a specific focus on PML and cases of Hepatitis B reactivation that are included in the approved labeling for anti-CD20 monoclonal antibodies but not reported in MS patients in this BLA.

I also agree that postmarketing reports should characterize IRR events and establish whether pre-treatment was used, if treatment of the IRR was required, and if any potential predictive characteristics were suspected.

I also agree that the relationship between ocrelizumab and malignancies, cholecystitis/cholelithiasis, and pancreatitis are not clear at this time and should be monitored in the post-marketing period. In particular, malignancies in the postmarketing setting may be detected late in absence of frequent contact with a healthcare provider as occurred in the clinical trials.

9. Advisory Committee Meeting

An advisory committee meeting is not planned.

[28] There was an additional pregnancy in the 90 day safety update that delivered a normal baby.

10. Pediatrics

This application did not evaluate use in pediatrics.

11. Other Relevant Regulatory Issues

Please refer to the clinical efficacy review.

12. Labeling

Prescribing Information
If ocrelizumab is approved, I have the following general labeling recommendations:

- DOSAGE AND ADMINISTRATION:
    1. Recommendations for pre-treatment as performed in the clinical trials may help mitigate potential risks of infusion reactions.
- Safety information in the WARNINGS AND PRECAUTIONS sections:
    1. I recommend WARNIGNS and PRECAUTIONS for infusion reactions, infections, and malignancies. I also recommend a warning for depression and suicide because of the similar frequency as observed for interferon beta-1a and because interferon beta-1a has a warning in the labeling.
- I recommend separate tables of common adverse reactions in Section 6 for RMS and PPMS if approved for both indications.
-

Other Labeling
A Medication Guide will be an important tool in educating patients and caregivers about the other events identified in WARNINGS and PRECAUTIONS and to facilitate prompt recognition and treatment.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

I agree with Dr. Boehm that a REMS is not required for safe use of ocrelizumab. I agree that labeling can adequately explain the risk and symptoms of IRRs and provide recommendations regarding pre-treatment, management, and recommendations for discontinuation. I agree that labeling can also describe the potential risk for infection and can provide information regarding the observed malignancy risk imbalance.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

I agree with Dr. Boehm's recommendation that a long term safety study to collect data on (b) (4) breast malignancy, should be a PMR. The Sponsor has proposed (b) (4) for which DEPI has provided preliminary comments; a full protocol would be reviewed (b) (4)

I suggest a pregnancy registry as a PMR.

Recommended Comments to the Applicant
The risks for serious and opportunistic infections, including PML and Hepatitis B reactivation, should be monitored in the post-marketing setting. The risks for malignancies, IRRs, pancreatitis, and cholecystitis/cholelithiasis should also be monitored in the post-marketing setting.

APPEARS THIS WAY ON ORIGINAL

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/s/

SALLY U YASUDA
10/25/2016

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	761053
Priority or Standard	Priority
Submit Date(s)	4/28/16
Received Date(s)	4/28/16
PDUFA Goal Date	12/28/16
Division/Office	Division of Neurology Products/ODE1
Reviewer Name(s)	Gerard Boehm MD, MPH
Review Completion Date	9/14/16
Established Name	Ocrelizumab
(Proposed) Trade Name	OCREVUS
Applicant	Genentech, Inc.
Formulation(s)	Injection: 300 mg/10 mL (30 mg/mL) in a single-use vial
Dosing Regimen	Initial dose: 600 mg dose is administered as two separate IV infusions; first as a 300 mg infusion followed 2 weeks later by a second 300 mg infusion. Subsequent doses: 600 mg dose is administered as a single IV infusion every 6 months.
Applicant Proposed Indication(s)/Population(s)	Relapsing forms of Multiple sclerosis, Primary Progressive Multiple Sclerosis
Recommendation on Regulatory Action	Approvable
Recommended Indication(s)/Population(s) (if applicable)	

Table of Contents

Table of Tables

Table of Figures

Glossary

AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Refer to Clinical Review

1.2. Conclusions on the Substantial Evidence of Effectiveness

Refer to Clinical Review

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

In their BLA for Ocrelizumab, Genentech seeks approval for the treatment of patients with relapsing forms of multiple sclerosis (RMS) and for the treatment of patients with primary progressive multiple sclerosis (PPMS). This review evaluates the safety of ocrelizumab. If efficacy is demonstrated and the benefits of ocrelizumab outweigh the risks in either RMS or PPMS, then I recommend that approval be accompanied by labeling language including warnings and a medication guide to mitigate the risks.

This document reviews the risk profile of ocrelizumab. Ocrelizumab is associated with infusion related reactions (IRRs), infections, malignancies including breast cancer, and depression. These adverse reactions have potential for more serious outcomes in the post marketing period in which patients are monitored less frequently than in the clinical trial setting. Warnings in the labeling and a Medication Guide for patients may mitigate potentially serious outcomes of these adverse reactions. A recommendation regarding approvability can only be made based on a consideration of benefit and risk. I will provide an assessment of the risk, and recommendations for labeling in an effort to mitigate the risk if efficacy is demonstrated and it is determined that the benefits outweigh the risk such that ocrelizumab would be approved for either indication.

Risk:

Ocrelizumab is associated with IRRs that occurred in 35% of patients in the all MS trials pool, even in the setting of pretreatment with methylprednisolone that was required in the clinical trials. The IRRs occurred most frequently after the first dose but continued to occur with subsequent infusions. Most of the infusion reactions were mild and occurred during the nfusion period, although some also occurred within 24 hours of the infusion, after the patient had left the clinic. Infections were commonly reported in the MS trials overall (54%) and in the controlled trials where they occurred more commonly with ocrelizumab than with comparator, although SAEs due to infections occurred less frequently with ocrelizumab than with comparator. Opportunistic infections were not identified in MS patients treated with ocrelizumab. Ocrelizumab was associated with malignancies in the MS trials, with an approximate 3 fold increase for ocrelizumab vs comparator in the controlled trials. In particular there was an imbalance in the controlled trials for breast cancer associated with ocrelizumab (with 6 cases in women exposed to ocrelizumab vs none in comparator). There were 8 cases (8/1,398 females, 0.6%) in the all MS trials (Pool B). One case of breast cancer in a male occurred in a Rheumatoid Arthritis Trial, an unexpected occurrence given the background rate of breast cancer in men. Depression TEAEs and depression and suicide related SAEs occurred more frequently in ocrelizumab-treated subjects than in interferon beta-1a subjects. Interferon beta 1-a product labeling has a Warning statement for Depression and Suicide.

There is uncertainty regarding potential for more serious outcomes in the post marketing period in which patients are monitored less frequently than in the clinical trial setting. Warnings in the labeling and a Medication Guide for patients may mitigate potentially serious outcomes of these adverse reactions.

Analysis and Recommendation with Respect to Safety:

If ocrelizumab is approved, I recommend Warnings IRRs, infections, malignancies, and depression/suicidality. I recommend guidance for pre-treatment to mitigate the risk of infusion reactions. I recommend a Medication Guide to describe these risks and symptoms of concern. , I recommend enhanced pharmacovigilance post marketing for events of serious infections, including opportunistic infections, with special focus on PML and Hepatitis B reactivation; cholecystitis/cholelithiasis; and pancreatitis. I recommend the following post marketing requirements:

- Long-term observational post marketing requirement to characterize safety with emphasis on the risk of malignancies and infections.
- Pregnancy registry.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Please refer to Dr. Rodichok's review of clinical efficacy.	
Current Treatment Options	• Please refer to Dr. Rodichok's review of clinical efficacy.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Please refer to Dr. Rodichok's review of clinical efficacy.	
Risk	Safety database The safety database for ocrelizumab includes two Phase 3 interferon beta-1a controlled clinical trials in adults in RMS (WA21092 and WA20193) and their open label extensions, a Phase 2 dose finding trial in RMS (WA21493), and one placebo-controlled trial in PPMS (WA25046), as well as supportive data primarily from controlled and open label studies in Rheumatoid arthritis (RA) and limited supportive data from studies in patients with Systemic Lupus Erythematosus (SLE), Lupus Nephritis (LN), and Non-Hodgkin's Lymphoma (NHL). Drug exposure is adequate, was at or above the proposed doses, and the demographics of the clinical trial subjects reflects the intended population for use. Safety concerns • The most common AEs in the pooled RMS Phase 3 controlled phases (at least 5% and at least as frequent as interferon beta-1a) were: Upper respiratory tract infections (URI, 36%), Infusion related reactions (IRRs, 34%), Urinary tract infections (UTI, 14%), Depression (8%), Herpes infections (6%), Gastroenteritis (6%), Back pain (6%), and Insomnia (6%). The most common AEs in the PPMS controlled phase (at least 5% and at least 2% greater than placebo) were: IRRs (40%), URI (39%), Influenza (12%), Bronchitis (7%), and Cough (6%). • Eight deaths (0.4%, 0.18/100 PY) occurred in ocrelizumab-treated subjects	Given the established relationship between *other* anti-CD20 monoclonal antibodies and IRRs including fatal infusion reactions that mostly occurred with the first infusion of those drugs, the Sponsor required premedication to prevent/mitigate IRRs in the ocrelizumab trials. Whether more serious IRRs would occur in the absence of pretreatment with ocrelizumab is unknown. Labeling including IRRs as a Warning, with recommendations for pre-treatment could mitigate the potential risk. Ocrelizumab is associated with a risk of infections, and uncertainty exists in whether outcomes of infections would be more serious in an unmonitored outpatient setting or in patients with greater risk for immunosuppression. Labeling infections as a Warning would highlight the need for awareness of the potential for infections and may mitigate the risk for serious outcomes.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	in controlled and open label MS studies (Pool B): 1 of suicide in a patient with no signs or symptoms of depression prior to the event but with felony charges 2 days prior to the event, 1 of metastatic pancreatic cancer diagnosed approximately 51 months after beginning ocrelizumab, 1 of aspiration pneumonia in a patient with a history of dysphagia, 1 of pneumonia reported as desquamative pneumonia with associated bacterial component in a translated autopsy report for which a role for ocrelizumab cannot be ruled out, 1 of pulmonary embolism approximately 10 months after the last dose of ocrelizumab, 1 due to systemic inflammatory response syndrome (SIRS) for which a role for ocrelizumab cannot be ruled out, 1 sudden death more than 1 year after the last dose, 1 due to injury (fall from great height) more than 1 year after last dose. There were too few deaths during controlled phases of the MS trials to support conclusions about relative mortality risks. • Forty-five deaths (1.5%, 0.61/100 PY) occurred in All RA Trials (Pool E). The 37 deaths that occurred during treatment or within 1 year of the last dose included 7 pneumonia (6/7 had received other immunosuppressants), 6 sepsis/septic shock (4/6 had received corticosteroids and methotrexate), 3 respiratory failure, 3 lung cancer, 3 sudden death/death, 2 myocardial infarction, and 1 each of brain edema, breast cancer, carbon monoxide poisoning, disseminated intravascular coagulation, gastric cancer, gastrointestinal carcinoma, gastrointestinal hemorrhage, ischemic cerebral infarction, multi-organ failure, pulmonary embolism, ruptured cerebral aneurysm, toxicity to various agents, and traffic accident. Although the mortality rate for ocrelizumab and placebo were comparable in the controlled trials, the ocrelizumab groups had an increased number of	Ocrelizumab is associated with an increased risk of malignancies, particularly breast cancer. Labeling malignancies as a Warning would highlight the need for awareness of the potential. This may be particularly important in the outpatient setting in which patients may be seen less frequently than in the clinical trials. Malignancies should be further characterized in the post marketing setting. There is an imbalance in SAEs with terms related to depression and suicide in RMS and PPMS controlled trials for ocrelizumab vs comparator. TEAEs related to depression in RMS controlled trials were similar for ocrelizumab compared to interferon which has a Warning for Depression and Suicide. A Warning for ocrelizumab may help mitigate the risk. Five SAEs of pancreatitis occurred in ocrelizumab patients, 3 of them in patients with risk factors, and none in comparator patients. The relationship between the risk for pancreatitis and use of ocrelizumab is unknown. Post

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	infection/sepsis related deaths (5) compared to placebo (0). • Ocrelizumab is associated with IRRs. All patients in MS trials were pretreated with methylprednisolone prior to each infusion; pre-treatment with oral analgesic/antipyretic and an oral antihistamine was recommended. TEAEs of IRRs occurred in 35% in All MS Trials (Pool B), and approximately 2 to 3 times more frequently than comparator in controlled trials. There were few discontinuations or SAEs of IRRs (1% or fewer). IRRs occurred most frequently with the first dose but continued to occur with subsequent doses. Most (60-80%) occurred during the infusion but 18% to 38% occurred within 24 hours of the infusion but after leaving the clinic in RMS and PPMS controlled trials. No deaths were attributed to IRRs in ocrelizumab treated MS patients. The most common symptoms of IRRs related to ocrelizumab were pruritus, rash, throat irritation, flushing, urticaria, and oropharyngeal pain in RMS with similar IRRs in PPMS that also reported pyrexia commonly. 73% of IRRs were mild in Pool B. Antihistamines were the most commonly administered treatments for IRRs. In MS controlled trials, ocrelizumab patients pretreated with oral antihistamine and methylprednisolone generally had a least a 2-fold lower incidence in IRRs compared with pretreatment with methylprednisolone alone. Potential for more serious reactions in the absence of pre-treatment is unknown. • Infections were commonly reported in the MS trials overall (54%) and in the controlled trials. There was a slightly greater risk of infections with ocrelizumab compared to interferon in RMS Pool A and compared to placebo in the controlled phase of the PPMS trial. In controlled trials, infection SAEs occurred less frequently in ocrelizumab treated patients	marketing reports should be monitored for additional cases. There was an imbalance in AEs related to cholecystitis/cholelithiasis. Given that a similar imbalance was not seen in the RA trials, that these events are not mentioned in labeling for the approved antiCD20 monoclonal antibodies, and that these events are expected in the background, inclusion of these events in labeling is not recommended at this time. Reports of these events in the post marketing period should be monitored. Because the risk of adverse outcomes in pregnancy has not been characterized, and because ocrelizumab will be used in women of childbearing potential, a pregnancy registry should be considered as a post marketing requirement.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	than comparator patients. Infections resulted in few discontinuations. The most common infections and greater than interferon in RMS controlled trials were upper respiratory tract infections, herpes infections, lower respiratory tract infections, and gastroenteritis. The most common infections and greater than placebo in the PPMS controlled trial were upper respiratory tract infections, influenza, lower respiratory tract infections, and bronchitis; herpes infections also occurred at a rate greater than placebo. Opportunistic infections were not identified in MS patients treated with ocrelizumab. The greatest risk for infections was following the first dose in the controlled RMS trials. Whether outcomes of infections would be more serious in an unmonitored outpatient setting is unknown. • An increase in malignancies is observed for ocrelizumab compared to interferon in Pool A (2.5 fold increase) and compared to placebo in the in the PPMS controlled trials (2.9 fold increase). In particular, there is an imbalance in breast cancer in the controlled trials in which 2 cases (0.3% of females) occurred in ocrelizumab vs none in interferon beta-1a in RMS Pool A and 4 cases (1.6% of females) occurred in the PPMS controlled trial in ocrelizumab vs none in placebo, all occurring at least 1 year after starting treatment with ocrelizumab. There were with 8 breast cases (8/1,398 females, 0.6%) in all MS trials (Pool B). In the all RA trial pool, 7 patients were diagnosed with breast cancers: 6 females (6/2,341 females, 0.3%) and 1 male (1/585 males; 0.2%), an unexpected event given the background incidence of male breast cancer. • There was no imbalance in SAEs or TEAEs in the *Psychiatric disorders* SOC in the controlled trials in RMS or PPMS. However, in there was an imbalance in depression, and suicide attempt SAEs that occurred only in	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	ocrelizumab patients and not in comparator patients (based on a small number of events). Depression TEAEs occurred less frequently in ocrelizumab-treated patients than placebo in the PPMS controlled trial, but occurred slightly more frequently than interferon (8% vs 7%) in the RMS Controlled Trials (Pool A). Because interferon beta-1a labeling has a warning for depression and suicide, I recommend considering a warning for ocrelizumab. Safety in the post-market setting The risk for serious outcomes of adverse events including infections and malignancies in the post marketing period when patients are likely to be observed less frequently than in clinical trials is unknown. Other uncertainties • SAEs of pancreatitis occurred in 5 ocrelizumab treated patients and none in the comparator subjects in controlled trials. Three of the patients with pancreatitis had known risk factors. The relationship to ocrelizumab is not clear at this time. • Cholecystitis/cholelithiasis occurred more frequently with ocrelizumab but the significance of this finding is not clear. • The risk of adverse outcomes in pregnancy has not been characterized	
Risk Management	• Product labeling with Warnings and a Medication Guide regarding the risks of IRRs, infections, malignancies, and depression/suicide may mitigate the risks of serious outcomes of these events. • A post-marketing requirement for an observational safety study will help to evaluate the main safety risks of ocrelizumab in the post-	Warnings and a Medication Guide with information regarding the main safety risks may help mitigate serious outcomes of these risks in the post-marketing setting.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	marketing setting.	A post-marketing requirement for an observational safety study will help to evaluate the main safety risks of ocrelizumab in the post-marketing setting.

2 Therapeutic Context

2.1. Analysis of Condition

Refer to Clinical Review

2.2. Analysis of Current Treatment Options

The following table summarizes safety and tolerability issues with currently approved Multiple Sclerosis treatments. Note- currently there is no approved treatment for Primary Progressive Multiple Sclerosis.

Table 1. Summary of approved treatments for Multiple Sclerosis

Product (s) Name	Year of Approval	Dosing/route/ Administration	Important Safety and Tolerability Issues/ Other comments
Glatiramer *(Copaxone)*	1996	20 mg/day, SQ qd	Immediate post injection reaction; chest pain; local lipoatrophy & skin necrosis; may interfere with immune system. Contraindicated in patients with known hypersensitivity to glatiramer or mannitol.
Beta interferon 1 b *(Betaseron)*	1993	0.25mg, increase by 0.0625mg q 6 wks. SQ qod	Depression, suicide and psychotic disorders; Liver injury; anaphylaxis and other allergic reactions; congestive heart failure; decreased peripheral blood counts. Autoimmune disorders (including autoimmune hepatitis). Flu-like symptoms. Local injection reaction. Contraindicated in patients with a history of hypersensitivity to IFNβ o any other component of the formulation.
Beta interferon 1b *(Extavia)*	2009		
Beta interferon 1 a *(IFNß1a)*	1996	30 µg, increase by 7.5 µg q 3 wks IM q week.	
Beta interferon 1a *(Rebif)*	2002	22 or 44 µg, SQ three times/week	
Mitoxantrone *(Novantrone)*	2000	12mg/m² IV, q 3 mo	Cardiotoxicity, secondary acute myelogenous leukemia, severe myelosuppression, fetal harm.
Natalizumab *(Tysabri)*	2004	300 mg IV over 1 h, q 4 weeks	PML and other opportunistic infections; Hypersensitivity reactions; hepatotoxicity. Available through restricted distribution program (TOUCH®). Contraindicated in patients with prior PML and in

			patients who had hypersensitivity to TYSABRI.
Fingolimod *(Gilenya)*	2010	0.5 mg, PO qd	First dose bradycardia & AV block; Infections including herpes, cryptococcal and PML; Liver injury; Macular edema; PRES; increased BP.
Teriflunomide *(Aubagio)*	2012	7 or 14 mg, PO qd	Hepatotoxicity, Teratogenicity. Immunosuppression, infections, peripheral neuropathy, skin reactons, increased blood pressure, respiratory effects. Contraindicated in patients with severe hepatic impairment and patients who are pregnant or may become pregnant.
Dimethyl fumarate *(Tecfidera)*	2013	120 mg for 7 days, PO then 240 mg bid	Lymphopenia; flushing; PML. Contraindicated in (b) (4).
Pegilated interferon *(Plegridy)*	2014	125 mcg every 14 days	Hepatic injury, depression and suicide, seizure, anaphylaxis, injection site reactions, congestive heart failure, decreased peripheral blood counts, autoimmune disorders.
Alemtuzumab *(Lemtrada)*	2015	2 injections total	Autoimmune diseases (hemolytic anemia, thyroiditis).
Daclizumab *(Zinbryta)*	2016	150 mg monthly, sc	Boxed warning for hepatic injury including autoimmune hepatitis as well as other immune mediated disorders. Warnings for hypersensitivity reactions, infections, and depression/suicide. Contraindicated in pre-existing hepatic disease or hepatic impairment, history of autoimmune hepatitis or other autoimmune condition involving the liver, history of hypersensitivity to daclizumab or any component of formulation.

Source: individual products labeling.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Refer to Clinical Review

3.2. Summary of Presubmission/Submission Regulatory Activity

Refer to Clinical Review

3.3. Foreign Regulatory Actions and Marketing History

Refer to Clinical Review

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

4.2. Product Quality

4.3. Clinical Microbiology

4.4. Nonclinical Pharmacology/Toxicology

4.5. Clinical Pharmacology

Please refer to the Clinical Pharmacology review. The following information regarding pharmacokinetics and pharmacodynamics is from of the Clinical Overview provided by the applicant and reflects the findings most relevant to safety.

- Terminal elimination half-life is 26 days.
- B cell depletion in blood was complete and sustained on average for 6 months after first drug administration, although up to 5% of patients showed repletion greater than lower limit of normal (LLN) or baseline (whichever was lower) at least at 1 time point between infusions; repletion occurred less frequently in patients with higher exposures.

- Median time to repletion (Phase 2 study WA21493) was 72 weeks after the last infusion. Ninety percent of all patients had B cells repleted to the LLN or baseline (whichever was lower) by approximately 2.5 years after last infusion.

In RA studies, the majority of patients demonstrated depletion of B cells within 7 days from the infusion.

4.5.1. Mechanism of Action

In their Clinical Overview, Genentech wrote that the precise mechanism(s) by which ocrelizumab exerts its therapeutic clinical effects in MS are not fully elucidated but involve immunomodulation through reduction in the number and function of B cells.

4.6. Devices and Companion Diagnostic Issues

N/A

4.7. Consumer Study Reviews

N/A

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Refer to Clinical Review
Studies contributing safety data are identified in Section 8.

5.2. Review Strategy

The clinical review was spilt with Dr. Lawrence Rodichok responsible for review of efficacy, while I reviewed safety. My approach to the safety review is described in Section 8 of this review.

6 Review of Relevant Individual Trials Used to Support Efficacy

Refer to Clinical Review

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Refer to Clinical Review

8 Review of Safety

8.1. Safety Review Approach

Although Genentech seeks approval for Multiple Sclerosis (MS) treatment indications in BLA 761053, ocrelizumab has also been studied in patients with Rheumatoid arthritis (RA), Systemic Lupus Erythematosus (SLE)/Lupus Nephritis (LN), and Non-Hodgkin's Lymphoma (NHL). This safety review will primarily focus on the experience for MS patients. The safety data from trials for other treatment indications are intended to support the MS safety data. The safety data from RA studies are the most robust and useful supporting data, with data from the other indications of lesser value due to their limited patient enrollment and/or early study terminations.

Genentech seeks approval for 2 MS indications, Relapsing forms of Multiple Sclerosis (RMS) and Primary Progressive Multiple Sclerosis (PPMS). The MS development program included 4 clinical trials; RMS trials WA21092 and WA21093, PPMS trial WA25046 and a Phase II dose finding trial WA21493. The RMS phase III trials WA21092 and WA21093, were identically designed and during their 96 week controlled phases exposed 825 patients to ocrelizumab and 826 patients to IFN beta 1-a. In the PPMS trial WA25046, 486 patients were exposed to ocrelizumab and 239 subjects to placebo during the 120 week controlled phase. During the MS Phase II dose finding study, WA21493, 110 subjects were exposed to ocrelizumab.

After completion of the controlled phases of these trials, patients could enroll in open label phases. After early withdrawal or completion of a trial, patients were enrolled in a safety follow up (SFU) phase where safety monitoring continued (at least 24 weeks, longer in patients whose B cell counts had not returned to normal/baseline) in patients no longer receiving ocrelizumab.

The sponsor pooled safety data for analyses. Genentech and DNP discussed and agreed on the data pools during the pre-BLA meetings. Below, I summarize the safety data pools for the ocrelizumab BLA.

Pool A: Phase III RMS Controlled Treatment- Includes data from controlled phase of trials WA21092 and WA21093 with 826 exposed to ocrelizumab and 825 exposed to IFN B1-a

Pool B: MS All Exposure- Includes data from RMS trials WA21092, WA21093 (controlled and open label), PPMS trial WA25046, and Phase II dose finding trial WA21493 with 2147 exposed to ocrelizumab

Pool C: Phase III RMS All Exposure - Includes data from controlled phase and open label phase of trials WA21092 and WA21093 with 1448 exposed to ocrelizumab

PPMS trial WA25046: Includes data from this Phase III PPMS Controlled Trial with 486 exposed to ocrelizumab and 239 exposed to placebo

Pool D: Phase II and Phase III RA Controlled Treatment- Includes data from 7 placebo-controlled double-blind controlled treatment periods of RA studies with 2133 exposed to ocrelizumab (1186 to 400mg, 947 to 1000mg) and 981 to placebo

Pool E: RA All Exposure- Includes data from nine RA studies (double-blind controlled treatment, OLE and SFU periods) with 2926 exposed to ocrelizumab

This review relies primarily on Pools A, B, PPMS for MS safety presentations and Pools D and E for RA safety presentations. I do not present data from Pool C (all RMS experience) in my review because these data are a subset of Pool B and do not appear to provide additional useful information.

In this review, I summarize information from the sponsor's presentations, and, when needed, supplement them with analyses that I conducted using data provided in the Summary of Clinical Safety (SCS), Integrated Summary of Safety (ISS), 90 Day Safety Update (SU), and sponsor provided data sets. The sponsor provided datasets were initially assessed via the Office of Computational Science (OCS) JumpStart team. The OCS also provided tools for demographic variable stratified analyses. Many of the analyses that I performed were carried out using the sponsor provided datasets and the JMP software program. For the adverse event section in this review, the presentations first focus on events reported from all MS trials (controlled and open label phases) in order to identify commonly reported events and infrequent events of potential concern. I then present data from controlled phases of MS trials in an effort to identify quantitative evidence (relative differences in risk by treatment) for drug relatedness.

Ocrelizumab belongs to the class of anti-CD20 monoclonal antibodies. Genentech explained in their clinical overview that CD20 is a cell surface antigen found on pre-B cells, mature and memory B cells but not on lymphoid stem cells or plasma cells. Ocrelizumab selectively depletes CD20-expressing B cells, but capacity for B-cell reconstitution and pre-existing humoral immunity are preserved, as is innate immunity and total T cell numbers. Genentech included adverse events associated with the class of anti-CD20 monoclonal antibodies as events of special interest for further analyses. These events included serious infections, malignancies, and infusion related reactions.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Safety Population Exposure

Genentech defined the Safety Population as:

> ...all patients who received any study drug and underwent at least one assessment of safety. Randomized patients who received an incorrect treatment from what was intended were included in the safety population and were summarized in the group according to the treatment actually received. Patients who received more than one study medication were summarized in the ocrelizumab group.

In the ISS and SCS, the sponsor summarized Safety Population exposure in text and tables (ISS Table 2 and SCS Table1). Inconsistencies between these sources prompted an Information Request from DNP for clarification. The sponsor responded in a 5/10/16 submission that the text summarized the exposure for the safety population, while the tables incorrectly included the intention to treat (ITT) population. The sponsor provided corrected tables that summarized exposure for the Safety Population.

In MS trials, ocrelizumab was given as one infusion or two infusions administered 2 weeks apart. Patients were considered to have received a dose of treatment if at least part of one infusion of that dose (either day 1 or day 15 for dual infusions) was given. If a dose was completely missed instead of delayed, the next dose number was based on the number of previous doses received.

The duration of observation for a patient was calculated as: (Date of last contact* – date of first Dose) + 1

> * Earliest of
> 1) date of the clinical cutoff date for the reporting event
> 2) date of last contact from the study completion page (for WA21092 and WA21093),
> 3) date subject completed or discontinued early from the study completion end of study page (for WA25046)
> 4) date of death.

For placebo and active control patients who switched to active ocrelizumab treatment, non-ocrelizumab exposure ended on the study day prior to their first active dose of ocrelizumab. The duration of observation within a dose is defined in a similar way as: (Day prior to first infusion in n+1th Dose* – date of first infusion in nth Dose) +1 *With the exception of the last dose received by the patient where date of last contact is used as defined above

All patients in MS trials were exposed to the ocrelizumab dose intended for approval, or to a higher ocrelizumab dose. Genentech seeks approval for a 600mg dose administered every 6 months (initial dose split into 300mg separated by 2 weeks). The MS RMS trials dosed ocrelizumab at the 600mg (initial dose split into 300mg separated by 2 weeks) every 24 weeks. The PPMS trial administered ocrelizumab as two 300mg infusions separated by 2 weeks, every 24 weeks. The MS dose finding study WA21493 had two ocrelizumab dosing arms, 600mg and 2,000mg, administered as split doses (300mg, 1,000mg) separated by 2 weeks, every 24 weeks. The RA development program studies evaluated ocrelizumab doses ranging from 20 to 2,000 mg.

The submitted patient exposure numbers demonstrate that exposure in MS development program studies exceeded ICH guidelines for chronically administered medications (i.e., n=1,500 exposed, n=300-600 for 6 months, n=100 for 1 year). Genentech identified a total of 5,406 individuals exposed to ocrelizumab, across all studied indications. The following table summarizes the exposure to ocrelizumab in the development program.

Table 2 Safety Population, Size and Denominators, all Ocrelizumab Trials

Safety Database Exposure for Ocrelizumab			
Clinical Trial Groups	Ocrelizumab	Interferon B1-a	Placebo
Phase III Controlled trials conducted for RMS indication (pool A)	825	826	-
Phase III Controlled trial conducted for PPMS indication	486	-	239
Phase II Dose finding RRMS	110	54	54
Subtotal MS (Pool B)*	**2,147**		
Placebo controlled trials for RA (Pool D)	2,341	-	981
Active controlled trial for RA (ACT4562g)**	15	-	-
Subtotal for RA (Pool E)***	**2,926**	-	-
SLE (WA20499)	33	-	10
LN (WA20500)	253		125

NHL (BO18414C)	47	-	-
Normal volunteers	-	-	-
Total Exposed	**5,406**	-	-

* Total number of patients exposed to ocrelizumab includes patients who switched from placebo or active controls to ocrelizumab outside the controlled treatment period. 623 patients from IFN B-1a (Rebif®) arm in WA21092 and WA21093 received ocrelizumab in OLE, 103 patients from placebo or IFN B-1a (Avonex®) arm received ocrelizumab from Dose 2 onward.
** ACT4562g: infliximab was the active control.
*** Total number of patients exposed to ocrelizumab included patients who switched from placebo or active controls to ocrelizumab outside the controlled treatment period

The following table summarizes exposure by duration in MS trials and supports that exposure within the MS development program exceeded ICH guidelines.

Table 3 Duration of Exposure in MS trials, ISS

Number of patients exposed to Ocrelizumab, MS All Exposure (Pool B):			
>23 weeks	>47 weeks	>71 weeks	>95 weeks
N=1,880	N=1,640	N=1,457	N=1,388

The mean number of ocrelizumab doses for the overall MS population was 4.7 (median 5) and the mean cumulative dose was 2,825 mg (median 3,000mg, range 9-8,220mg).

In addition to the summaries of patients exposed to ocrelizumab, Genentech provided person time observation for the MS and RA populations. The total person time observation for ocrelizumab in MS trials (pool B) was 4,485 PY (SCS, p.45). The total person time observation for ocrelizumab in RA trials (pool E) was 7,324 PY (SCS, p.45).

90 Day Safety Update
Genentech updated the exposure in the MS trials in their 90 Day Safety Update. The overall exposure in MS trials increased to 2,279 patients. This increase came from those patients randomized to placebo in the controlled phase of the PPMS trial, who then entered the OLE and received ocrelizumab. The MS overall person time increased to 5,711PYs, with the increase coming from RMS and PPMS patients who started/continued OLE ocrelizumab treatment.

The following table summarizes MS trial exposure by duration through the 90 Day Safety Update.

Table 4 Duration of Exposure in MS trials, through the 90 Day Safety Update

Number of patients exposed to Ocrelizumab, MS All Exposure (Pool B):

>23 weeks	>47 weeks	>71 weeks	>95 weeks
N=2,104	N=2,063	N=1,719	N=1,502

The mean number of ocrelizumab doses for the overall MS population was 5.6 (median 6) and the mean cumulative dose was 3,393 mg (median 3,900mg, range 9-9,420mg).

The 90 Day Safety Update included no exposure changes for the trials in other indications. These trials had already been completed/terminated when the BLA was submitted.

8.2.2. Relevant characteristics of the safety population:

MS occurs more frequently in temperate climates and women are more commonly affected than men (1.5-1 to 2.5-1). MS incidence is low in childhood, rapidly increases after adolescence, reaches a peak between 25 and 35 years, and then slowly declines. Whites, particularly of northern European descent, seem to have the highest risk of MS, though two recent studies in the United States suggest that MS incidence in Blacks has increased.[1]

The demographic characteristics of the ocrelizumab MS trial population appeared to represent the intended treatment population, although the age and race distributions of study patients were limited. For all MS trials, the median age was 40 years (range 18 - 58 years), 62% of patients were female and 92% were white. The following table summarizes the demographic baseline characteristics for MS patients enrolled in ocrelizumab trials.

Table 5 Summary of Demographic Data – MS All Exposure Population (Pool B)

	All Exposure Ocrelizumab (n=2147)
Age (years)	
Mean	39.5
Median	40.0
Min-Max	18-58
<40 years	1044
>=40 years	1103
Sex	
Male	819 (38.1%)
Female	1328 (61.9%)
Race	
White	1974 (91.9%)
Black or African American	74 (3.4%)

[1] Ascherio A, Munger KL. Epidemiology of Multiple Sclerosis: From Risk Factors to Prevention-An Update. Semin Neurol. 2016 April;36(2):103-14.

American Indian or Alaska Native	11 (0.5%)
Asian	5 (0.2%)
Native Hawaiian or Pacific Islander	1 (<0.1%)
Other	63 (2.9%)
Unknown	18 (0.8%)
Ethnicity	
Not Hispanic or Latino	1726 (80.4%)
Hispanic or Latino	242 (11.3%)
Not reported	161 (7.5%)
Unknown	17 (0.8%)
Region	
Rest of the World	1680 (78.2%)
USA	467 (21.8%)
Sub-region	
EU/Switzerland/Norway	1092 (50.9%)
Latin America	119 (5.5%)
Non-EU+Israel+Africa	347 (16.2%)
USA/Canada/Australia	589 (27.4%)

When viewing the RMS trials and PPMS trial separately, there were slight differences in the demographic characteristics of the populations. In RMS trials, 66% of ocrelizumab patients were female, compared to 49% in the PPMS trial. In RMS trials, the mean age of ocrelizumab patients was 37.2 years compared to 44.6 years in the PPMS trial. 90% of ocrelizumab patients in the RMS trials were White compared to 93% in the PPMS trial. In the RMS trials, 26% of ocrelizumab patients were from the USA compared to 13% in the PPMS trial.

Patients with RMS were enrolled in studies WA21092 and WA21093. Patients were recruited from centers in the US, Europe, Central and South America, Africa and Australasia for Study WA21092 and in the US, Canada, Europe, and Central and South America for Study WA21093. The PPMS trial WA25046 enrolled patients from 29 countries including Australia, Austria, Belgium, Bulgaria, Brazil, Canada, Switzerland, Czech Republic, Germany, Spain, Finland, France, United Kingdom, Greece, Hungary, Israel, Italy, Lithuania, Mexico, Netherlands, Norway, New Zealand, Peru, Poland, Portugal, Romania, Russian Federation, Ukraine, and USA. The Phase II MS trial WA21493 enrolled patients from 79 centers in Europe and North America.

MS trial selection criteria resulted in a relatively healthy population that excluded patients with a variety of concomitant illnesses which could limit generalizability of safety data when considering less restrictive post marketing use. The studies excluded potential participants based on the type and severity of MS but also used the following exclusion criteria: NYHA class III or IV congestive heart failure, known active bacterial, viral (including positive laboratory screening tests for some infections such as hepatitis-B, hepatitis-C and syphilis), fungal,

mycobacterial infection or other infection, excluding fungal infection of nail beds, infection requiring hospitalization or treatment with IV antibiotics within 4 weeks prior to baseline visit or oral antibiotics within 2 weeks prior to baseline visit, history or known presence of recurrent or chronic infection (e.g., HIV, syphilis, tuberculosis), history of progressive multifocal leukoencephalopathy, and receipt of a live vaccine within 6 weeks prior to the baseline visit.

8.2.3. Adequacy of the safety database:

The ocrelizumab MS trial safety database is adequately sized with a sufficient number of patients treated for an appropriate duration. Genentech intends to recommend a single dose (600mg every 6 months) in their proposed labeling and all MS trial subjects received doses of at least 600mg. The demographic characteristics of the MS trial patients were similar to the intended treatment population, although there were limited patients in the extremes of ages and in race groups other than White. The MS trials excluded patients with particular concomitant diseases which may limit generalizability of the development program safety data if ocrelizumab is used in a less restrictive manner when marketed.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The safety data provided by Genentech appeared reliable and consistent but the presentations were occasionally limited and accessing certain information in the application was difficult. Genentech was responsive when difficulties were identified and quickly addressed deficiencies in their responses to Information Requests. Approximately 12 Information Requests, many with multiple sub-requests, for additional safety information were sent during the course of the review.

Genentech's datasets were assessed by the Office of Computational Science's JumpStart program and no major issues were identified. During the course of the review, using the provided datasets, I was able to replicate analyses performed by Genentech and presented in the ISS. For individual patients of interest, I compared data across different sources and did not find discrepancies between datasets, narratives, CRFs, listings, or summary tables.

Genentech's initial presentation of narrative summaries from RA trials was insufficient, but when asked to address this problem, they quickly provided an acceptable solution. Because of the way safety data were presented, narrative summaries for AEs from RA trials could have been located in up to 5 different reports, with no indication of the exact location of a given narrative. When DNP raised this issue, Genentech provided tables that allowed for easier access via links to specific narratives.

In some cases, Genentech's ISS presentations were inadequate, requiring Information Requests for additional analyses and explanations. For example, in their presentation of vital sign and lab data, Genentech only provided their conclusions that there were no important changes, but did not provide results of analyses to support these conclusions. The Division requested additional analyses and explanations in order to complete the safety evaluation.

The submissions were generally well constructed although there were occasional instances where clickable links would take the reader to an incorrect page. These occurrences were relatively infrequent and did not result in meaningful delays in the review.

8.3.2. Categorization of Adverse Events

Genentech used common definitions of AE, SAEs, and TEAEs. Genentech's coding process for verbatim AE terms was adequate and should allow for accurate estimates of event risks. Genentech's assessment of AEs, and AEs of special interest was also appropriate. In cases where coding of AEs led to splitting of potentially related events (ex. Infections), Genentech included presentations that were based on groupings or baskets of similar events that allowed for an improved assessment over the results based only on the MedDRA coded terms.

MS trial protocols defined an AE as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. AEs included unfavorable and unintended signs, abnormal laboratory findings, symptoms, or diseases temporally associated with the use of a (investigational) medicinal product, whether or not considered related to the medicinal (investigational) product. Pre-existing conditions which worsened during a study were reported as AEs. Treatment emergent AEs were those AEs that started on or after the start date of study treatment or AEs that increased in intensity during treatment. Genentech included all AEs recorded through the entire observation period and did not exclude events occurring after stopping treatment. For the safety presentations, serious MS relapses were included as AEs, but non-serious MS relapses were excluded.

MS trial protocols defined Serious Adverse Events as any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any adverse event that, at any dose, fulfils at least one of the following criteria: fatal, life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, or was medically significant or required intervention to prevent one or other of the outcomes listed above.

During MS trials, AEs were elicited through open ended questioning. AE verbatim terms were coded to preferred terms using MedDRA v.18.0 for ISS presentations and MedDRA v.18.1 for 90 Day Safety Update presentations. AEs were graded for severity according *to National Cancer*

Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0; Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life threatening; Grade 5 = fatal). Genentech presented AE risks both as percentages (# events/#patients x 100) and as rates (#events/person years exposure x 100).

Genentech selected infusion-related reactions (IRRs), infections, and malignancies as AEs of special interest based on the safety profile of B cell depleting therapy and/or ocrelizumab in particular. Genentech provided additional analyses for these events.

IRRs were defined as events occurring between the start of ocrelizumab/placebo infusion and within 24 hours of the completion of the infusion. These events were captured on a special form within the CRF.

Infections were analyzed using two definitions. The first definition considered all AEs coded to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) of Infections and Infestations. The second definition was broader in that it included all AEs coded to the MedDRA SOC of Infections and Infestations plus any AE from other MedDRA SOCs if pathogen information was provided by the investigator on the AE case report form (CRF). Infections were defined as serious if the investigator judged an event as serious, or, more conservatively, if a non-serious infection was treated with an intravenously (IV) administered anti-infective treatment. In addition to the presentation of data by MedDRA SOC, similar AEs were grouped using AE grouping terms (AEGT) and Standardized MedDRA Queries (SMQs) and were used as screening tools or for selected data presentations. These predefined baskets included upper respiratory tract infections, urinary tract infections, gastrointestinal infections, skin infections, lower respiratory tract infections, herpes virus associated infections, infectious biliary disorders, sepsis/systemic inflammatory response syndrome (SIRS), and central nervous system (CNS) infections.

A similar approach was used to screen for potential opportunistic infections. In this case, as no SMQ for opportunistic infections has been adopted, a basket of preferred terms (PTs) was used to identify potential opportunistic infections for detailed medical review.

Malignancy AEs were defined using the SMQs of Malignant Tumors. The incidence rate (IR) of first malignancy (number of first malignancy events per 100PY exposure, limited to time to first event) in Pool B (MS population) and Pool E (RA population) was calculated in order to assess malignancy rates in ocrelizumab treated patients compared with epidemiology data. The incidence rates of malignancy were also standardized to the US population to allow comparison with the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) database (using the 2000 US standard population [Census Report, 1996]) and restricted to the age range of the MS clinical studies; 15 to 59 years old).

In a response to a request from the Division, Genentech also searched for anaphylactic reactions, DRESS events, and autoimmune events. The potential for anaphylactic reactions was assessed in Pool B and Pool E using the SMQ 'anaphylactic reactions' and the Sampson's criteria (Sampson et al. 2006). In addition, occurrence of drug reaction with eosinophilia and systemic symptoms (DRESS) was also assessed. A new MedDRA DRESS SMQ candidate was recently approved and is expected to be formally available under the MedDRA version 19.0. As the MedDRA DRESS SMQ is not available for version 18.0, a similar step-wise approach was used (described in Section 2.1.4.1.6) to identify DRESS cases. Genentech searched for autoimmune events using a basket over 100 AE terms.

8.3.3. Routine Clinical Tests

General Lab Tests
During RMS trials WA21092 and 21093, hematology, chemistry, and urinalysis lab tests were performed at every visit except delayed dosing visits and unscheduled visits. During PPMS trial WA25046, hematology, chemistry, and urinalysis lab tests were performed at Screen, BL, W12, W24, W36, W48, W60, W72, W84, W96, W108, W120. The general laboratory analytes measured during MS trials included albumin, alkaline phosphatase, ALT, amylase, AST, basophils, urea, calcium, cholesterol, creatine kinase, creatinine, eosinophils, gamma glutamyl transferase, glucose, urine glucose, hematocrit, hemoglobin, lactate dehydrogenase, lipase, lymphocytes, monocytes, neutrophils, phosphorus, platelets, potassium, urine protein, red blood cell count, sodium, bilirubin, total protein, triglycerides, TSH, and white blood cell count.

Genentech's discussion of lab results for these trials (Pool A) in the ISS was limited to patients with abnormal results. The Division requested mean and median change from baseline analyses for Pool A and Genentech provided these tables in a 6/7/16 submission. Mean change from baseline analyses in the PPMS trial were included in the CSR.

Genentech summarized lab result abnormalities by treatment for the RMS trials controlled phase (Pool A) and the PPMS trial controlled phase. Lab results that were outside normal range and that changed by a predetermined percentage from baseline were classified as abnormal. I include Genentech's criteria for abnormal lab results below.

Roche Reference Ranges for Laboratory Tests and Definition of a Clinically Relevant Change from Baseline

Laboratory Test Class Laboratory Test	SI Unit	Reference Range [1, 2]	Marked Abnormality Range	Direction of Change	Clinically Relevant Change from Baseline
Hematocrit	fraction	M 0.37 - 0.49 F 0.36 - 0.46 [b]	0.31 - 0.56	Increase Decrease	≥ 15 % ≥ 15 %

Hemoglobin	g/L	M 130 - 180 F 120 - 160 [b]	110 - 200	Increase Decrease	≥ 15 % ≥ 15 %
Leukocytes (WBC)	10^9/L	4.5 - 11.0	3.0 - 18.0	Increase Decrease	≥ 30 % ≥ 30 %
Platelets	10^9/L	150 - 350	100 - 550	Increase Decrease	≥ 50 % ≥ 30 %
Erythrocytes (RBC)	10^{12}/L	M 4.50 - 5.30 F 4.10 - 5.10 [b]	3.80 - 6.10	Increase Decrease	≥ 15 % ≥ 15 %
Basophils	10^9/L	0 - 0.20	0 - 0.40	Increase	≥ 100 %
Lymphocytes	10^9/L	1.00 - 4.80	0.70 - 7.60	Increase Decrease	≥ 30 % ≥ 30 %
Monocytes	10^9/L	0 - 0.80	0 - 1.70	Increase	≥ 100 %
Neutrophils	10^9/L	1.80 - 7.70	1.50 - 9.25	Increase Decrease	≥ 20 % ≥ 20 %
Eosinophils	10^9/L	0 - 0.45	0 - 0.90	Increase	≥ 100 %
ASAT (SGOT)	U/L	M 0 - 40 [c] F 0 - 25 [b]	0 - 80	Increase	≥ 50 %
Lactic Dehydrogenase	U/L	0 – 210 [c]	0 - 420	Increase	≥ 50 %
CPK total	U/L	M 60 - 400 [a] F 40 - 150 [b]	≤800	Increase	≥ 50 %
Alkaline Phosphatase	U/L	M 0 - 115 [c] F 0 - 100 [b]	0 - 220	Increase	≥ 50 %
ALAT (SGPT)	U/L	M 0 - 55 [c] F 0 - 30 [b]	0 - 110	Increase	≥ 50 %
Total Bilirubin	µmol/L	0 - 17 [c]	0 - 34	Increase	≥ 75 %
Gamma-GT	U/L	M 0 - 94 [c] F 0 - 70 [b]	0 - 190	Increase	≥ 50 %
BUN	mmol/L	2.9 - 8.9	0 - 14.3	Increase	≥ 50 %
Creatinine	µmol/L	0 - 133	0 - 154	Increase	≥ 50 %
TSH	µU/L	0 - 5.0 [c]	0 - 10.0	Increase	≥ 30 %
Albumin	g/L	35.0 - 55.0	≥ 30	Decrease	≥ 20 %
Total Protein	g/L	60 - 80	55 - 87	Increase Decrease	≥ 20 % ≥ 20 %
Triglycerides (fasting)	mmol/L	0.45 - 1.69	0 - 2.83	Increase	≥ 100 %
Cholesterol	mmol/L	0 - 6.18	0 - 8.30	Increase	≥ 30 %

Potassium	mmol/L	3.4 - 4.8	2.9 - 5.8	Increase Decrease	≥ 20 % ≥ 20 %
Sodium	mmol/L	135 - 145	130 - 150	Increase Decrease	≥ 7 % ≥ 7 %
Calcium	mmol/L	2.10 - 2.60	2.00 – 2.90	Increase Decrease	≥ 10 % ≥ 10 %
Phosphorus inorganic	mmol/L	0.84 - 1.45	0.75 - 1.60	Increase Decrease	≥ 30 % ≥ 30 %
Blood Glucose	mmol/L	3.90 - 6.10	2.80 - 11.10	Increase Decrease	≥ 75 % ≥ 75 %
Proteinuria	0 to 4+	0 - 1	0 - 1	Increase	≥ 2 units [d]

Glycosuria	0 to 4+	0 - 1	0 - 1	Increase	≥ 2 units [d]
Hematuria	0 to 4+	0 - 1	0 - 1	Increase	≥ 2 units [d]
Leukocyturia	0 to 4+	0 - 1	0 - 1	Increase	≥ 2 units [d]

To look for persistence, Genentech classified abnormalities as single, not last; or last, replicated.

Submission Specific Laboratory Tests
Genentech explored the effects on lymphocytes and immunoglobulins during MS trials. Ocrelizumab is an anti-CD20+ monoclonal antibody that depletes select B lymphocytes (pre-B cells, mature and memory B cells, but not lymphoid stem cells or plasma cells). Genentech explained that CD19 is a surrogate cell surface marker used for the count of B-cells in blood following therapy with the anti-CD20 antibody ocrelizumab. Genentech assessed and summarized changes in CD19+ B lymphocytes; CD3+, CD4+, CD8+ T lymphocytes; and CD16+56+ NK lymphocytes. In addition, Genentech measured levels of IgG, IgM, and IgA immunoglobulins.

Vital Signs
In RMS trials WA21092 and 21093 and the PPMS trial WA25046 pulse rate, systolic and diastolic blood pressure, respiration rate and temperature were obtained while the patient was in the semi supine position (after 5 minutes). On infusion visits, the vital signs were taken within 45 minutes prior to the methylprednisolone infusion in all patients. In addition, vital signs were obtained prior to ocrelizumab/ocrelizumab placebo infusion, then every 15 minutes (± 5 minutes) for the first hour; then every 30 minutes (± 10 minutes) until 1 hour after the end of the infusion. On non-infusion days, the vital signs were taken at any time during the visit.

ECGs
In RMS trials WA21092 and 21093 and the PPMS trial WA25046 ECGs were performed at screening, baseline (prior to first infusion), study week 72, and at the withdrawal of treatment visit. ECGs were reviewed by study site investigators for abnormalities. Abnormalities were reported as AEs. No systematic analysis of ECG intervals was undertaken.

8.4. Safety Results

8.4.1. Deaths

Deaths were infrequently reported in the MS trials. There were too few deaths during controlled phases to support conclusions about relative mortality risks by treatment. There were 2 deaths in MS ocrelizumab patients that appeared to be related to infections (pneumonia; SIRS/DIC/ multi-organ failure).

Deaths were reported more commonly in the RA trials than in MS trials and infections were commonly reported as the cause of death in ocrelizumab patients. In the RA controlled trials,

the overall mortality rates were similar for the ocrelizumab and placebo treatment groups. Although the overall mortality rates were comparable, the ocrelizumab treatment groups had an increased number of infection and/or sepsis related deaths (5) compared to placebo (0).

All MS Trials (Pool B)

Genentech reported 11 deaths in MS trials (8 ocrelizumab, 2 IFN beta-1a, 1 PBO) by the ISS data cutoff date. For all MS trials, 0.4% (8/2,149) of ocrelizumab patients died. The mortality rate was 0.18/100PY (8/4,485PY). No additional ocrelizumab deaths were reported in the 90 day safety update.

RMS trials, Controlled phase (Pool A)
The mortality risks in the RMS trials were similar for the ocrelizumab (0.12%, 1/825) and IFN (0.24%, 2/826) treatment groups. One interferon patient committed suicide and another died following a mechanical ileus. I summarize the details for the ocrelizumab patient death below.

Suicide
WA21093-234069-1936964 This 32 year old male patient committed suicide (oral gunshot) on study day 576. The patient's last infusion of ocrelizumab occurred on study day 508. The CSR summary reported that the patient displayed no signs or symptoms of depression prior to the suicide and that the C-SSRS assessment did not identify suicidal ideation or behavior. Two days prior to committing suicide the subject was notified that he has been indicted for felony related to child pornography.
Reviewer comment: There is no obvious link between ocrelizumab and this event.

PPMS trial, Controlled phase
The mortality risk for ocrelizumab was 0.8% (4/486) and was 0.4% (1/239) for placebo during the PPMS trial WA25046. The placebo patient died following a traffic accident. The causes of death for the ocrelizumab patients were pneumonia, pulmonary embolism, aspiration pneumonia, and metastatic pancreatic cancer. I provide details for these ocrelizumab deaths below.

Metastatic Pancreatic Cancer
WA25046-208392-21404 A 48 year old female received ocrelizumab from (b) (6) to (b) (6). On (b) (6) she presented with jaundice and was subsequently diagnosed with pancreatic cancer. Her condition worsened and she died on (b) (6).
Reviewer comment: There is no obvious link between ocrelizumab and this event, although a possible contribution of ocrelizumab cannot be excluded.

Aspiration Pneumonia
WA25046-208690-26307 This 43 year old male with a history of dysphagia received ocrelizumab from (b) (6) to (b) (6). On (b) (6) he developed a fever and productive cough. He was hospitalized for pneumonia and on admission was "conscious, oriented, cooperative, eupneic and hemodynamically stable." His condition worsened despite treatment with antibiotics, inhaled and intravenous steroids, and oxygen therapy. He was transferred to the ICU. An X-ray showed infiltrates in two-thirds of the left lung and the right upper lung. Oxygenation continued to worsen and the family decided against orotracheal intubation. He died on (b) (6) and the reported cause of death was respiratory failure with severe probable aspiration pneumonia.
Reviewer comment: There is no obvious link between ocrelizumab and this event, and the event of aspiration pneumonia is likely related to the patient's dysphagia.

Pneumonia
WA25046-208367-30302 A 49 year old male received ocrelizumab from (b) (6) to (b) (6). In an IR response dated 5/27/16, Genentech reported that this patient was a non-smoker. During the first ocrelizumab infusion he experienced an IRR characterized by hyperthermia (highest temp 39.7 C), tachycardia (highest HR 125bpm), hypertension (highest BP 180/100 mmHg), nausea, hypotension (lowest BP 100/50 mmHg), pruritus, and vomiting and was hospitalized for 1 day. He did not experience another IRR, but was diagnosed with hypertension and prescribed enalapril, which he refused to take. On 12/22/2011, a family member reported that the patient developed difficulty breathing and progressive weakness and that he died at home on (b) (6). The cause of death determined by post-mortem exam was desquamative pneumonia with associated bacterial component, with cardio-pulmonary failure and evidence of atherosclerosis of the heart and kidney.
Reviewer comment: Ocrelizumab could have contributed to this event. The exact diagnosis is not clear in this case. The translated (Ukranian to English) autopsy report identified "a serous desquamative pneumonia with associated bacterial component" as the cause of death.

Pulmonary Embolism
WA25046-208159-44002 A 55 year old male received ocrelizumab from (b) (6) to (b) (6). He discontinued from ocrelizumab treatment in 7/2012 and entered the SFU phase. He was hospitalized for an infection with no identified focus that was diagnosed as "virosis". On (b) (6), he was hospitalized with pain, pallor, diaphoresis, low blood pressure and a HR of 135 bpm. He subsequently experienced cardiac arrest and failed cardio-pulmonary resuscitation. A post mortem exam documented a massive embolism in the pulmonary artery.
Reviewer comment: There is no obvious link between ocrelizumab and this event and the interval between last dose and death suggests a low likelihood that ocrelizumab contributed to this death.

MS Trial WA21493

Three deaths occurred during or following the RRMS Phase II dose finding study WA21493. One death (ocrelizumab) occurred during the controlled treatment period and was due to systemic inflammatory response syndrome (SIRS). The remaining 2 deaths occurred during the SFU and were more than 1 year after receiving the final dose of ocrelizumab (unknown cause, injury).

SIRS, DIC, multi-organ failure
WA21493-140942-1515 A 41 year old female received her first dose of ocrelizumab on (b) (6) and experienced a moderate IRR and tolerated the second infusion, 15 days later, without incident. On (b) (6), she made her week 12 visit and underwent an MRI. 20 minutes after the MRI she felt weak and was unable to drive home. Later that evening, her husband reported that she developed shivering, vomiting, elevated body temperature (not quantified) and that she tried to bite him. A head CT showed "freckles of whiter matter hypo-density that could be due to underlying disease or ischemia in the supratentorial, periventricular area, more on left hand side; no signs of intracranial hemorrhage and more pronounced calcification in falx. She experienced seizures and status epilepticus precluded an LP. Labs included elevated lipase and amylase and her platelet count declined from $229x10^3$/ul earlier in the day to 165 $x10^3$/ul. She was treated with diazepam, methylprednisolone, mannitol 20%, metronidazole, ceftriaxone, dexamethasone, phenobarbital, and glucose. On (b) (6) she continued to experience seizures and was transferred for seizure control and respiratory support. Seizures stopped following treatment with midazolam and she regained consciousness. Her mental status fluctuated, she continued to have an elevated temperature and lab results included ALT 1,123 U/L (normal range: 6 - 37 U/L), AST 1,405 U/L (normal range: 10 - 36 U/L), urea 11.9 mmol/L (normal range: 2.5 – 7.5 mmol/L), creatinine 149µmol/L (normal range: 30 -127µmol/L), bilirubin total 31 mmol/l, direct 10.7 mmol/l, amylase 863 U/L (normal range: 20 -112 U/L), C reactive protein 17.2 mg/L (normal range: 0 - 5 mg/L), procalcitonin 10.1ng/mL (normal range: less than 0.5 mg/mL), neutrophil count 16.3 x 103/µL (2 - 8.3 x 103/µL), WBC count was 17.5 x 103/µL (normal range: 4 - 10 x 103/µL and platelet count 65.8 x 103/µL (normal range: 140 - 400 x 103/µL). She developed diarrhea and tested negative for C. difficile. She was treated with oral vancomycin and metronidazole. She developed petechiae and was diagnosed with DIC. Her kidney, liver and pancreatic function (as measured by lab results) worsened. She developed hypotension and required inotropic support. A head CT revealed massive brain edema. She died on (b) (6). A post-mortem exam documented incipient pneumonia, primary biliary cirrhosis grade III, decubitus ulcers. A second autopsy read did not confirm the primary biliary cirrhosis. Finding in this second report were: transforaminal herniation, massive brain edema and diffuse hypoxic ischemic changes most likely due to diffuse preterminal ischemia and presence of an isolated terminal fungal embolus of less than 24 hours.
Reviewer comment: The narrative appears to describe sepsis without obvious source resulting in multi-organ failure and death. Ocrelizumab potentially could have contributed to this event through increased susceptibility to infection or contribution to the inflammatory response.

Sudden death
WA21493-140977-2301 A 35 year old male completed the treatment phase of the study after receiving the week 72 infusion of ocrelizumab on (b) (6) and entered the SFU. On (b) (6) he was found dead in bed. A post-mortem exam was not performed. The narrative reported that 1 week prior to death the patient was hospitalized and received intrathecal corticosteroids. No other information was provided about the patient's medical status around the time of death.
Reviewer comment: There is insufficient information to determine the cause of death or assess the role of ocrelizumab in this event. The interval between last dose and the event suggests a low likelihood that ocrelizumab contributed to this death.

Injury
WA21493-141024-5303 A 34 year old male completed the treatment phase of the study after receiving the week 72 infusion of ocrelizumab on (b) (6), and entered the SFU. On (b) (6), the patient was involved in an accident (fall from great height) and died. Post-mortem exam noted extensive injuries including craniocerebral trauma and subarachnoid hemorrhage, hemorrhage in the brain matter, cerebral ventricles and non-penetrating trauma to the chest and abdomen.
Reviewer comment: There is no obvious link between ocrelizumab and this event, although there is limited information about the nature of the accident and no information about the psychological state of the patient prior to the event. The interval between last dose and the event suggests a low likelihood that ocrelizumab contributed to this death.

All RA Trials (Pool E)

Genentech reported 45 ocrelizumab patient deaths in RA trials (1.5%, 45/2,926). The overall mortality rate for ocrelizumab patients in RA trials (Pool E) was 0.61/100PY (45/7,324PY), 3.4-fold higher than the mortality rate in the MS trials.

I reviewed the deaths in the RA development program and selected certain deaths for summary in this document. Three deaths I do not consider further (WA20494-97786-20301 "B-cell lymphoma", WA20495-114575-72312 "death", and WA18230-55846-1363 "cough") because the patients only received a single dose of ocrelizumab and death occurred >=350 days after the single dose. In addition, I do not summarize 5 deaths that occurred >=1 year after last dose of ocrelizumab, given the remote likelihood of an association between ocrelizumab and the events. The reported causes of death for these 5 cases were dementia, myocardial infarction, respiratory failure, subdural hematoma, and sudden death.

For the remaining 37 deaths, the reported causes were: pneumonia (7), sepsis/septic shock (6), respiratory failure (3), lung cancer (3), sudden death/ death (3), myocardial infarction (2), brain edema(referred to as Cerebral and Pulmonary Edema below)*, breast cancer, carbon monoxide

poisoning, disseminated intravascular coagulation, gastric cancer, gastrointestinal carcinoma, gastrointestinal hemorrhage, ischemic cerebral infarction, multi-organ failure, pulmonary embolism, ruptured cerebral aneurysm, toxicity to various agents, and traffic accident. I summarize those events below.

Carbon monoxide poisoning
WA20494-97783-20101 This 62 year old female patient died several days after being rescued from an accidental house fire and experiencing cardiac arrest.

Road Traffic accident
ACT2847G-08935-1604 This 40 year old female died in a motor vehicle accident (no details provided) after being lost to follow up. She received a single dose of ocrelizumab and was found to be in violation of the protocol based on inability to identify when treatment with MTX began.

Pneumonia
WA20494-97862-44804 On study day 260, this 70 year old female who also received corticosteroids and methotrexate during the trial, developed symptoms of pneumonia, was admitted to a hospital and had a WBC count of 1500/mm3. Her course worsened despite antibiotic treatment. Sputum cultures, blood cultures, Mycobacterium cultures and urine PCR for Pneumococcus and Legionella were negative. She developed multi-organ failure and died.

WA20496-137425/15101 On study day 339, this 80 year old female who also received corticosteroids and methotrexate during the trial, was admitted to a hospital with lethargy, decreased oral intake, hypotension, altered mental status, dehydration, acute renal insufficiency, a 6^{th} rib fracture, and a left lower lobe infiltrate on chest x-ray. She had a WBC count of 22,000. Despite treatment with antibiotics, and per family request, treatment was stopped and she was discharged home, where she died. Cited potential contributors beside study drug included rib and compression fractures and MTX treatment.

JA21963-154309-12010 On study day 61, this 60 year old male patient who also received corticosteroids and methotrexate during the trial, was diagnosed with sepsis by a local internist and was prescribed PL granules, paracetamol and cefpodoxime and returned home. Two days later he collapsed at home and was admitted to a hospital with a BP of 70/40, SpO2 77%, thrombocytopenia, hepatic and renal impairment (not specified) and chest CT showed infiltrates in bilateral posterior lung fields. He was diagnosed with pneumonia, sepsis, septic shock, disseminated intravascular coagulation (DIC) and multi-organ failure and died.

WA20494-114676-46406 On study day 82, this 67 year old female who also received corticosteroids and methotrexate during the trial, was admitted to a hospital with fever, cough dyspnea, and epigastric pain. She did not improve with treatment and was transferred to a second hospital with the diagnosis of pneumonia. Labs included a WBC count of 1.2 $x10^3$/uL.

Her condition did not improve and she died with final diagnoses of pneumonia, congestive heart failure, respiratory failure, and sepsis.

WA18230-55852-1736 On study day 56, this 73 year old female who also received methotrexate during the trial was treated with amoxicillin for fevers with shortness of breath and cough. Blood and urine cultures were negative. Four days later she developed diarrhea and abdominal pain. X-ray of the chest and abdomen (to rule out obstruction or perforation) were both normal. CT of abdomen and pelvis (including contrast) was repeated. This showed no change in the right kidney from a previous scan; left kidney, liver, spleen and adrenals were all normal; there was no focal bowel-related mass. There was diverticular change in the sigmoid colon, but this was not acute. There was no free fluid, free gas or intra-abdominal collection. A sputum culture was subsequently positive for MRA and a repeat chest x-ray showed right sided consolidation. She was found unresponsive in bed and did not respond to resuscitative measures. No autopsy was performed.

WA20497-109410-15410 This 46 year old female received ocrelizumab from (b) (6). During the trial she also received adalimumab, tocilizumab, and abatacept. Her last available study CD19 count was from 9/30/09 and was 20 uL (reference range 80-616 uL).On (b) (6), she was hospitalized with pneumonia and was also diagnosed with cirrhosis (no details provided). Her condition worsened and she developed ARDS, and acute renal failure. She developed sepsis and hepatorenal syndrome and died. A CD19 count prior to death was 39 uL.

WA20494-137293-24301 This 81 year old male received ocrelizumab on (b) (6), and (b) (6) On (b) (6) he underwent excision of a malignant melanoma. On (b) (6) he developed pneumonia and was treated with antibiotics and supportive care. He died on (b) (6).

Respiratory failure
WA20495-110578-50703 This 60 year old female with a history of upper airway infection and pneumonia was treated with corticosteroids and methotrexate during the trial, and received ocrelizumab from (b) (6). She entered the SFU and on 8/12/10 her CD19 count was below LLN. The narrative did not identify use of immunosuppressants at this time. On (b) (6) she presented with malaise, decreased appetite, productive cough, labored breathing, cyanosis, altered mental status, hyperglycemia, and hypotension. A chest x-ray demonstrated a right lower lobe infiltrate with effusions. She was treated with antibiotics, and mechanical ventilation. She was diagnosed with pneumonia, respiratory distress syndrome, sepsis, renal failure, cardiac failure, hepatic failure, and metabolic acidosis. A bronchoscopically obtained sputum specimen was positive for MRSA and negative for Pneumocystis jirovecci. She died on (b) (6). A post mortem exam was not performed.

WA20494-119481-23802 This 77 year old female was treated with ocrelizumab from (b) (6) through (b) (6). On (b) (6) she fell and fractured her maxilla and pelvis. She underwent surgical repair of her maxillary fractures. Her hospitalization was complicated by acute respiratory failure that was presumed due to a pulmonary embolus. While on a ventilator she developed pneumonia and was treated with antibiotics, nebulizers, and steroids. Her respiratory status did not improve and she was made comfort care only and died on (b) (6). No post mortem exam was performed.

WA20497-117465-15255 This 60 year old female was hospitalized on study day 168 for productive cough, severe dyspnea, and cyanosis. A chest x-ray showed opacities in the inferior portions of both lungs. Later that day the patient experienced cardiac arrest and died. No other information was provided.

Sepsis/septic shock
WA20494-97822-32615 This 61 year old female with a history of diverticular disease who also received corticosteroids and methotrexate during the trial, received her first dose of ocrelizumab on (b) (6). On (b) (6) she underwent an elective colectomy. Her hospital course was complicated by development of an anastomotic fistula and she subsequently underwent a Hartmann's procedure. Three days later she experienced electrolyte imbalance and lung failure, renal failure, and cardiac arrest. On (b) (6) she was diagnosed with sepsis (no details provided) and was treated with antibiotics. She died the same day.

WA20497-117462-15107 This 56 year old female being treated with MTX and prednisone received a dose of ocrelizumab on study day 555 and was hospitalized on study day 621 after she developed lumbar pain and had a urinalysis that was positive for WBCs. Shortly after admission she developed acute respiratory insufficiency which was attributed to sepsis. She did not respond to treatment with antibiotics and she died the day following admission. There were no additional lab tests and no autopsy.

WA20497-117462-15109 This 66 year old female who also received corticosteroids and methotrexate during the trial, was hospitalized on study day 718 (163 days after her most recent ocrelizumab infusion) with COPD and bronchopneumonia that progressed to sepsis and death on study day 727. Chest x-ray showed consolidation in the right lung, inferior lobe, and she had a WBC count of 27,000 (nl 4,000-10,000) with 5% bands. She was treated with Ceftriaxone for 7 days and her condition deteriorated and she died.

WA18230-73501-2078 This 57 year old female received ocrelizumab on (b) (6) and received a single dose retreatment on (b) (6). On (b) (6) she developed a diverticular perforation and underwent a surgical procedure which was considered successful. Postoperatively she experienced a wound infection with dehiscence. Two months later ((b) (6)), she reportedly developed sepsis from the wound infection. WBC count was reported as 34,000/uL (ULN

10,000u/L) at that time. She was treated with antibiotics and underwent an additional surgery (not specified). She died on (b) (6).

WA20497-120733-20004 This 79 year old female received ocrelizumab infusions on (b) (6) and (b) (6). She experienced several SAEs including pulmonary alveolar hemorrhage, systemic candidiasis, and staphylococcal bacteremia. On (b) (6) she was hospitalized for oral ulcers, dysphagia, and poor intake and was diagnosed with esophageal candidiasis. During that hospitalization she also developed pneumonia requiring antibiotics and mechanical ventilation. After removal from mechanical ventilation she experienced dyspnea and the family decided against further mechanical ventilation. Her hospital course also included leukopenia and colitis. Her B-cell count was reported as 0.1% (no details). She subsequently developed a fever (38 Celsius) and elevated WBC (13,700uL/ml), bradycardia, hypotension and decreased urine output and died.

WA20496-137365-13163 This 52 year old female with chronic renal insufficiency, initially received placebo in this trial and subsequently received her first dose of ocrelizumab on (b) (6). She also received methotrexate and prednisone during the trial. Her trial SAEs included mycobacterium abscessus infection. On (b) (6) she was diagnosed with sepsis. Blood cultures were negative and sputum grew acinetobacer Baumanei. She was treated with colistin. On (b) (6) she died due to sepsis. Her last available CD19 count was from 2/10 and at that time it was 1 (reference range 80-616 uL).

Myocardial infarction
WA20494-97740-14402 This 42 year old female with a history of interstitial lung disease, cor pulmonale, cardiomegaly, mitral valve disease, decreased systolic function, diabetes mellitus type II, and tobacco abuse received her first dose of ocrelizumab on (b) (6). On (b) (6) she experienced a myocardial infarction and died. No details were provided about this event.

WA20494-115074-31702 This 64 year old male died suddenly on study day 121. The narrative reported that he was found unconscious and mentioned ventricular fibrillation, which the emergency physician felt was likely due to preceding myocardial infarction. He failed resuscitative efforts and no post mortem exam was performed.

Multi-organ failure
WA20495-110708-63503 This 58 year old female received her first dose of ocrelizumab on (b) (6) and her last dose on (b) (6). On (b) (6) she presented to an ED with nausea, vomiting, diarrhea, and dysuria. Her BP was 92/68 and HR was 100. Chest x-ray showed atelectasis and abdominal CT was “insignificant”. ECG did not show evidence of ischemia. CK and troponin were elevated as were lactic acid, AST, ALT, and creatinine (6.29mg/dL). Her WBC count was 43.8 (reference range 3.8 – 10.7 x 10E3/UL), and hemoglobin was normal. Urinalysis found 20-30 white cells, 2+ bacteria. The prothrombin time (PT) and international normalized

ratio (INR) were elevated and Partial thromboplastin time (PTT) was normal. She was treated with fluids, vasopressor therapy, and antibiotics. She became anuric and required mechanical ventilation. Blood and stool cultures were negative. She was diagnosed with renal failure secondary to rhabdomyolysis (etiology not clear) with plans to dialyze. EEG was performed to assess mental status changes and was indicative of encephalopathy. A head CT showed evidence of infarcts that were presumed due to hypotension. She was diagnosed with sepsis, DIC, and TTP. HIV infection was ruled out. CSF analysis showed increased red cell count of 873 (reference range 0/cmm), increased white cell count of 75 (reference range 0 – 5 /cmm) and increased spinal fluid protein of 256 (reference range 12 – 60 mg/dl). A repeat EEG showed electrical cortical silence, consistent with brain death. She was declared brain dead on (b) (6) and a post mortem exam was not performed.

*Cerebral and Pulmonary edema
WA20494-114738-42801 This 46 year old female received her first ocrelizumab dose on (b) (6) and her last dose on (b) (6). Thirty weeks after her last infusion she died at home with no information about the event. A post mortem exam identified the cause of death as cerebral and pulmonary edema.

Sudden death/ Death
WA20495-110589-51803 This 55 year old female with a history of microcytic anemia received her first dose of ocrelizumab on (b) (6) and her last dose on (b) (6). On (b) (6) she was found at home unresponsive and incontinent of stool and urine. Paramedics reported that an ECG showed sinus tachycardia and that she exhibited seizure activity. In the ED she was hypotensive and tachycardic. Pupils were fixed and dilated, there were absent corneal reflexes and negative doll's exam. There was no cough or gag responses. Clinical examination suggested the patient was brain dead. CT of the brain revealed effacement of the quadrigeminal plate cistern and likely tonsillar herniation into the foramen magnum. EEG revealed absence over all regions of the head of identifiable electrical activity of cerebral origin. The patient was declared dead on (b) (6) (Study Day 513).

WA20497-109478-17958 This 47 year old female with a history of asthma and hyperlipidemia received her first dose of ocrelizumab on (b) (6). On study day 743, 14 days after her most recent ocrelizumab infusion, she was found dead at home. An autopsy determined the cause of death was sudden cardiac death due to ischemic heart disease.

WA20495-115592-70101 This 61 year old male with a history of myocardial infarction x 2, angioplasty, hypertension, dyslipidemia, and remote history of tobacco abuse, received his first dose of ocrelizumab on (b) (6) and his last dose on (b) (6) On (b) (6) he complained of not feeling well prior to losing consciousness. He was transported to an ED where he was pronounced dead. An autopsy was not performed.

WA20494-114738-42801 This 46 year old female with a history of hypertension received her first dose of ocrelizumab on (b) (6) and her last dose on (b) (6) She died at home on (b) (6) (no details provided) and the cause of death identified by a post mortem exam was cerebral and pulmonary edema.

Breast Cancer
WA20494-114676-46405 This 46 year old female received her first dose of ocrelizumab on (b) (6) and her last dose on (b) (6) She detected a right sided breast mass by self-exam on 12/25/08. A needle biopsy on (b) (6) showed invasive ductal carcinoma. She withdrew from the study and underwent pre-surgical chemotherapy. A scheduled surgery on (b) (6) was cancelled due to new increase in breast mass size with ulceration. She underwent additional chemotherapy but her disease progressed and she died on (b) (6).

Gastric cancer
WA20496-137368-12246 This 38 year old female received her first dose of ocrelizumab on (b) (6) and her last dose on (b) (6). She entered the SFU on 6/3/10 when the sponsor terminated the trial. On (b) (6) she presented with lower abdominal tenderness and bloating. A laparoscopic peritoneal biopsy showed poorly differentiated adenocarcinoma consistent with gastric origin and she was diagnosed with Krukenberg tumor with primary gastric cancer. Tumors were present throughout the abdominal cavity. She underwent surgery and chemotherapy. Her disease progressed and she died on (b) (6).

Gastrointestinal carcinoma
WA18230-68466-1914 This 66 year old female received her first dose of ocrelizumab on (b) (6) and her last dose on (b) (6). On (b) (6), she was hospitalized with abdominal pain and constipation. She was diagnosed with “bowel cancer” and underwent surgery. She died on (b) (6). No other information was provided.

Lung Cancer
WA20495-117904-66302 This 58 year old female with a history of tobacco abuse received her first dose of ocrelizumab on (b) (6) On 12/16/08 she was diagnosed with lung cancer (details of diagnosis and treatment not provided). She continued in the trial and her last dose of ocrelizumab was (b) (6). On (b) (6) she developed a deep venous thrombosis and an ulcer on the right foot that required a below the knee amputation. Her lung cancer was progressing on 12/16/09 and the patient refused further workup. On (b) (6) she developed aphasia and weakness which was reported as a cerebrovascular accident. She received hospice care and died on (b) (6).

WA20495-119482-66501 This 63 year old female with a history of cigarette smoking was treated with ocrelizumab from (b) (6) to (b) (6) Trial SAEs included pneumonia, cellulitis, GI hemorrhage, diverticulitis, UTI, and carotid artery stenosis. On (b) (6), during her

evaluation for diverticulitis, a CT showed a 5cm mass on her left adrenal gland. Work up included a CT scan of the abdomen, chest, and brain, and a fine needle aspiration of an enlarged right inguinal lymph node. She was diagnosed with lung adenocarcinoma with brain metastases. She died on (b) (6).

WA20496-137449-17397 This 72 year old female with a history of heavy smoking (not quantified) was treated with an ocrelizumab infusion on (b) (6). On (b) (6) she developed cough, congestion, and shortness of breath. A chest x-ray showed a RUL density. Work up included CT scan, PET scan, and CT guided biopsy which demonstrated a poorly differentiated adenocarcinoma. She was treated with chemotherapy and radiation therapy. She died on (b) (6).

Gastrointestinal hemorrhage
WA20496-137447-17244 This 59 year old female with a history of gastroesophageal reflux disease, and s/p gastric bypass surgery for weight loss, received her first dose of ocrelizumab on (b) (6). She took low dose aspirin for cardiovascular prophylaxis but no NSAIDs. On study day 111 she was diagnosed with a gastric ulcer by gastroscopy. She was treated with esomeprazole and her aspirin was stopped. On (b) (6), 4 months after her last ocrelizumab infusion, she collapsed at home and was vomiting bright red blood. She was taken to an ED and died despite volume replacement and an exploratory laparotomy. An autopsy was not performed.
Ischemic cerebral infarction

WA20497-109545-18622 This 63 year old female with a history of atrial fibrillation, brain ischemia, and angioplasty of the left carotid artery received her first dose of ocrelizumab on (b) (6). On day 15 of the trial, approximately 70 minutes after the second study drug infusion, she experienced atrial fibrillation that lasted 19 hours. The patient had forgotten to take her medications that morning. She was hospitalized and by the following day was in sinus rhythm. On (b) (6), she presented with vomiting, dehydration, and an oral ulcer. Labs included a leukocyte count 0.43 x 10^9/L, erythrocyte count 2.13 T/L, platelet count 17 x 10^9/L, ALT 14.69 U/L and AST 9.49 U/L. Pancytopenia was diagnosed, and the event was considered possibly related to methotrexate treatment. She was discontinued from the trial and was treatment included antibiotics, an antifungal, steroids, Filgastrim, PRBCs, and platelets. On (b) (6), she experienced a cerebral infarction. A head CT showed a hypodense, irregular area in the left occipital lobe region suggesting ischemic change. She died on (b) (6). A post mortem exam showed major-grade encephalomalacia of the left cerebral hemisphere in the course of the ischemic infarct and the reported cause of death was ischemic stroke of the left brain hemisphere.

Ruptured cerebral aneurysm
WA20497-117462-15110 This 74 year old female received her first ocrelizumab infusion on (b) (6). On study day 187, 5 days after her last infusion, she reported feeling ill and was

confused and agitated. At a hospital she reportedly was confused but had no focal neurological deficiencies. A head CT showed a hemorrhagic cerebral infarct. Cerebral angiography demonstrated a ruptured aneurysm of the right middle cerebral artery. She had a clip placed 3 days later. Two days after surgery she became comatose and died. No autopsy was performed.

Pulmonary embolism
WA20497-117320-19394 This 45 year old female received her first ocrelizumab infusion on (b) (6). On (b) (6) she died at home and the husband reported that she had an autopsy and that the cause of death was a pulmonary embolism.

Toxicity to various agents
WA20494-97782-20002 This 58 year old male with a history of anemia and goiter (s/p thyroidectomy), hypercholesterolemia, hypertension, and depression, received his first ocrelizumab infusion on (b) (6) He attended a study visit on (b) (6). He was found dead on (b) (6). The body had decomposition changes. The autopsy report established as final diagnosis: intoxication by the combined effects of multiple medications (doxepin, propoxyphene, dextromethorphan and fluoxetine); hypertensive heart disease (cardiomegaly 580 g and L ventricular hypertrophy) and osteoarthritis. It was unclear whether the drug intoxication was an intentional act or accidental overdose, for this reason the manner of death was certified as indeterminate.

Disseminated Intravascular coagulation
WA20495-141477-90901 This 70 year old male received ocrelizumab from (b) (6). Trial SAEs after starting ocrelizumab included pharyngitis, interstitial lung disease, and pleurisy. On 2/4/11 he received etanercept. On (b) (6), 556 days after his last ocrelizumab infusion, he was diagnosed with pneumonia and SIRS. He developed sepsis, acute renal failure, pulmonary hemorrhage, and ARDS (minimal details provided regarding these events). On (b) (6) he developed DIC and died 2 days later.

RA trials, controlled phases (Pool D)
In the RA controlled trials, Pool D, the mortality rate/100PY was 0.78 for placebo compared to 0.50 for ocrelizumab 400mg, and 0.66 for ocrelizumab 1000mg. Although the overall mortality rates were comparable, the ocrelizumab treatment groups had an increased number of infection and/or sepsis related deaths (5) compared to placebo (0).

The reported causes of death for the placebo patients were myocardial infarction (n=2), acute respiratory failure, acute rheumatoid vasculitis, diffuse large B-cell lymphoma, congestive heart failure, and adenocarcinoma of the colon.

The reported causes of death for the ocrelizumab patients in pool D were (400mg) septic shock (n=2), pulmonary embolism, ruptured cerebral aneurysm, acute respiratory failure, (1000mg)

pneumonia (n=3), sepsis, acute myocardial infarction, ischemic cerebral infarction, (100mg) pneumonia, (2000mg) traffic accident (5/20/16 Submission, response to reviewer questions).

Deaths in Trials of other Indications

In the SLE trial WA20499, the CSR identified 2 deaths in ocrelizumab exposed patients, both infection-related. Patient 120728/04601, a 42 year old female, received ocrelizumab on (b) (6). She developed symptoms of an upper respiratory tract infection on (b) (6) and was treated with amoxicillin/clavulanic acid. Her condition worsened and she refused to seek additional medical help. Her family reported that she died and that no autopsy was performed. Patient 97625/06163 a 27 year old female received ocrelizumab on (b) (6) and (b) (6) She was diagnosed with pneumocystis jiroveci pneumonia 49 days after her second dose of ocrelizumab. Her hospital course was complicated by lupus nephritis/renal failure and she died.

During LN trial WA20500, the CSR identified 14 deaths (6 placebo, 8 ocrelizumab). The reported causes of death for the ocrelizumab patients were pneumonia (3), intracerebral bleed, acute renal failure, acute respiratory distress syndrome with disseminated intravascular coagulation, septic shock, and urosepsis. During the safety follow up, an additional death due to legionella pneumonia was reported. The reported causes of death for the placebo group were myocardial infarction (2), pulmonary embolism, cardio-respiratory arrest, cardiac insufficiency, and acute myeloid leukemia.

Two deaths were reported for trial BO18414. Patient 1382 died from underlying disease progression, 5 months after discontinuing ocrelizumab for insufficient response. Patient 1242 died from a pulmonary embolism 10 months after final study treatment. This 60 year old male discontinued ocrelizumab after the third dose due to development of bronchiolitis obliterans. The narrative noted that at the time of the PE event and death the patient was chair/bed bound.

8.4.2. Serious Adverse Events

In the ocrelizumab MS trials, no single SAE was reported by at least 1% of exposed patients. The most commonly reported SAEs were infections (urinary tract, pneumonia, appendicitis), fractures, seizures, MS relapse, infusion related reactions, cholelithiasis/cholecystitis, breast cancer, suicide attempt, pancreatitis, and back pain. There were no SAEs of aplastic anemia, pancytopenia, rhabdomyolysis, Stevens Johnson Syndrome, Toxic Epidermal Necrolysis, liver failure, or renal failure in MS trials.

SAEs were reported infrequently in the controlled phases of MS trials. In the controlled phase of RMS trials, individual SAEs generally occurred too infrequently to allow for robust

comparisons of risk by treatment, but SAEs reported more frequently with ocrelizumab included fractures, breast cancer, and cholelithiasis/cholecystitis. During the controlled phase of the PPMS trial, SAEs reported more frequently among ocrelizumab compared to placebo patients included IRRs, pneumonia, breast cancer, pancreatitis, cholelithiasis/cholecystitis, and back pain.

To assess SAEs, I examined Genentech's presentations and tables, and then read CRFs and narrative summaries for common SAEs and for select events of interest. This review starts by identifying SAEs occurring in at least 5 MS patients from the overall MS population (Pool B). Events from controlled trials are presented to look for quantitative evidence of drug relatedness. A similar approach is used for data from RA trials. The sponsor provided analyses of infections, malignancies, and IRRs and so those events will be considered separately, in the relevant sections of this review. I review narratives for select SAEs that were common and appeared to occur more frequently with ocrelizumab, or for infrequent, unexpected SAEs that may be of concern.

All MS trials (Pool B)
232 of the 2147 patients (10.8%) exposed to ocrelizumab in the development program experienced one or more SAEs. Below, I list SAEs reported by at least 5 subjects in the ISS.

Table 6 SAEs Reported by at least 5 patients, All MS trials (Pool B)

MedDRA System Organ Class MedDRA Preferred Term	All Exposure to Ocrelizumab (n=2147; 4,485PY)
Total with at least 1 SAE	10.8% (232)
#/100PY	5.2 (232)
Infections and Infestations	**3.0% (64)**
Urinary tract infection[1]	0.7% (16)
Pneumonia[2]	0.4% (11)
Appendicitis	0.3% (7)
Nervous System Disorders	**1.6% (35)**
Seizure[3]	0.4% (8)
Multiple sclerosis relapse	0.4% (8)
Injury, Poisoning, and Procedural Complications	**1.5% (32)**
Fractures[4]	0.6% (13)
Infusion related reaction	0.3% (7)
Gastrointestinal Disorders	**1.1% (23)**
Pancreatitis[5]	0.2% (5)
Neoplasms Benign, Malignant, and Unspecified	**0.8% (18)**
Breast cancer[6]	0.3% (7)

Psychiatric Disorders	**0.7% (15)**
Suicide attempt[7]	0.3% (7)
General Disorders and Administration Site Conditions	**0.6% (13)**
Musculoskeletal and Connective Tissue Disorders	**0.6% (13)**
Back pain	0.3% (6)
Hepatobiliary disorders	**0.5% (11)**
Cholecystitis/Cholelithiasis[8]	0.4% (9)
Cardiac Disorders	**0.4% (8)**
Reproductive System and Breast Disorders	**0.4% (8)**
Respiratory, Thoracic, and Mediastinal Disorders	**0.3% (7)**
Blood and Lymphatic System Disorders	**0.3% (6)**
Renal and Urinary Disorders	**0.3% (6)**
Metabolism and Nutrition Disorders	**0.2% (5)**

[1] Includes events coded to urinary tract infection, pyelonephritis, pyelonephritis acute, bacterial pyelonephritis, urosepsis, cystitis,
[2] Includes events coded to pneumonia, bronchopneumonia,
[3] Includes events coded as seizure, epilepsy, partial seizures with secondary generalization
[4] Includes events coded to ankle fracture, upper limb fracture, femoral neck fracture, femur fracture, fibula fracture, humerus fracture, lower limb fracture, lumbar vertebral fracture, multiple fractures, radius fracture, skull fracture, tibia fracture
[5] Includes pancreatitis acute, pancreatitis
[6] Includes events coded to Invasive ductal breast carcinoma, breast cancer, and invasive breast carcinoma
[7] Includes events coded to Suicide attempt and Completed suicide
[8] Includes terms coded to Cholecystitis, Cholecystitis acute, Cholecystitis chronic, and Cholelithiasis

There were no SAEs of aplastic anemia, pancytopenia, rhabdomyolysis, Stevens Johnson Syndrome, Toxic Epidermal Necrolysis, liver failure, or renal failure in MS trials.

90 Day Safety Update
Two SAEs PTs were reported <5 times in the ISS, but following the addition of new safety data were reported at least 5 times in the 90 Day Safety Update (cellulitis n=5, and depression n=5).

Genentech provided a table of SAEs with rates from the ISS (#SAEs/person years) compared to the 90 Day Safety Update rate, which reflected the updated SAE totals and the additional exposure. I reviewed the table to look for events where there appeared to be an increase in rate in the 90 Day Safety Update data compared to the ISS data.

When comparing the ISS SAE rates to the 90 Day Safety Update SAE rates, there were few notable differences. There was an increase in pneumonia rate in the 90 Day Safety Update. In

the ISS, the SAE rate for pneumonia was 0.2/100PY (11/4,485PY) compared to 0.3/100PY (19/5,711PY) in the 90 Day Safety Update. To allow for direct risk comparisons, I combined pneumonia and bronchopneumonia PTs that were separate in the ISS (see table above). In the 90 Day Safety Update, these events were already combined. The sponsor explained that the difference in coding was due to the use of MedDRA 18.0 for the ISS and MedDRA 18.1 for events reported in the 90 Day Safety Update.

There were no SAEs of aplastic anemia, pancytopenia, rhabdomyolysis, Stevens Johnson Syndrome, Toxic Epidermal Necrolysis, liver failure, or renal failure in MS trials in the 90 Day Safety Update.

RMS Trials Controlled Phase (Pool A)
In the RMS controlled trials, the overall risk for SAEs was similar for the interferon beta-1a patients (8.7%, 72/826) and the ocrelizumab patients (6.9%, 57/825). In the table below, I identify the SAEs where the risk was higher among ocrelizumab patients compared to interferon beta-1a patients as well as select SAEs of potential interest.

Table 7 SAEs Occurring More Frequently with Ocrelizumab compared to Interferon beta-1a, and Select SAEs of Potential Interest, RMS Trials Controlled Phase, (Pool A)

MedDRA System Organ Class MedDRA Preferred Term	IFN beta-1a (n=826)	Ocrelizumab (n=825)
Patients with at least one SAE	**8.7% (72)**	**6.9% (57)**
Infections and Infestations	**2.9% (24)**	**1.3% (11)**
Urinary tract infections[1]	0.4% (3)	0.2% (2)
Cellulitis	0.1% (1)	0.2% (2)
Biliary sepsis	0	0.1% (1)
Device related infection	0	0.1% (1)
Herpes Simplex	0	0.1% (1)
Upper respiratory tract infection	0	0.1% (1)
Nervous System Disorders	**1.3% (11)**	**1.0% (8)**
Seizure[2]	0.4% (3)	0.5% (4)
Cerebral infarction	0	0.1% (1)
Dizziness	0	0.1% (1)
Head discomfort	0	0.1% (1)
Hydrocephalus	0	0.1% (1)
Sciatica	0	0.1% (1)
Injury, Poisoning, and Procedural Complications	**1.2% (10)**	**0.7% (6)**
Fractures [3]	0.1% (1)	0.5% (4)
Craniocerebral injury	0	0.1% (1)
Meniscus injury	0	0.1% (1)

Procedural pain	0	0.1% (1)
Psychiatric disorders	**0.8% (7)**	**0.5% (4)**
Depression	0	0.2% (2)
Suicide attempt	0	0.1% (1)
Neoplasms Benign, Malignant, and Unspecified	**0.5% (4)**	**0.7% (6)**
Invasive ductal breast carcinoma	0	0.2% (2)
Thyroid adenoma	0	0.2% (2)
Malignant melanoma	0	0.1% (1)
Renal cancer	0	0.1% (1)
Gastrointestinal Disorders	**0.5% (4)**	**0.6% (5)**
Gastritis	0	0.2% (2)
Gastrointestinal inflammation	0	0.1% (1)
Ileus paralytic	0	0.1% (1)
Pancreatitis[4]	0	0.1% (1)
Hepatobiliary disorders	**0.4% (3)**	**0.7% (6)**
Cholecystitis/Cholelithiasis[5]	0.2% (2)	0.7% (6)
Reproductive system and breast disorders	**0.5% (4)**	**0.4% (3)**
Dysmenorrhea	0	0.1% (1)
Endometriosis	0	0.1% (1)
Menometrorrhagia	0	0.1% (1)
Cardiac disorders	**0.4% (3)**	**0.4% (3)**
Atrial flutter	0	0.1% (1)
Cardiac failure congestive	0	0.1% (1)
Musculoskeletal and connective tissue disorders	**0.2% (2)**	**0.4% (3)**
Arthritis	0	0.1% (1)
Muscle spasms	0	0.1% (1)
Vertebral osteophyte	0	0.1% (1)
Respiratory, thoracic, and mediastinal disorders	**0.4% (3)**	**0.2% (2)**
Asthma	0	0.1% (1)
Pneumonia aspiration	0	0.1% (1)
Metabolism and nutrition disorders	**0.1% (1)**	**0.4% (3)**
Dehydration	0	0.1% (1)
Hypoglycemia	0	0.1% (1)
Hypokalemia	0	0.1% (1)
General disorders and administration site conditions	**0**	**0.4% (3)**
Chest pain	0	0.4% (3)

Blood and lymphatic system disorders	**0.2% (2)**	**0**
Immune system disorders	**0.1% (1)**	**0.1% (1)**
Renal and urinary disorders	**0.2% (2)**	**0**
Skin and subcutaneous tissue disorders	**0.1% (1)**	**0.1% (1)**
Dermatitis bullous	0	0.1% (1)
Vascular disorders	**0.1% (1)**	**0.1% (1)**
Peripheral venous disease	0	0.1% (1)
Eye disorders	**0.1% (1)**	**0**
Surgical and medical procedures	**0.1% (1)**	**0**

[1] Includes events coded to Cystitis, Urinary tract infection and Pyelonephritis
[2] Includes events coded to seizure, epilepsy
[3] Includes events coded to ankle fracture, upper limb fracture, humerus fracture, lower limb fracture, lumbar vertebral fracture, skull fracture
[4] Includes events coded to pancreatitis, pancreatitis acute
[5] Includes events coded to Cholecystitis, cholecystitis acute, cholecystitis chronic, and cholelithiasis

PPMS Trial Controlled Phase
In the PPMS study, the overall risk for serious adverse events was similar for placebo patients (22.2%, 53/239) and ocrelizumab patients (20.4%, 99/486). In the table below, I identify the SAEs where the risk was higher among ocrelizumab patients compared to placebo patients along with additional events of interest identified in the Pool A analyses above.

Table 8 SAEs Occurring More Frequently with Ocrelizumab compared to Placebo, and Select SAEs of Potential Interest, PPMS Trial Controlled Phase

MedDRA System Organ Class MedDRA Preferred Term	Placebo (n=239)	Ocrelizumab (n=486)
Patients with at least 1 SAE	**22.2% (53)**	**20.4% (99)**
Infections and infestations	**5.9% (14)**	**6.2% (30)**
Urinary tract infection[1]	2.1% (5)	2.3% (11)
Pneumonia[2]	0.8% (2)	1.4% (7)
Appendicitis	0	0.4% (2)
Bronchitis	0	0.4% (2)
Cellulitis	0	0.4% (2)
Abscess limb	0	0.2% (1)
Bursitis infective	0	0.2% (1)
Diverticulitis	0	0.2% (1)
Erysipelas	0	0.2% (1)
Gastroenteritis	0	0.2% (1)
Gastrointestinal infection	0	0.2% (1)

Impetigo	0	0.2% (1)
Infected dermal cyst	0	0.2% (1)
Mastitis	0	0.2% (1)
Neutropenic sepsis	0	0.2% (1)
Peritonitis	0	0.2% (1)
Post procedural cellulitis	0	0.2% (1)
Viral infection	0	0.2% (1)
Viral pericarditis	0	0.2% (1)
Injury, Poisoning, and Procedural Complications	**4.6% (11)**	**3.9% (19)**
Fractures[3]	2.1% (5)	1.9% (9)
Infusion related reaction	0	1.0% (5)
Tendon rupture	0	0.4% (2)
Post lumbar puncture syndrome	0	0.2% (1)
Postoperative fever	0	0.2% (1)
Subdural hematoma	0	0.2% (1)
Nervous system disorders	**3.8% (9)**	**3.7% (18)**
Multiple sclerosis relapse	0.8% (2)	1.0% (5)
Seizures[4]	0.8% (2)	0.4% (2)
Syncope	0	0.2% (1)
Trigeminal neuralgia	0	0.2% (1)
Hemorrhage intracranial	0	0.2% (1)
Intracranial pressure increased	0	0.2% (1)
Migraine	0	0.2% (1)
Multiple sclerosis	0	0.2% (1)
Optic neuritis	0	0.2% (1)
Primary progressive multiple sclerosis	0	0.2% (1)
Sciatica	0	0.2% (1)
Neoplasms benign, malignant, and unspecified	**2.9% (7)**	**1.6% (8)**
Breast cancer[5]	0	0.8% (4)
Anaplastic large-cell lymphoma	0	0.2% (1)
Endometrial cancer	0	0.2% (1)
Malignant fibrous histiocytoma	0	0.2% (1)
Pancreatic carcinoma metastatic	0	0.2% (1)
Gastrointestinal disorders	**1.3% (3)**	**2.1% (10)**
Pancreatitis acute	0	0.4% (2)
Abdominal pain lower	0	0.2% (1)
Colitis ischemic	0	0.2% (1)
Crohn's disease	0	0.2% (1)
Diarrhea	0	0.2% (1)

Duodenal ulcer hemorrhage	0	0.2% (1)
Fecaloma	0	0.2% (1)
Gastric ulcer hemorrhage	0	0.2% (1)
Gastrointestinal polyp hemorrhage	0	0.2% (1)
Incarcerated umbilical hernia	0	0.2% (1)
Musculoskeletal and connective tissue disorders	**2.5% (6)**	**1.2% (6)**
Back pain	0.4% (1)	0.8% (4)
Muscular weakness	0	0.2% (1)
Osteoarthritis	0	0.2% (1)
General disorders and administration site conditions	**1.3% (3)**	**1.2% (6)**
Edema peripheral	0	0.4% (2)
Drug intolerance	0	0.2% (1)
Non-cardiac chest pain	0	0.2% (1)
Renal and urinary disorders	**1.3% (3)**	**1.0% (5)**
Proteinuria	0	0.2% (1)
Urethral stenosis	0	0.2% (1)
Hepatobiliary disorders	**0.8% (2)**	**0.8% (4)**
Cholecystitis/Cholelithiasis[6]	0.4% (1)	0.6% (3)
Bile duct stenosis	0	0.2% (1)
Blood and lymphatic system disorders	**0.4% (1)**	**0.8% (4)**
Agranulocytosis	0	0.2% (1)
Febrile neutropenia	0	0.2% (1)
Microcytic anemia	0	0.2% (1)
Cardiac disorders	**0.8% (2)**	**0.6% (3)**
Myocardial infarction	0	0.4% (2)
Sinus tachycardia	0	0.2% (1)
Respiratory, thoracic, and mediastinal disorders	**0.8% (2)**	**0.6% (3)**
Pneumonia aspiration	0	0.2% (1)
Pulmonary embolism	0	0.2% (1)
Psychiatric disorders	**0**	**0.8% (4)**
Suicide attempt	0	0.4% (2)
Depression suicidal	0	0.2% (1)
Suicidal ideation	0	0.2% (1)
Reproductive system and breast disorders	**0.8% (2)**	**0.4% (2)**
Cervical polyp	0	0.2% (1)
Metrorrhagia	0	0.2% (1)
Vascular disorders	**0.8% (2)**	**0.2% (1)**

Dry gangrene	0	0.2% (1)
Peripheral arterial occlusive disease	0	0.2% (1)
Metabolism and nutrition disorders	**0.4% (1)**	**0.2% (1)**
Dehydration	0	0.2% (1)
Skin and subcutaneous tissue disorders	**0.4% (1)**	**0.2% (1)**
Pruritus allergic	0	0.2% (1)
Eye disorders	**0**	**0.2% (1)**
Cataract	0	0.2% (1)
Immune system disorders	**0**	**0.2% (1)**
Drug Hypersensitivity	0	0.2% (1)

[1] Includes events coded to Pneumonia and Bronchopneumonia
[2] Includes events coded to Urinary tract infection, Pyelonephritis, Pyelonephritis acute, Bacterial pyelonephritis, and Urosepsis
[3] Includes events coded to Ankle fracture, femoral neck fracture, femur fracture, fibula fracture, hip fracture, lumbar vertebral fracture, multiple fractures, radius fracture, tibia fracture, and upper limb fracture
[4] Includes events coded to Seizure and Partial seizures with secondary generalization
[5] Includes events coded to Breast cancer, Invasive ductal breast carcinoma, and Invasive breast carcinoma
[6] Includes events coded to Cholecystitis acute, Cholecystitis chronic, and Cholelithiasis

MS trial WA21493 Controlled Phase
During the controlled phase of WA21493 (first 24 weeks), few SAEs were reported and the frequencies were similar across treatment groups. 3.7% (2/54) of placebo patients reported SAEs compared to 1.8% (1/55) of ocrelizumab 600mg patients, 3.6% (2/55) of ocrelizumab 1000mg patients and 3.7% (2/54) Avonex patients. The SAEs reported for the ocrelizumab patients were abdominal pain upper (ocrelizumab 600mg), systemic inflammatory response syndrome, and anxiety (both ocrelizumab 1000mg).

Summary of Select SAE narratives from MS trials

Cholecystitis, Cholecystitis acute, Cholecystitis chronic, and Cholelithiasis
When considered together, there appeared to be an imbalance in SAEs coded to the preferred terms Cholecystitis, Cholecystitis acute, Cholecystitis chronic, and Cholelithiasis under the SOC Hepatobiliary Disorders. Despite this slight imbalance in these cases observed in MS trials, the evidence does not support mention in labeling at this time. These events can occur commonly in females of the age group that make up the cases. Similar imbalances in these events by treatment were not observed in the RA controlled trials. The labeling for the approved antiCD20 monocloncal antibodies does not include language about cholelithiasis/cholecystitis events. Post marketing reports should be monitored for these events.

I identified the 9 ocrelizumab patients (WA21092-207489-1922476, WA21092-207507-1922509, WA21092-207862-1921442, WA21092-234569-1926571, WA21093-209753-1930902, WA21093-233895-1936213 WA25046-208244-47503, WA25046-208392-21411, WA25046-245827-31105) with these events and summarize the cases below.

All 9 patients with a Cholecystitis/cholelithiasis SAE were female. The average age was 43 (median 46 years, range 21-53 years). The average duration of treatment with ocrelizumab prior to onset of the SAE was 360 days (median 376 days, range 116-602 days). The average cumulative dose of ocrelizumab prior to onset was 1,766mg (median 1,800mg, range 600-3,600mg). Only one narrative identified a prior history of cholelithiasis/cholecystitis. Eight of the nine patients underwent cholecystectomy for treatment of the SAE. One of the nine patients experienced a pancreatitis SAE that was attributed to cholelithiasis (WA25046-208392-21411 narrative summarized with pancreatitis cases below). One additional patient not included in the 9 above was identified who experienced a pancreatitis SAE that was attributed to cholelithiasis, but cholelithiasis was characterized only as an AE and not an SAE (WA25046-208701-38002 narrative summarized with pancreatitis cases below)

One additional case described a patient with chronic calculous cholecystitis who developed biliary sepsis. I summarize that case below.

Biliary sepsis
WA21092-244362-1928501 55 year old male received first dose on (b) (6) and a second dose on (b) (6). On 1/24/13 he presented with fever, abdominal pain, nausea, and constipation. He was BP was 70/40mmHg, his heart rate was 109 bpm, and his WBC count was 51 x 10^9. An abdominal ultrasonography showed hepatomegaly and exacerbated chronic calculous cholecystitis and he was diagnosed with biliary sepsis. He was treated with antibiotics, dopamine, and noradrenaline. On (b) (6), the event was resolved and he was discharged from the hospital. He continued in the trial and completed the controlled phase and entered the open label phase and had no additional SAEs.

Two additional patients with Cholecystitis SAEs were reported in the 90 Day Safety Update.
A 21 year old female who previously had SAEs of pancreatitis (WA21092-234569-1926571, see below) was diagnosed with cholecystitis on study day 332 and underwent cholecystectomy. She continued in the trial. The second case involved a 23 year old female (WA21092-235965-1927654) presented to an ER (symptoms not listed) 948 days after her first infusion and had an ultrasound that showed hepatomegaly and a gallstone of 2 cm in the neck of the gallbladder. She was diagnosed with cholecystitis, and underwent a cholecystectomy. She continued in the trial.

Cases of pancreatitis are concerning events in drug development programs and are routinely assessed for potential relationship to experimental treatments. There were 5 SAEs of

pancreatitis in MS ocrelizumab patients. Two cases noted the presence of cholelithiasis, one case was attributed to hypertriglyceridemia, and 2 cases did not have an identified cause. The divergent etiologies for these cases do not suggest a clear relationship to ocrelizumab and therefore do not support inclusion of this event in labeling at this time. Post marketing reports should be monitored for additional cases. Below I summarize 5 SAEs of pancreatitis in patients receiving ocrelizumab during the MS trials.

Pancreatitis, Pancreatitis acute
WA21092-207782-1923291 This 29 year old female received her first dose of ocrelizumab on (b) (6). Ocrelizumab was discontinued following this first dose due to an infusion related reaction that included urticarial, pruritus, hypotension, rash and throat itching. She entered the SFU. On 8/20/12 she was started on commercial interferon beta-1a. On (b) (6) she developed abdominal pain, which improved with omeprazole and an aluminum-magnesium antacid. On (b) (6), she was diagnosed with pancreatitis due to elevated triglycerides (854mg/dL, normal 50-160mg/dL). She had a documented elevated lipase (371U/L, normal 0-190U/L). She was treated with simvastatin and fenofibrate and she improved. She was discharged from the hospital on (b) (6).

WA21092-234569-1926571 This 21 year old female received her first ocrelizumab dose on (b) (6). She experienced separate SAEs of gastritis on 3/21/13 and 4/12/13. On (b) (6), she developed nausea, vomiting, and abdominal pain and labs included a lipase of 760 (units, normal range not reported). She was diagnosed with pancreatitis. Abdominal CT was normal and U/S did not show stones. EGD showed mile pyloric stenosis. She improved and was discharged on (b) (6). On (b) (6), she again experienced nausea, vomiting, and abdominal pain. Lipase was 635-913 (units and normal range not reported). She was diagnosed with a second episode of pancreatitis. CT of the abdomen and RUQ U/S were normal. Following treatment with pain medications, a PPI, pancrealipase, and an antibiotic (for a UTI), she improved and was discharged on (b) (6). She continued in the trial.

WA21093-233905-1936451 This 41 year old female received her first dose of ocrelizumab on (b) (6). Ocrelizumab was stopped on (b) (6) due to an AE of speech disorder. On (b) (6), she developed abdominal pain. A CT scan and abdominal U/S were negative. Labs during the hospitalization included an amylase of 256 U/L (normal 28-100 U/L) and lipase of 588 U/L (normal range 13-60 U/L). She was treated with pain medications and nystatin for a candida infection (thrush). A follow up CT was performed due to persistent pain and the pancreas appeared normal. She was discharged from the hospital on (b) (6).

WA25046-208392-21411This 53 year old female received her first dose of ocrelizumab on (b) (6). On (b) (6), she had an AE of cholelithiasis (no details provided). On (b) (6), she developed vomiting and abdominal pain and was hospitalized and diagnosed with pancreatitis. An U/S showed a slightly thickened gall bladder with small stones and bile ducts were not

dilated. During the hospitalization she had an amylase result of 944 U/L (normal range not provided). A repeat ultrasound on (b) (6) showed an enlarged liver, gallbladder with thin walls and numerous stones, undilated bile ducts, and the pancreas was slightly hyperechogenic and enlarged within the head. She underwent an ERCP which showed the ampulla of the Vater surrounded by inflammatory infiltration in the descending duodenum. She had moderately dilated intrahepatic and extrahepatic bile ducts; and injected contrast medium showed stones. Biliary sphincterotomy was performed, however, no stones were detected and the bile flow through the ampulla was maintained. Her condition improved and she was discharged from the hospital on (b) (6) She continued in the trial.

WA25046-208701-38002 This 42 year old male received his first dose of ocrelizumab on (b) (6). On (b) (6), 57 days after his most recent ocrelizumab infusion, he developed abdominal pain, nausea, fever, and jaundice. A U/S was consistent with pancreatitis (no details provided). He was also diagnosed with cholelithiasis (non SAE, no details provided). He underwent cholecystectomy. His pancreatitis was resolved and he was discharged from the hospital on (b) (6). He continued in the trial.

I summarize an SAE of ITP with ocrelizumab. The role of ocrelizumab in this event is not clear.

Immune thrombocytopenic purpura
WA21493-141003-4354 This 45 year old female received her first dose of ocrelizumab on (b) (6). She received her final dose of ocrelizumab on (b) (6) and completed the treatment phase of the study. On (b) (6), her CD3/CD4 count was 532, CD 19 was 76 (units not reported) and immunoglobulin levels were normal (values not provided). On (b) (6) she had a platelet count of 16 x 109/L (normal range: 140-450 x 109/L) and her CD3/CD4 count was 424 and CD 19 was 59. She was diagnosed with idiopathic thrombocytopenia. On (b) (6) she was started on intravenous methylprednisolone 100 mg daily and one tablet of ascorbic acid/ferrous sulfate. She did not experience any bleeding. On (b) (6) she had a hemoglobin of 126, hematocrit 0.39, erythrocytes 449, leucocytes 15.7, and platelets 80 (units and normal ranges not provided). The narrative reported that subsequent platelet counts were 206 on 5/17/12, 212 on 5/21/12 and 192 on 6/28/12. Her ITP was considered stabilized on chronic corticosteroids, but ongoing.

Serious skin reactions are events of concern in drug development programs. Below I summarize an SAE of dermatitis bullosa. The role of ocrelizumab in this event is not clear.

Dermatitis bullosa
WA21093-233958-1936676 This 32 year old male received his first ocrelizumab infusion on (b) (6). On (b) (6), 57 days following his most recent ocrelizumab infusion, he developed a non-serious rash that was attributed to poison ivy and was treated with triamcinolone IM followed by a 4 day course of methylprednisolone PO. On (b) (6) after progressing, the rash

was diagnosed as a bullous drug eruption with “large, tense, coalescing multiple blisters, 2 x 3 cm on the left thigh inferior, left thigh superior and left anterior proximal thigh.” Treatment with steroids was extended. On (b) (6) the patient counted 30 lesions present in various stages, on the arms, legs, face, abdomen, groin and penis. No mucous membrane lesions were reported. Biopsies of the thigh lesions found epidermis exhibiting compact layers of parakeratotic scale with attenuated granular zone, superficial pale keratinocytes and relatively uniform psoriasisiform acanthosis, variable spongiosis and a few small spongiotic pustules. Perivascular predominantly mononuclear inflammation was also noted without conspicuous eosinophils. The diagnosis was psoriatic spongiotic dermatitis with features of psoriasis. Ocrelizumab was permanently discontinued on (b) (6) due to bullous drug eruption. On (b) (6) the dermatologist noted recurrence of blisters. On (b) (6) the event was considered resolved.

Below I summarize a report of agranulocytosis in an ocrelizumab patient. The role of ocrelizumab in this event is not clear although her improvement in neutrophil count following treatment and lack of recurrence while continuing in the trial seems reassuring.

Agranulocytosis
WA25046-208244-47506 This 38 year old female received her first ocrelizumab infusion on (b) (6). At baseline, laboratory work-up showed monocytes 0.18 × 109/L (normal range: 0.12-0.92 × 109/L), erythrocytes 4.5 × 1012/L (normal range: 4.1-5.6 × 1012/L), leukocytes 5.65 × 109/L (normal range: 3.8-10.70 × 109/L) and platelet count 290 × 109/L (normal range: 140-400 × 109/L). On (b) (6), she had a temperature of 39°C, sore throat, and bilateral lower limb spasticity. She was hospitalized and lab results included leukocyte count 0.52 × 109/L, neutrophil count 0 × 109/L, lymphocyte count 0.36 x 109/L, monocyte count 0.16 × 109/L, platelet count 159 × 103/L, hemoglobin 12.1 g/dL. She was diagnosed with agranulocytosis. Blood culture, urine culture, toxoplasmosis, hepatitis A, B and C, human immunodeficiency virus (HIV), cytomegalovirus (CMV) and Epstein-Barr virus (EBV) were negative. She was treated with antibiotics and filgrastim. On 4/18/13, her neutrophil count was 0.17 × 109/L and on 4/21/13 it was 2.3 × 109/L (normal range 1.5-7.7 × 109/L). The event was considered resolved on (b) (6) and she was discharged from the hospital. She continued to receive ocrelizumab and completed the controlled phase on (b) (6). On (b) (6) she decided to drop out of the trial for personal reasons and she did not enter the SFU.

During the review of SAEs, I identified a report of splenic vein thrombosis and another of portal vein thrombosis. These are unusual events in MS development programs so I provide summaries below. The role of ocrelizumab in these events is not clear.

Splenic vein thrombosis
WA21093-234088-1937266 This 35 year old female received her first ocrelizumab infusion on (b) (6). The narrative noted that she was taking norethindrone as oral contraceptive. On

(b) (6), 5 days after her most recent ocrelizumab infusion, she developed abdominal pain. The pain worsened and on (b) (6), she presented to an ED. A CT showed splenic infarcts with thrombus in a splenic vein branch and cholelithiasis. She was treated with heparin, warfarin, pneumococcal vaccine, and pain medication. On (b) (6) the heparin was stopped and she was discharged from the hospital on rivaroxaban. She continued in the study.

Portal vein thrombosis
WA21092-206568-1920925 This 49 year old female received her first ocrelizumab infusion on (b) (6). No concomitant medications were reported. On (b) (6), 34 days after her most recent infusion, she developed fever, abdominal pain, diarrhea, and vomiting, and was hospitalized. An U/S and CT scan of abdomen and pelvis were done which showed thrombi in portal vein, splenic vein and mesenteric veins; liver steatosis; small liver lesions consistent with hemangiomas and slightly enlarged spleen and uterus. She was diagnosed with portal vein thrombosis and treated with nadroparin, rivaroxaban, and warfarin. She was discharged on (b) (6) On (b) (6) she was admitted for what appeared to be a work up of her portal vein thrombosis (reported as a second event of portal vein thrombosis). Imaging did not appear to show evidence of malignancy. No test results for hypercoagulability (ex. Protein C, S, lupus anticoagulant, homocysteine, antithrombin III, etc.) were reported. She was discharged and discontinued from the trial.

SAEs All RA trials (Pool E)
Genentech reported that the rate of SAEs for the Pooled RA trials was 14.4/100PY (1058/7323.9PY). Below, I identify the SOCs/SAEs reported at least 5 times.

Table 9 SOCs/SAEs reported at least 5 times, All RA trials (Pool E)

MedDRA System Organ Class MedDRA Preferred Term	Exposure to Ocrelizumab (n=2925, 7323.9 PY)
Total SAEs/100 PY	14.1 (1058)
Infections and Infestations	**3.8 (276)**
Pneumonia	0.7 (51)
Urinary tract infection	0.3 (20)
Cellulitis	0.2 (14)
Sepsis	0.2 (14)
Gastroenteritis	0.2 (12)
Herpes zoster	0.1 (9)
Bronchitis	0.1 (8)
Diverticulitis	0.1 (7)
Appendicitis	0.1 (5)
Bronchopneumonia	0.1 (5)
Pneumocystis Jirovecii Pneumonia	0.1 (5)

Pneumonia bacterial	0.1 (5)
Pyelonephritis	0.1 (5)
Septic shock	0.1 (5)
Musculoskeletal and Connective Tissue Disorders	**1.6 (117)**
Rheumatoid arthritis	0.6 (41)
Osteoarthritis	0.2 (18)
Foot deformity	0.1 (9)
Arthralgia	0.1 (7)
Intervertebral disc protrusion	0.1 (6)
Neoplasms Benign, Malignant, and Unspecified	**1.3 (92)**
Basal cell carcinoma	0.2 (12)
Uterine Leiomyoma	0.1 (7)
Malignant melanoma	0.1 (6)
Prostate cancer	0.1 (6)
Breast cancer	0.1 (5)
Injury, Poisoning, and Procedural Complications	**1.2 (91)**
Infusion related reaction	0.2 (13)
Femur fracture	0.1 (6)
Hip fracture	0.1 (6)
Humerus fracture	0.1 (5)
Multiple fractures	0.1 (5)
Tendon rupture	0.1 (5)
Upper limb fracture	0.1 (5)
Cardiac Disorders	**1.1 (85)**
Myocardial infarction	0.2 (18)
Coronary artery disease	0.2 (12)
Acute myocardial infarction	0.1 (8)
Atrial fibrillation	0.1 (8)
Angina pectoris	0.1 (7)
Gastrointestinal Disorders	**1.0 (74)**
Gastrointestinal hemorrhage	0.1 (7)
Respiratory, Thoracic, and Mediastinal Disorders	**0.9 (65)**
Chronic obstructive pulmonary disease	0.2 (12)
Interstitial lung disease	0.1 (7)
Pulmonary embolism	0.1 (7)
Nervous System Disorders	**0.7 (51)**
Cerebrovascular accident	0.1 (5)
Transient ischemic attack	0.1 (5)
Vascular Disorders	**0.5 (33)**
Deep vein thrombosis	0.2 (11)

General Disorders and Administration Site Conditions	**0.4 (32)**
Chest pain	0.1 (10)
Pyrexia	0.1 (5)
Renal and Urinary Disorders	**0.4 (29)**
Acute kidney injury	0.1 (8)
Blood and Lymphatic System Disorders	**0.3 (21)**
Hepatobiliary disorders	**0.3 (19)**
Cholelithiasis	0.1 (9)
Cholecystitis/Cholecystitis acute	0.1 (8)
Eye Disorders	**0.2 (13)**
Cataract	0.1 (9)
Metabolism and Nutrition Disorders	**0.2 (12)**
Psychiatric disorders	**0.2 (11)**
Reproductive System and Breast Disorders	**0.2 (11)**
Surgical and Medical Procedures	**0.1 (8)**
Pregnancy, Puerperium, and Perinatal Conditions	**0.1 (5)**

RA Controlled trials (Pool D)
In the RA controlled trials, ocrelizumab was associated with an increased risk of infection SAEs that appeared to be dose-related. The following table identifies SAEs from RA controlled trials where the frequency was greater in at least 1 of the ocrelizumab dose groups compared to placebo.

Table 10 SAEs/100PY, Where the frequency in at least 1 ocrelizumab dose group was > placebo, RA Controlled Trials, Pool D

MedDRA System Organ Class MedDRA Preferred Term	Placebo (n=981, 903 PY)	OCR 400mg (n=1186, 1004PY)	OCR 1000mg (N=947, 906PY)
Eye Disorders	**0.11 (1)**	**0.60 (6)**	**0.11 (1)**
Cataract	0.11 (1)	0.30 (3)	0.11 (1)
Glaucoma	0	0.30 (3)	0
Macular hole	0	0.10 (1)	0
Retinal detachment	0	0.10 (1)	0
General Disorders and Administration Site Conditions	**0.11 (1)**	**0.20 (2)**	**0.22 (2)**
Influenza like illness	0	0.10 (1)	0
Pyrexia	0	0	0.11 (1)
Surgical failure	0	0	0.11 (1)
Respiratory, Thoracic, and Mediastinal Disorders	**0.78 (7)**	**1.10 (11)**	**0.99 (9)**

Alveolitis	0	0	0.11 (1)
Chronic obstructive pulmonary disease	0	0.4 (4)	0
Interstitial lung disease	0.11 (1)	0.10 (1)	0.44 (4)
Pneumonitis	0	0	0.11 (1)
Pulmonary alveolar hemorrhage	0	0	0.11 (1)
Vocal cord polyp	0	0	0.11 (1)
Infections and Infestations	**3.43 (31)**	**4.38 (44)**	**6.40 (58)**
Bronchitis	0.11 (1)	0.20 (2)	0
Urinary tract infection	0.22 (2)	0.40 (4)	0.66 (6)
Pneumonia	1.11 (10)	0.80 (8)	1.21 (11)
Appendicitis	0	0.20 (2)	0
Appendicitis perforated	0	0	0.11 (1)
Bronchopneumonia	0	0.2 (2)	0.11 (1)
Pneumocystits Jiroveci pneumonia	0	0.2 (2)	0.11 (1)
Pseudomembranous colitis	0	0.2 (2)	0
Pulmonary tuberculosis	0	0.2 (2)	0
Septic shock	0	0.2 (2)	0
Borrelia infection	0	0.1 (1)	0
Cellulitis gangrenous	0	0.1 (1)	0
Clostridium difficile	0	0.1 (1)	0
Colitis	0	0.1 (1)	0
Conjunctivitis	0	0.1 (1)	0
Diverticulitis	0	0.1 (1)	0
Enterocolitis viral	0	0.1 (1)	0
Gastroenteritis	0	0.1 (1)	0.44 (4)
Hepatitis B	0	0.1 (1)	0
Herpes simplex	0	0.1 (1)	0
Histoplasmosis	0	0.1 (1)	0
Kidney infection	0	0.1 (1)	0
Lower respiratory tract infection	0	0.1 (1)	0
Mycobacterium Kansasii infection	0	0.1 (1)	0
Pneumonia bacterial	0	0.1 (1)	0.22 (2)
Prostate infection	0	0.1 (1)	0
Pyelonephritis chronic	0	0.1 (1)	0
Sepsis	0	0.1 (1)	0.11 (1)

Acute sinusitis	0	0	0.11 (1)
Atypical pneumonia	0	0	0.11 (1)
Bursitis infective	0	0	0.11 (1)
Dengue fever	0	0	0.11 (1)
Diarrhea infectious	0	0	0.11 (1)
Epididymitis	0	0	0.11 (1)
Fungal esophagitis	0	0	0.11 (1)
Gastroenteritis salmonella	0	0	0.11 (1)
Gastroenteritis viral	0	0	0.11 (1)
Herpes zoster	0	0	0.11 (1)
Herpes zoster oticus	0	0	0.11 (1)
Infection	0	0	0.11 (1)
Esophageal candidiasis	0	0	0.11 (1)
Otosalpingitis	0	0	0.11 (1)
Pilonidal cyst	0	0	0.11 (1)
Pyelonephritis	0	0	0.11 (1)
Sinusitis	0	0	0.11 (1)
Sycosis Barbae	0	0	0.11 (1)
Systemic candida	0	0	0.11 (1)
Upper respiratory tract infection	0	0	0.11 (1)
Urosepsis	0	0	0.11 (1)
Varicella zoster pneumonia	0	0	0.11 (1)
Cardiac disorders	**1.22 (11)**	**1.20 (12)**	**1.21 (11)**
Coronary artery disease	0.11 (1)	0.20 (2)	0.11 (1)
Angina pectoris	0.11 (1)	0.30 (3)	0
Atherosclerosis coronary artery	0	0.20 (2)	0
Tachycardia	0	0.10 (1)	0
Ventricular extrasystoles	0	0.10 (1)	0
Atrial fibrillation	0.11 (1)	0	0.33 (3)
Acute coronary syndrome	0	0	0.11 (1)
Atrial flutter	0	0	0.11 (1)
Atrioventricular block complete	0	0	0.11 (1)
Cardia failure	0	0	0.11 (1)
Sinus bradycardia	0	0	0.11 (1)
Injury, Poisoning, and Procedural Complications	**1.88 (17)**	**1.59 (16)**	**1.43 (13)**
Humerus fracture	0	0.20 (2)	0

Contusion	0	0.10 (1)	0
Femoral neck fracture	0	0.10 (1)	0
Limb crushing injury	0	0.10 (1)	0
Multiple fractures	0	0.10 (1)	0
Thermal burn	0	0.10 (1)	0
Toxicity to various agents	0	0.10 (1)	0
Upper limb fracture	0	0.10 (1)	0.22 (2)
Infusion related reaction	0.11 (1)	0.10 (1)	0.66 (6)
Limb traumatic amputation	0	0	0.11 (1)
Musculoskeletal and Connective Tissue Disorders	**2.33 (21)**	**1.79 (18)**	**1.88 (17)**
Osteoarthritis	0.11 (1)	0.50 (5)	0.44 (4)
Arthralgia	0.11 (1)	0.20 (2)	0
Back pain	0	0.10 (1)	0.11 (1)
Muscular weakness	0	0.10 (1)	0
Rotator cuff syndrome	0	0.10 (1)	0
Spinal column stenosis	0	0.10 (1)	0
Spondylitis	0	0.10 (1)	0
Osteoporotic fracture	0	0	0.22 (2)
Osteochondritis	0	0	0.11 (1)
Spondylolisthesis	0	0	0.11 (1)
Blood and Lymphatic System Disorders	**0.55 (5)**	**0.40 (4)**	**0.77 (7)**
Autoimmune hemolytic anemia	0	0.10 (1)	0
Febrile neutropenia	0	0.10 (1)	0.11 (1)
Granulocytopenia	0	0.10 (1)	0.11 (1)
Neutropenia	0	0.10 (1)	0
Agranulocytosis	0	0	0.11 (1)
Cytopenia	0	0	0.11 (1)
Leukopenia	0	0	0.11 (1)
Pancytopenia	0	0	0.11 (1)
Gastrointestinal Disorders	**1.33 (12)**	**1.00 (10)**	**1.10 (10)**
Abdominal wall mass	0	0.10 (1)	0
Gastritis	0	0.10 (1)	0
Gastrointestinal hemorrhage	0	0.10 (1)	0.11 (1)
Gastroesophageal reflux disease	0	0.10 (1)	0
Hemorrhoidal hemorrhage	0	0.10 (1)	0

Hiatus hernia	0	0.10 (1)	0
Nausea	0	0.10 (1)	0.11 (1)
Peptic ulcer hemorrhage	0	0.10 (1)	0
Diarrhea	0	0	0.22 (2)
Abdominal hernia obstructive	0	0	0.11 (1)
Gastric ulcer hemorrhage	0	0	0.11 (1)
Gastrointestinal hemorrhage	0	0	0.11 (1)
Gastrointestinal inflammation	0	0	0.11 (1)
Subileus	0	0	0.11 (1)
Metabolism and Nutrition Disorders	**0.33 (3)**	**0.20 (2)**	**0.11 (1)**
Diabetic ketoacidosis	0	0.10 (1)	0
Neoplasms Benign, Malignant, and Unspecified	**1.22 (11)**	**0.60 (6)**	**1.21 (11)**
Bladder transitional cell carcinoma	0	0.10 (1)	0
Rectal cancer	0	0.10 (1)	0
Thyroid neoplasm	0	0.10 (1)	0
Basal cell carcinoma	0.11 (1)	0	0.22 (2)
B-cell lymphoma	0	0	0.11 (1)
Bronchial carcinoma	0	0	0.11 (1)
Lung adenocarcinoma	0	0	0.11 (1)
Malignant melanoma	0	0	0.11 (1)
Ovarian cancer	0	0	0.11 (1)
Ovarian Theca cell tumor	0	0	0.11 (1)
Squamous cell carcinoma of the lung	0	0	0.11 (1)
Uterine cancer	0	0	0.11 (1)
Vascular Disorders	**0.89 (8)**	**0.50 (5)**	**0.11 (1)**
Aortic aneurysm	0	0.10 (1)	0
Aortic stenosis	0	0.10 (1)	0
Vasculitis necrotizing	0	0.10 (1)	0
Nervous System Disorders	**0.33 (3)**	**0.90 (9)**	**0.66 (6)**
Autonomic neuropathy	0	0.10 (1)	0
Carpal tunnel syndrome	0	0.10 (1)	0
Headache	0	0.10 (1)	0
Leukoencephalopathy	0	0.10 (1)	0

Neuropathy peripheral	0	0.10 (1)	0
Ruptured cerebral aneurysm	0	0.10 (1)	0
Subarachnoid hemorrhage	0	0.10 (1)	0
Transient ischemic attack	0	0.10 (1)	0
Cerebral infarction	0	0	0.11 (1)
Dementia	0	0	0.11 (1)
Ischemic cerebral infarction	0	0	0.11 (1)
Seizure	0	0	0.11 (1)
Somnolence	0	0	0.11 (1)
VIII Nerve paralysis	0	0	0.11 (1)
Reproductive System and Breast Disorders	**0.11 (1)**	**0.30 (3)**	**0.11 (1)**
Cervical dysplasia	0	0.10 (1)	0
Ovarian cyst	0	0.10 (1)	0
Uterine prolapse	0	0	0.11 (1)
Surgical and Medical Procedures	**0**	**0.30 (3)**	**0**
Hip arthroplasty	0	0.10 (1)	0
Joint arthroplasty	0	0.10 (1)	0
Knee arthroplasty	0	0.10 (1)	0
Hepatobiliary Disorders	**0.11 (1)**	**0.10 (1)**	**0.22 (2)**
Cholelithiasis	0	0	0.22 (2)
Cholecystitis acute	0.11 (1)	0	0
Cholecystitis	0	0.10 (1)	0
Renal and Urinary Disorders	**0.11 (1)**	**0.10 (1)**	**0.55 (5)**
Nephrolithiasis	0	0.10 (1)	0.11 (1)
Focal segmental glomerulosclerosis	0	0	0.11 (1)
Renal failure	0	0	0.11 (1)
Renal infarct	0	0	0.11 (1)
Urinary incontinence	0	0	0.11 (1)
Psychiatric Disorders	**0**	**0.20 (2)**	**0.22 (2)**
Depression	0	0.20 (2)	0
Anxiety	0	0	0.22 (2)
Endocrine Disorders	**0.22 (2)**	**0**	**0.11 (1)**
Hyperthyroidism	0	0	0.11 (1)
Skin and Subcutaneous Tissue Disorders	**0.11 (1)**	**0**	**0**
Pregnancy, Puerperium, and Perinatal Conditions	**0**	**0.10 (1)**	**0.11 (1)**

Abortion spontaneous	0	0.10 (1)	0
Bronchogenic cyst	0	0	0.11 (1)
Investigations	**0**	**0.10 (1)**	**0**
Hemoglobin abnormal	0	0.10 (1)	0
Immune System Disorders	**0**	**0.10 (1)**	**0**
Hypersensitivity	0	0.10 (1)	0
Ear and Labyrinth Disorders	**0.11 (1)**	**0**	**0.11 (1)**
Vestibular disorder	0.11 (1)	0	0
Deafness bilateral	0	0	0.11 (1)
Congenital, Familial, and Genetic Disorders	**0**	**0.10 (1)**	**0**
Hydrocele	0	0.10 (1)	0

In the following paragraphs I summarize the pancreatitis SAEs reported during the RA trials.

WA20494-114672-45707 This 65 year old female received her first dose of ocrelizumab on (b) (6). On (b) (6) (study day 811) she developed abdominal pain and nausea. On (b) (6) she presented to an ED for evaluation. Lab results included: WBC 16.34/uL (ref range: 3.3-11), amylase (B) 1701 (ref range 36-126 U/L), lipase 4233 U/L (22-51), direct bilirubin 2.2 mg/dL (0 – 0.4), total bilirubin 3.9 mg/dL (0.2 – 1.2), AST 314 U/L (<35), CRP 1.7 mg/dL (<0.5). She was hospitalized and received pain medications, intravenous hydration, and antibiotics. An abdominal ultrasound on (b) (6) revealed gallbladder sludge, small stones and pancreatitis. On (b) (6), she underwent ERCP with endoscopic papillotomy with stent insertion and endoscopic retrograde biliary drainage. On (b) (6) she had endoscopic papillotomy, CRE balloon dilation of papilla and stone retrieval. Follow up amylase and lipase returned to normal values (not provided). There was one residual common bile duct stone. As symptoms improved the patient was discharged on (b) (6) when these events were considered resolved.

WA20496-137401-15560 This 44 year old female with a history of cholelithiasis, s/p cholecystectomy, received her first dose of ocrelizumab on (b) (6). On (b) (6), 109 days after her last ocrelizumab dose, she was hospitalized for abdominal pain and nausea and was diagnosed with pancreatitis. Details of the diagnostic evaluation were not provided. Treatment included pain medication, H2 blocker, and anti-nausea medication. The event was considered resolved 4 days later.

WA20496-137416-17042 This 51 year old female received her first dose of ocrelizumab on (b) (6). On (b) (6), approximately 19 weeks after her dosing with study medication, she developed nausea, vomiting, and diarrhea. Four days later she developed right upper quadrant abdominal pain and was admitted to hospital with suspected pancreatitis. Lab results included: WBC (26% high from ULN), neutrophils (> 2x ULN), AST (50% high of ULN), and serum lipase (3xUNL). A CT scan of abdomen showed mild small bowel thickening and minimal pancreatic

inflammation. The abdominal ultrasound showed gallbladder thickening at upper normal limit with no stone and MRCP was normal. She was treated with esomeprazole, hydrocortisone, promethazine, metoclopramide, and morphine. The event was resolved 15 days later.

SAEs in Trials for other Indications

WA20499-SLE
Nine of the 23 ocrelizumab and no placebo patients experienced one or more SAEs. The reported SAEs were cytomegalovirus, pneumonia, pneumocystis jirovecii pneumonia, septic shock, upper respiratory tract infection, urinary tract infection, nephrolithiasis, nephrotic syndrome, renal failure, anemia, thrombocytopenia, pericarditis, gastritis, hyperbilirubinemia, systemic lupus erythematosus, syncope, and asthma.

WA20500-LN
During the first 48 weeks (controlled phase) of WA20500, 27% (34/125) of placebo patients experienced one or more SAE compared to 36% (45/126) of ocrelizumab 400mg patients and 22% (28/127) of ocrelizumab 1000mg patients. SAEs of interest among ocrelizumab patients included pneumonia (n=10), neutropenia (n=5), agranulocytosis (n=3), febrile neutropenia (n=2), appendicitis (n=1). During the SFU an additional 22 SAEs were reported and included infections and events related to progression of underlying disease. No SAEs of cholecystitis or cholelithiasis were reported.

BO 18414-NHL
Six patients (13%, 6/47) experienced SAEs. The reported SAEs were infusion related reactions (2), obliterative bronchiolitis, pleural effusion, bone pain, and neoplasm malignant.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

For RMS trials WA21092/WA21093, and PPMS trial WA25046, the protocols required permanent discontinuation of study treatment for the following:

- Life threatening (Grade 4) IRR that occurred during a previous ocrelizumab infusion
- Ongoing pregnancy
- Active hepatitis B or C infection (new onset, or reactivation for hepatitis B)
- Active TB (new onset or reactivation)
- PML
- Patient's decision or treating Investigator's decision in the best clinical interest of the patient.

RMS trials WA21092/WA21093, but not PPMS trial WA25046 had the following 2 additional permanent discontinuation criteria:

• ALT $\geq$ 10 × ULN, jaundice, or other clinical symptoms of liver dysfunction
• Persisting elevation of ALT > 3 × ULN, or other clinical symptoms of liver dysfunction that did not resolve with interferon beta-1a/placebo dose modification

RMS and PPMS trial patients who withdrew from the study treatment were encouraged to remain in the study for the full duration of the SFU (minimum of 48 weeks following the last infusion).

All MS Trials (Pool B)
69 ocrelizumab patients (3.2%, 69/2,147) discontinued from MS trials for AEs. In the following table, I identify the AEs leading to discontinuation of at least 3 ocrelizumab patients

Table 11 Discontinuations for AEs that occurred for at least 3 ocrelizumab patients, All MS Trials (Pool B)

MedDRA System Organ Class MedDRA Preferred Term	All Exposure to Ocrelizumab (n=2147; 4,485PY)
Patients who discontinued for 1 or more AEs	3.2% (69)
#/100PY	1.5 (69)
Injury, Poisoning, and Procedural Complications	**1.0% (21)**
Infusion related reaction	1.0% (21)
Neoplasms Benign, Malignant, and Unspecified	**0.5% (11)**
Breast cancer[1]	0.2% (5)
Infections and Infestations	**0.3% (7)**
Psychiatric Disorders	**0.3% (6)**
Nervous System Disorders	**0.2%(5)**
General Disorders and Administration Site Conditions	**0.2% (4)**
Musculoskeletal and Connective Tissue Disorders	**0.2% (4)**
Gastrointestinal Disorders	**0.1% (3)**

[1] Includes events coded to Invasive ductal breast carcinoma, Invasive breast carcinoma, and Breast cancer

90 Day Safety Update
In the 90 Day Safety Update, Genentech reported the discontinuation of 6 additional MS patients for adverse events. The new events leading to discontinuation were metastatic malignant melanoma, malignant melanoma, acute hepatitis C, infection, pulmonary tuberculoma, and congestive cardiomyopathy.

RMS Trials Controlled Phase (Pool A)
In the RMS trials, the risk for discontinuation for AEs was higher among interferon beta-1a patients (6.2%, 51/826) than ocrelizumab patients (3.5%, 29/825). The most common AE

leading to discontinuation among ocrelizumab patients was infusion related reactions (1.3%, n=11, IFN beta-1a n=0). No other preferred term was identified as leading to discontinuation of more than 1 ocrelizumab patient. The AEs leading to discontinuation of 1 ocrelizumab patient each were: influenza like illness, fatigue, chest pain, chills, anxiety, insomnia, suicidal ideation, suicide attempt, lymphocytosis, muscle rigidity, osteonecrosis, pain in extremity, psoriatic arthropathy, dermatitis bullous, erythema nodosum, headache, hydrocephalus, cellulitis, urinary tract infection, invasive ductal breast carcinoma, vertigo, gastritis, and diabetes mellitus inadequate control.

PPMS trial Controlled Phase
In the PPMS trial, the overall percentage of patients who discontinued for AEs was similar for ocrelizumab (4.1%, 20/486) and placebo (3.3%, 8/239) treatment groups. Notably, in the SOC Neoplasm Benign, Malignant and Unspecified (including Cysts and Polyps), 1 placebo patient (0.4%) discontinued compared to 7 ocrelizumab patients (1.4%). The AEs leading to treatment discontinuation of more than one ocrelizumab patient were: breast cancer (placebo n=0, ocrelizumab 0.8%, 4/486)[1] and infusion related reactions (placebo 0.4%, n=1; ocrelizumab 0.4%, n=2). The AEs leading to discontinuation of one ocrelizumab patient each were anaplastic large cell lymphoma, endometrial cancer, malignant fibrous histiocytoma, infectious colitis, pneumonia, urinary tract infection, viral infection, MS relapse, optic neuritis, alopecia, skin lesion, aortic valve incompetence, Crohn's disease, depression.
[1] Includes events coded as invasive ductal breast carcinoma, invasive breast carcinoma, and breast cancer.

MS trial WA21493 Controlled Phase
During the controlled phase (first 24 weeks) of the MS dose finding trial WA21493, few AEs led to discontinuation and the frequencies were similar across treatment groups. No placebo patients discontinued for AEs compared to 3.6% (2/55) of ocrelizumab 600mg patients, 1.8% (1/55) of ocrelizumab 1000mg patients and 1.9% (1/54) of Avonex patients. The AEs leading to discontinuation of ocrelizumab patients were hypersensitivity, infusion related reaction (ocrelizumab 600mg), and anxiety (ocrelizumab 1000mg). The Avonex patient discontinued for vomiting.

All RA Trials (Pool E)
3.8% (110/2926) of ocrelizumab patients in RA trials discontinued for AEs. IRRs were the only AEs leading to discontinuation of more than 3 ocrelizumab patients (0.9%, 25/2926). The other AEs leading to discontinuation of at least 2 ocrelizumab patients were malignant melanoma, prostate cancer (3 patients each); arthritis bacterial, herpes simplex, pulmonary TB, upper respiratory tract infection, bladder transitional cell carcinoma, breast cancer, squamous cell carcinoma of the lung, myocardial infarction, and nausea (2 patients each).

RA Controlled Trials (Pool D)

3.4% (32/947) of ocrelizumab 1000mg patients discontinued from RA controlled trials compared to 3.0% (35/1186) of ocrelizumab 400mg patients and 2.1% (21/981) of placebo patients. The only AEs that led to discontinuation of at least 2 ocrelizumab patients and that led to discontinuation more frequently compared to placebo was IRR (ocrelizumab 1000mg 1.0%, 9/947; ocrelizumab 400mg 0.9%, 11/1186; Placebo 0.1%, 1/903).

Discontinuations for AEs in Trials for other Indications

WA20499 - SLE
Aside from 2 deaths, no patients withdrew from this trial for an AE.

WA20500 - LN
By Week 48, 2.4% (3 /125) of PBO patients, 4.8% (6/126) of ocrelizumab 400 mg patients, and 3.1% (4/127) of ocrelizumab 1000 mg discontinued study drug due to an adverse event. One additional patient on ocrelizumab 1000 mg withdrew for an AE beyond Week 48. The events leading to discontinuation in the ocrelizumab 1000mg group were agranulocytosis (2), spontaneous abortion, cervical carcinoma, and herpes zoster. The events leading to discontinuation in the ocrelizumab 400mg group were IRR, angioneurotic edema, cryptococcal meningoencephalitis, suspected infection, renal cell carcinoma, and pneumocystis jiroveci. The events leading to discontinuation of the placebo patients were cerebral vasculitis, abscess limb, and hepatitis/thrombocytopenia.

BO18414 - NHL
4 of 47 patients withdrew from the study for AEs. The AEs leading to discontinuation were bronchiolitis obliterans, pleural effusion, neoplasm malignant, and IRR.

8.4.4. Significant Adverse Events

AEs Leading to Treatment Modification/Dose Interruptions

All MS Trials (Pool B)
Genentech reported that 4.9% (106/2147) of ocrelizumab patients had dose interruptions for AEs. The most common AEs resulting in dose interruptions (at least 5 patients) were IRR (n=20), urinary tract infections (n=8), nasopharyngitis (n=6), upper respiratory tract infection (n=6), and influenza (n=5).

In the 90 Day Safety Update, Genentech noted that an additional 9 patients had AEs leading to dose interruptions. These AEs leading to dose interruptions were similar to those listed above and after their inclusion, did not change the list of common AEs leading to dose interruptions above.

AEs by Intensity
All MS Trials (Pool B)
Genentech reported that 81% of MS patients had AEs that were Grade 1 or 2 in intensity. 302 patients (14%) had 460 AEs that were Grade 3. The most common Grade 3 events (reported at least 5 times) were IRR (n=37), headache (n=14), back pain (n=11), urinary tract infection (n=11), arthralgia (n=8), cholecystitis/cholecystitis acute/cholelithiasis (n=8), depression (n=7), fatigue (n=7), influenza (n=7), pneumonia (n=7), upper respiratory tract infection (n=5), and influenza-like illness (n=5). 38 patients (1.8%) had 43 events that were Grade 4 and all but 1 (hyperamylasemia) were reported as SAEs. There were 8 patients (0.4%) with Grade 5 or fatal events (all summarized above).

In the 90 Day Safety Update, Genentech reported that 80% of MS patients had AEs that were Grade 1 or 2. 355 patients had 552 AEs that were Grade 3. 45 patients had 51 AEs that were Grade 4 and all but 1 (hyperamylasemia) were reported as SAEs. There were 8 patients with Grade 5 or fatal events (all summarized above).

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The most commonly reported TEAEs in the MS trials were infections, IRRs, headache, back pain, arthralgia, fatigue, and depression. In the controlled trials, ocrelizumab patients had a higher risk than comparator patients for various infections, IRRs, cough, migraine, insomnia, and cholecystitis/cholelithiasis.

All MS Trials (Pool B)
80% (1,706/2,147) of patients treated with ocrelizumab experienced one or more TEAEs and 11,376 TEAEs were reported during MS trials. Events subsumed under the Infections and Infestations SOC were most commonly reported (1,169 patients reported 3,389 events). In the table below, I identify TEAEs reported by at least 1% of patients.

Table 12 AEs Reported for at least 1% of Ocrelizumab Patients, All MS Trials (Pool B)

MedDRA System Organ Class MedDRA Preferred Term	All Exposure to Ocrelizumab (n=2,147; 4,485PY)
Total with at least 1 AE	79.5% (1,706)
#/100PY	38.0 (1,706)
Infections and Infestations	**54.4% (1,169)**
Upper respiratory tract infection[1]	32.8% (705)
Urinary tract infection[2]	15.4% (331)
Influenza	5.9% (127)

Bronchitis[3]	5.6% (121)
Gastroenteritis[4]	5.3% (113)
Herpes infections[5]	5.2% (111)
Vulvovaginal infections[6, *]	4.1% (55)
Respiratory tract infection[7]	3.4% (72)
Tooth infection[8]	2.3% (49)
Viral infection	2.2% (47)
Otitis Media[9]	1.9% (40)
Conjunctivitis	1.5% (32)
Pneumonia[10]	1.2% (26)
Injury, Poisoning, and Procedural Complications	**41.5% (890)**
Infusion related reactions	34.2% (734)
Fractures[11]	2.5% (54)
Contusion	1.8% (38)
Ligament sprain	1.0% (22)
Nervous System Disorders	**26.4% (566)**
Headache	10.2% (218)
Parasthesia	3.5% (76)
Dizziness	3.1% (67)
Migraine	2.5% (53)
Hypoesthesia	2.1% (46)
Muscle spasticity	1.5% (32)
Neuralgia	1.3% (28)
Balance disorder	1.1% (23)
Sciatica	1.1% (23)
Syncope	1.0% (22)
Musculoskeletal and Connective Tissue Disorders	**25.2% (542)**
Back pain	7.5% (162)
Arthralgia	6.0% (129)
Pain in extremity	4.6% (98)
Muscle spasms	2.8% (60)
Musculoskeletal pain	2.5% (53)
Muscular weakness	2.4% (44)
Myalgia	1.9% (41)
Neck pain	1.3% (27)
General Disorders and Administration Site Conditions	**19.7% (422)**
Fatigue	6.6% (141)
Influenza like illness	2.8% (61)
Pyrexia	2.3% (50)
Edema peripheral	1.8% (38)

Gait disturbance	1.4% (29)
Asthenia	1.2% (25)
Pain	1.1% (23)
Gastrointestinal Disorders	**18.9% (406)**
Abdominal pain[12]	3.7% (80)
Diarrhea	3.1% (67)
Nausea	3.1% (66)
Constipation	2.7% (59)
Vomiting	1.9% (41)
Psychiatric Disorders	**15.5% (333)**
Depression	6.4% (137)
Insomnia	4.4% (94)
Anxiety	3.1% (66)
Skin and Subcutaneous Tissue Disorders	**13.6% (293)**
Rash	2.6% (55)
Alopecia	1.3% (28)
Pruritus	1.3% (27)
Eczema	1.1% (24)
Respiratory, Thoracic, and Mediastinal Disorders	**11.5% (246)**
Cough	3.4% (73)
Oropharyngeal pain	1.7% (37)
Investigations	**7.5% (160)**
Blood creatinine phosphokinase increased	1.1% (23)
Renal and Urinary Disorders	**6.6% (142)**
Micturition urgency	1.0% (21)
Reproductive System and Breast Disorders	**5.8% (125)**
Vascular Disorders	**5.8% (125)**
Hypertension	2.5% (54)
Eye Disorders	**5.2% (112)**
Vision blurred	1.0 (22)
Metabolism and Nutrition Disorders	**5.2% (111)**
Blood and Lymphatic System Disorders	**4.4% (94)**
Anemia	1.1% (24)
Ear and Labyrinth Disorders	**3.8% (81)**
Vertigo	1.7% (36)
Neoplasms Benign, Malignant, and Unspecified	**3.0% (65)**
Cardiac Disorders	**2.7% (59)**
Immune System Disorders	**2.0% (44)**
Hepatobiliary disorders	**1.5% (32)**
Endocrine Disorders	**1.1% (24)**

[1]Includes events coded to upper respiratory tract infection, sinusitis, pharyngitis, nasopharyngitis, rhinitis, viral upper respiratory tract infection, laryngitis, tonsillitis, acute tonsillitis, acute sinusitis, tracheitis, pharyngitis streptococcal, chronic sinusitis, pharyngitis bacterial, pharyngotonsilitis, upper respiratory tract infection bacterial, tonsillitis bacterial, viral rhinitis, viral tonsillitis, viral pharyngitis
[2]Includes events coded to urinary tract infection, pyelonephritis, pyelonephritis acute, bacterial pyelonephritis, urosepsis, cystitis, Escherichia urinary tract infection, kidney infection, urinary tract infection bacterial, and urinary tract infection fungal
[3] Includes events coded to bronchitis, bronchitis chronic, sinobronchitis, tracheobronchitis
[4] Includes events coded to gastroenteritis, gastroenteritis viral, gastroenteritis salmonella, gastrointestinal bacterial infection, enteritis, enteritis infectious, enterocolitis infectious, gastrointestinal viral infection, gastrointestinal infection
[5] Includes events coded to genital herpes, genital herpes simplex, herpes ophthalmic, herpes simplex, herpes zoster, herpes virus infection, ophthalmic herpes simplex, oral herpes, varicella
[6] Includes events coded to vaginal infection, vulvovaginal mycotic infection, vulvovaginal candidiasis, bacterial vaginosis, vaginitis bacterial
[7] Includes events coded to respiratory tract infection, respiratory tract infection viral, respiratory tract infection bacterial
[8] Includes events coded to tooth infection, tooth abscess
[9] Includes events coded to otitis media, otitis media acute, ear infection, ear infection viral
[10]Includes events coded to pneumonia, bronchopneumonia, pneumonia viral and
[11] Includes events coded to ankle fracture, clavicle fracture, facial bones fracture, femoral neck fracture, femur fracture, fibula fracture, foot fracture, hand fracture, humerus fracture, lower limb fracture, lumbar vertebral fracture, multiple fractures, radius fracture, rib fracture, skull fracture, spinal compression fracture, stress fracture, tibia fracture, thoracic vertebral fracture, upper limb fracture, wrist fracture
[12] Includes events coded to abdominal discomfort, abdominal pain, abdominal pain upper, abdominal pain lower, abdominal tenderness, epigastric discomfort, gastrointestinal pain
*Includes only females in the denominator of the risk calculation

In the 90 Day Safety Update, Genentech reported that 81% (1845/2297) of patients experienced one or more AEs. After the inclusion of data through the 90 Day Safety Update, the rate of AEs was 242/100PY compared to a rate of 254/100PY reported in the ISS. There was no meaningful change in the most commonly reported SOCs or AEs reported when comparing the data in the 90 Day Safety Update to the data presented in the ISS.

RMS Trials Controlled Phase (Pool A)
The percentage of patients in each treatment arm reporting one or more TEAEs was the same for ocrelizumab (83.3%, 687/825) and interferon beta-1a (83.3%, 688/826). The sponsor's AE table for RMS patients in proposed labeling identifies drug related AEs occurring in at least (b) (4) of ocrelizumab patients and more than comparator. In the table below, I identify all TEAEs

occurring in at least 2% of ocrelizumab patients and greater than interferon. I regrouped selected AE preferred terms that appeared to split related events into multiple different terms.

Table 13 AEs that occurred in >=2% of Ocrelizumab patients and more frequently than in interferon beta-1a patients, RMS Trials Controlled Phase (Pool A)

MedDRA System Organ Class MedDRA Preferred Term	IFN beta-1a (n=826)	Ocrelizumab (n=825)
Patients with at least one AE	**83.3% (688)**	**83.3% (687)**
Infections and Infestations	**52.4% (433)**	**58.4% (482)**
Upper respiratory tract infections[1]	29.0% (239)	35.8% (295)
Herpes infections[2]	3.5% (29)	5.9% (49)
Gastroenteritis[3]	4.1% (34)	5.7% (47)
Bronchitis[4]	3.6% (30)	4.2% (44)
Injury, Poisoning, and Procedural Complications	**18.8% (155)**	**40.4% (333)**
Infusion related reactions	9.7% (80)	34.3% (283)
Nervous System Disorders	**30.5% (252)**	**27.2% (224)**
Migraine	1.9% (16)	3.0% (25)
Musculoskeletal and connective tissue disorders	**25.1% (207)**	**24.7% (204)**
Back pain	4.5% (37)	6.4% (53)
Pain in extremity	4.2% (35)	4.7% (39)
Gastrointestinal Disorders	**18.9% (156)**	**20.7% (171)**
Abdominal pain[5]	3.6% (30)	4.7% (39)
Diarrhea	2.5% (21)	3.4% (28)
Constipation	2.1% (17)	2.8% (23)
Vomiting	1.3% (11)	2.1% (17)
Psychiatric disorders	**17.4% (144)**	**18.1% (149)**
Depression	6.5% (54)	7.8% (64)
Insomnia	4.6% (38)	5.6% (46)
Anxiety	3.3% (27)	3.4% (28)
Skin and subcutaneous tissue disorders	**12.7% (105)**	**14.2% (117)**
Pruritus	0.7% (6)	2.1% (17)
Respiratory, thoracic, and mediastinal disorders	**10.3% (85)**	**10.5% (87)**
Cough	1.5% (12)	3.0% (25)
Hepatobiliary disorders	**2.4% (20)**	**1.6% (13)**
Cholecystitis/Cholelithiasis[6]	1.0% (8)	1.6% (13)
Neoplasms Benign, Malignant, and	**1.8% (15)**	**2.7% (22)**

Unspecified		

[1]Includes events coded to upper respiratory tract infection, sinusitis, pharyngitis, nasopharyngitis, rhinitis, viral upper respiratory tract infection, laryngitis, tonsillitis, acute tonsillitis, acute sinusitis, tracheitis, pharyngitis streptococcal, chronic sinusitis, pharyngitis bacterial, pharyngotonsilitis, viral rhinitis, viral sinusitis, viral tonsillitis, viral pharyngitis
[2] Includes events coded to herpes simplex, herpes virus infection, herpes zoster, genital herpes, ophthalmic herpes simplex, oral herpes, varicella
[3] Includes events coded as enteritis, enteritis infectious, enterocolitis infectious, gastroenteritis, gastroenteritis viral, gastrointestinal infection, gastrointestinal viral infection
[4] Includes events coded to bronchitis bronchitis viral, sinobronchitis, tracheobronchitis
[5] Includes events coded to abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, epigastric discomfort, gastrointestinal pain
[6] Includes events coded to biliary sepsis, cholelithiasis, cholecystitis acute, cholecystitis chronic, cholecystitis, and gallbladder disorder

In the controlled phases of the RMS trials, there were 2 events of pancreatitis (pancreatitis, pancreatitis acute) in ocrelizumab patients and none in interferon patients.

PPMS Trial Controlled Phase
A higher percentage of ocrelizumab patients (95%, 462/486) reported one or more AE compared to placebo patients (90%, 215/239). The sponsor's AE table for PPMS patients in proposed labeling identifies drug related AEs occurring in at least (b) (4) of ocrelizumab patients and more than comparator. In the table below, I identify all TEAEs occurring in at least 2% of ocrelizumab patients and greater than placebo. I include other AEs where there was a suggestion of increased risk with ocrelizumab in prior analyses, but not in this trial. I regrouped selected AE preferred terms that appeared to split related events into multiple different terms.

Table 14 AEs that occurred in >=2% of Ocrelizumab patients and more frequently than in placebo patients, PPMS Trial Controlled Phase

MedDRA System Organ Class MedDRA Preferred Term	Placebo (n=239)	Ocrelizumab (n=486)
Patients with at least 1 SAE	**90.0% (215)**	**95.1% (462)**
Infections and infestations	**67.8% (162)**	**69.8% (339)**
Upper respiratory tract infection[1]	36.8% (88)	38.7% (188)
Influenza	8.8% (21)	11.5% (56)
Bronchitis[2]	5.4% (13)	6.6% (32)
Respiratory tract infection[3]	1.3% (3)	3.3% (16)
Herpes infections[4]	2.9% (7)	4.3% (21)
Viral infection	1.7% (4)	3.1% (15)

Injury, Poisoning, and Procedural Complications	**43.5% (104)**	**54.1% (263)**
Infusion related reactions	25.5% (61)	39.9% (194)
Musculoskeletal and Connective Tissue Disorders	**41.0% (98)**	**37.2% (181)**
Muscular weakness	2.5% (6)	2.9% (14)
Nervous System Disorders	**33.1% (79)**	**35.8% (174)**
Dizziness	4.6% (11)	5.1% (25)
Paresthesia	1.7% (4)	2.9% (14)
Neuralgia	0.8% (2)	2.5% (12)
Muscle spasticity	1.3% (3)	2.1% (10)
Sciatica	0.8% (2)	2.3% (11)
Migraine	1.3% (3)	1.4% (7)
General Disorders and Administration Site Conditions	**25.1% (60)**	**26.7% (130)**
Edema peripheral	5.0% (12)	5.3% (26)
Gait disturbance	3.3% (8)	3.9% (19)
Influenza like illness	2.1% (5)	2.9% (14)
Psychiatric Disorders	**24.7% (59)**	**18.3% (89)**
Insomnia	5.0% (12)	5.6% (27)
Skin and Subcutaneous Tissue	**18.4% (44)**	**20.4% (99)**
Rash	2.1% (5)	2.9% (14)
Eczema	2.1% (5)	2.3% (11)
Respiratory, Thoracic, and Mediastinal Disorders	**14.6% (35)**	**17.9% (87)**
Cough	3.3% (8)	6.0% (29)
Catarrh	0.8% (2)	2.1% (10)
Vascular Disorders	**10.9% (26)**	**11.1% (54)**
Hypertension	3.8% (9)	5.1% (25)
Hepatobiliary Disorders	**2.5% (6)**	**2.3% (11)**
Cholecystitis/Cholelithiasis[5]	0.4% (1)	1.2% (6)

[1] Includes events coded to upper respiratory tract infection, sinusitis, pharyngitis, nasopharyngitis, rhinitis, viral upper respiratory tract infection, laryngitis, tonsillitis, acute tonsillitis, tracheitis, pharyngitis streptococcal, chronic sinusitis, pharyngotonsilitis,
[2] Includes events coded to bronchitis, bronchitis viral, bronchitis chronic
[3] Includes events coded to respiratory tract infection, respiratory tract infection bacterial, respiratory tract infection viral
[4] Includes events coded to herpes simplex, herpes viral infection, herpes zoster, herpes zoster oticus, oral herpes
[5] Includes events coded to cholelithiasis, cholecystitis acute, cholecystitis chronic

In the controlled phase of the PPMS trials, there were 2 events of pancreatitis (both coded as pancreatitis acute) in ocrelizumab patients and none in placebo patients.

MS trial WA21493 Controlled Phase
During the controlled phase (first 24 weeks) of the MS dose finding trial WA21493, AEs were reported for 70.4% (38/54) of placebo patients, 63.6% (35/55) of ocrelizumab 600mg patients, 65.5% (35/55) of ocrelizumab 1000mg patients and 59.3% (32/54) of Avonex patients. In the table below, I identify TEAEs from the controlled phase that were reported by at least 5% of ocrelizumab patients and that were more frequent compared to placebo.

Table 15 AEs that occurred in at least 5% of Ocrelizumab patients and that occurred more frequently compared to placebo, Trial WA21493, Controlled Phase (Following first dose)

Adverse Event	Placebo n=54	Ocrelizumab 600mg n=55	Ocrelizumab 1000mg n=55	Avonex n=54
Infusion related reactions	11.1% (6)	34.5% (19)	47.3% (26)	-
Headache	7.4% (4)	7.3% (4)	14.5% (8)	14.8% (8)
Upper respiratory tract infection	3.7% (2)	9.1% (5)	12.7% (7)	3.7% (2)
Fatigue	1.9% (1)	3.6% (2)	10.9% (6)	5.6% (3)
Back pain	1.9% (1)	3.6% (2)	5.5% (3)	3.7% (2)
Anxiety	1.9% (1)	5.5% (3)	3.6% (2)	1.9% (1)
Insomnia	1.9% (1)	0	7.3% (4)	1.9% (1)
Influenza	0	1.8% (1)	5.5% (3)	0
Rash	0	5.5% (3)	0	1.9% (1)
Migraine	0	5.5% (3)	0	0

All RA Trials (Pool E)
In their TEAE presentation for the overall RA trials (Pool E), Genentech calculated the number of events/100PYs. In the following table, I identify the TEAEs that occurred at a rate of at least 1/100PYs.

Table 16 SOCs/TEAEs reported at a frequency of least 1/100PY, All RA trials (Pool E)

MedDRA System Organ Class MedDRA Preferred Term	Exposure to Ocrelizumab (n=2925, 7323.9 PY)
Total TEAEs/100 PY	246.2 (18030)
Infections and Infestations	**73.8 (5404)**

Upper Respiratory tract infection	12.3 (904)
Nasopharyngitis	8.1 (596)
Urinary tract infection	6.6 (487)
Bronchitis	5.8 (423)
Sinusitis	4.3 (314)
Influenza	3.0 (220)
Gastroenteritis	1.9 (142)
Pneumonia	1.8 (133)
Herpes zoster	1.6 (120)
Pharyngitis	1.6 (119)
Gastroenteritis viral	1.2 (89)
Oral herpes	1.2 (87)
Upper respiratory tract infection	1.1 (80)
Cystitis	1.0 (75)
Injury, Poisoning, and Procedural Complications	**30.9 (2262)**
Infusion related reaction	18.9 (1385)
Contusion	1.3 (93)
Fall	1.2 (88)
Gastrointestinal Disorders	**26.4 (1932)**
Nausea	4.0 (296)
Diarrhea	3.6 (262)
Dyspepsia	1.6 (116)
Constipation	1.4 (103)
Vomiting	1.3 (93)
Abdominal pain upper	1.1 (83)
Gastritis	1.1 (81)
Gastroesophageal reflux disease	1.1 (81)
Abdominal pain	1.0 (74)
Musculoskeletal and Connective Tissue Disorders	**21.0 (1536)**
Back pain	2.9 (210)
Rheumatoid arthritis	2.3 (170)
Arthralgia	1.6 (119)
Osteoarthritis	1.2 (85)
Pain in extremity	1.0 (75)
Skin and Subcutaneous Tissue Disorders	**12.0 (876)**
Rash	1.9 (139)
Nervous System Disorders	**11.8 (865)**
Headache	3.5 (258)
Dizziness	1.6 (116)
Respiratory, Thoracic, and Mediastinal Disorders	**0.9 (65)**

Cough	2.3 (168)
General Disorders and Administration Site Conditions	**8.1 (590)**
Edema peripheral	1.4 (100)
Fatigue	1.2 (91)
Metabolism and Nutrition Disorders	**6.9 (503)**
Hypercholesterolemia	1.0 (76)
Vascular Disorders	**6.8 (500)**
Hypertension	4.1 (301)
Psychiatric disorders	**5.8 (424)**
Insomnia	1.9 (140)
Depression	1.9 (139)
Hepatobiliary disorders	**3.9 (287)**
Drug induced liver injury	1.7 (127)
Blood and Lymphatic System Disorders	**3.9 (286)**
Anemia	1.5 (112)

RA Trials Controlled Phases (Pool D)
In a 7/14/16 response to a request from the Division, Genentech submitted a table of TEAEs from RA Trials Controlled phases (Pool D). I reviewed this table to identify TEAEs reported by at least 10 RA patients within an ocrelizumab dose group and with a relative risk compared to placebo of at least 2. I list those TEAEs in the table below.

Table 17 TEAEs/100PY, Where reported by at least 10 ocrelizumab patients in a dose group and where RR compared to placebo was >= 2.0, RA Controlled Trials, Pool D

MedDRA Preferred Term	Placebo (n=981, 903 PY)	OCR 400mg (n=1186, 1004PY)	OCR 1000mg (N=947, 906PY)
Infusion related reactions	19.5 (176)	39.0 (392)	41.4 (375)
Weight increased	0.3 (3)	1.0 (10)	1.1 (10)
Hyperlipidemia	0.6 (5)	0.8 (8)	1.3 (12)
Hypercholesterolemia	0.8 (7)	2.1 (21)	1.5 (14)
Palpitations	0.4 (4)	1.0 (10)	0.3 (3)
Acute sinusitis	0.1 (1)	0.4 (4)	1.2 (11)
Oral herpes	0.4 (4)	2.1 (21)	1.4 (13)
Tooth abscess	0.2 (2)	1.0 (10)	1.0 (9)
Conjunctivitis	0.3 (3)	1.3 (13)	2.1 (19)
Dyspnea	0.7 (6)	1.8 (18)	0.9 (8)
Flushing	0.2 (2)	0.5 (5)	1.5 (14)
Dermatitis contact	0.6 (5)	0.5 (5)	1.1 (10)
Abdominal pain	0.9 (8)	1.8 (18)	1.4 (13)

Bursitis	0.4 (4)	0.8 (8)	1.2 (11)
Arthralgia	0.9 (8)	2.3 (23)	0.8 (7)

In addition to the common TEAEs listed above, I reviewed TEAEs that emerged as potentially related to ocrelizumab based on data from the MS trials.

Unlike the MS trials, there did not appear to be an increased risk for cholelithiasis/cholecystitis/acute cholecystitis events with ocrelizumab in the controlled phases of RA trials. In RA trials there were 8 events coded to cholelithiasis/cholecystitis/acute cholecystitis in the placebo group (0.9/100PY) compared to 2 (0.2/100PY) in the ocrelizumab 400mg group and 5 (0.6/100PY) in the ocrelizumab 1000mg group.

In the controlled phases of RA trials, no placebo or ocrelizumab 400mg patients had an AE of pancreatitis or acute pancreatitis compared to 2 patients (0.2/100PY) in the ocrelizumab 1000mg group.

AEs in Trials for other Indications

WA20499 - SLE
50% of the placebo patients (5/10) experienced an AE compared to 91% (10/11) ocrelizumab 400 mg patients, and 67% of (8/12) of the ocrelizumab 1000 mg patients. The most commonly reported AEs by SOC were Infections and Infestations (placebo 30%, 3/10; ocrelizumab 400mg 73%, 8/11; ocrelizumab 1000mg 50%, 6/12) ; Gastrointestinal Disorders (placebo 20%, 2/10; ocrelizumab 400mg 45.5%, 5/11; ocrelizumab 1000mg 25%, 3/12), Nervous System Disorders (placebo 10%, 1/10; ocrelizumab 400mg 36.4%, 4/11; ocrelizumab 1000mg 25%, 3/12), and Psychiatric Disorders (placebo 10%, 1/10; ocrelizumab 400mg 27.3%, 3/11; ocrelizumab 1000mg 25%, 3/12).

WA20500 - LN
The CSR for this study identified TEAEs that occurred in at least 10% of any treatment group during the first 48 weeks of the trial. In the following table, I identify the TEAEs that occurred in at least 10% of an ocrelizumab treatment group and that were more frequent than in the placebo group.

Table 18 AEs Occurring in at least 10% of Ocrelizumab patients and that occurred more frequently compared to placebo, Trial WA20500

MedDRA Preferred Term	Placebo n=125	Ocrelizumab 400mg n=126	Ocrelizumab 1000mg n=127
Anemia	4.0% (5)	10.3% (13)	4.7% (6)
Leukopenia	5.6% (7)	13.5% (17)	8.7% (11)

Neutropenia	4.0% (5)	11.1% (14)	7.9% (10)
Diarrhea	18.4% (23)	18.3% (23)	22.0% (28)
Nausea	4.8% (6)	10.3% (13)	3.1% (4)
Infusion related reactions	8.8% (11)	11.9% (15)	14.2% (18)
Upper respiratory tract infection	12.8% (16)	15.1% (19)	15.0% (19)
Urinary tract infection	7.2% (9)	17.5% (22)	11% (14)

BO18414 - NHL
In this trial which used 3 different ocrelizumab dosing regimens (200 mg/m2 for 8 doses n=15; 375 mg/m2 for 8 doses n=16; 375 mg/m2 for 1 dose followed by 750 mg/m2 for7 doses n=16) the only AEs reported by at least 10% of subjects were IRRs, asthenia, and nasopharyngitis.

8.4.6. Laboratory Findings

General Laboratory Results
There did not appear to be consistent evidence of effects of ocrelizumab on general lab test results in the MS trials. Mean changes in lab results were generally similar by treatment with few exceptions. Increases in creatine kinase in ocrelizumab patients compared to interferon were observed RMS trials. Similar mean change differences were not observed in the PPMS trial. A higher percentage of ocrelizumab patients in RMS trials also had high abnormal creatine kinase lab results compared interferon, with the majority of these being single occurrences. The clinical significance of this finding is not known. There were no cases of rhabdomyolysis or myopathy AEs in ocrelizumab patients and myalgia AEs occurred more frequently in comparator patients compared to ocrelizumab patients in the RMS and PPMS trials. Ocrelizumab patients more frequently had low neutrophil and low lymphocyte count results than placebo patients in the PPMS trial. Ocrelizumab did not appear to result in increased risk for transaminase elevations and no Hy's law cases were identified in any ocrelizumab patients.

Mean Change from Baseline Analyses

RMS Trials Controlled Phase (Pool A)
Mean change from baseline for lab test results did not strongly suggest ocrelizumab-related effects for the majority of tested analytes. The interferon beta-1a group experienced mean increases in alanine transaminase, aspartate transaminase and gamma glutamyl transferase values and decreases in platelets and white blood cell counts compared with the ocrelizumab group. Lymphocytes decreased slightly in both treatment groups. Ocrelizumab patients experienced mean increases in creatine kinase while patients in the interferon beta-1a group generally experienced mean decreases. The significance of these results is not clear. I provide creatine kinase mean changes from baseline below.

Table 19 Mean change from baseline creatine kinase, RMS trials Controlled Phase (Pool A)

Study Week	Interferon beta-1a	Ocrelizumab
Week 2	-16.8	-5.4
Week 12	-10.5	15.9
Week 24	-3.9	8.5
Week 36	-16.0	13.2
Week 48	-6.7	14.6
Week 60	-3.2	9.6
Week 72	-1.4	13.6
Week 84	12.7	12.2
Week 96	-2.8	16.5

PPMS Trial Controlled Phase
Mean Change from Baseline Analyses
Ocrelizumab patients experienced mean declines in lymphocytes starting at week 12 that were lower than the mean changes in the placebo group and that remained steady through week 120. I provide those results below.

Table 20 Mean change from baseline lymphocytes, PPMS trial Controlled Phase

Study Week	Placebo	Ocrelizumab
Week 12	0.166	-0.336
Week 24	-0.014	-0.331
Week 36	0.009	2.913
Week 48	-0.040	-0.236
Week 60	-0.031	-0.288
Week 72	-0.026	-0.342
Week 84	-0.007	-0.312
Week 96	0.163	-0.367
Week 108	-0.011	-0.273
Week 120	-0.061	-0.340

The differential mean change in creatine kinase by treatment that was observed in the RMS trials was not observed in the PPMS trial. Although the mean changes in creatine kinase were small and similar when comparing treatment groups, the mean changes in creatine kinase were higher in placebo patients compared to ocrelizumab patients at most trial visits (CSR WA25046).

Lab Abnormalities

RMS Trials Controlled Phase (Pool A)
In the table below, I identify analytes for which ocrelizumab patients more frequently had a lab abnormality compared to interferon beta-1a. The risk differences for these abnormalities were low and the abnormalities generally were not persistent.

Table 21 Lab Analytes for which ocrelizumab patients more frequently had an abnormal result compared to interferon beta-1a, RMS Trials Controlled Phase (Pool A)

Analyte	Value	Interferon	Ocrelizumab
Calcium low	N	823	818
	Single, not last	3.0% (25)	3.7% (30)
	Last or replicated	0.2% (2)	0
	Any abnormality	3.3% (27)	3.7% (30)
Creatine Kinase high	N	823	818
	Single, not last	5.7% (47)	7.8% (64)
	Last or replicated	1.2% (10)	0.6% (5)
	Any abnormality	6.9% (57)	8.4% (69)
Eosinophils high	N	823	818
	Single, not last	0.1% (1)	0.5% (4)
	Last or replicated	0	0.1% (1)
	Any abnormality	0.1% (1)	0.6% (5)
Hematocrit (high)	N	823	817
	Single, not last	0.1% (1)	0.2% (2)
	Last or replicated	0	0
	Any abnormality	0.1% (1)	0.2% (2)
LDH (high)	N	822	818
	Single, not last	0	0.2% (2)
	Last or replicated	0	0
	Any abnormality	0	0.2% (2)
Neutrophil (high)	N	823	818
	Single, not last	1.9% (16)	5.7% (47)
	Last or replicated	0.4% (3)	1.3% (11)
	Any abnormality	2.3% (19)	7.1% (58)
Sodium (low)	N	823	818
	Single, not last	0.1% (1)	0.5% (4)
	Last or replicated	0	0
	Any abnormality	0.1% (1)	0.5% (4)
Bilirubin (high)	N	820	816
	Single, not last	0.1% (1)	0.5% (4)
	Last or replicated	0	0

	Any abnormality	0.1% (1)	0.5% (4)
WBC (high)	N	823	818
	Single, not last	0.2% (2)	0.4% (3)
	Last or replicated	0	0
	Any abnormality	0.2% (2)	0.4% (3)

Interferon beta-1a patients more frequently had ALT, AST, lymphocyte (low), neutrophil (low), white blood cell (low) results that met the abnormal criteria compared to ocrelizumab.

PPMS Trial Controlled phase
In the table below, I identify analytes for which ocrelizumab patients more frequently had a lab abnormality compared to placebo. The risk differences for these abnormalities were low and the abnormalities were infrequently replicated.

Table 22 Lab Analytes for which ocrelizumab patients more frequently had an abnormal result compared to placebo, PPMS Trial Controlled Phase

Analyte	Value	Placebo	Ocrelizumab
Calcium low	N	239	481
	Single, not last	2.1% (5)	2.5% (12)
	Last or replicated	0.4% (1)	0.2% (1)
	Any abnormality	2.5% (6)	2.7% (13)
Creatinine high	N	239	481
	Single, not last	0	0
	Last or replicated	0	0.2% (1)
	Any abnormality	0	0.2% (1)
Eosinophils high	N	239	482
	Single, not last	0.8% (2)	0.6% (3)
	Last or replicated	0	0.4% (2)
	Any abnormality	0.8% (2)	1.0% (5)
GGT (high)	N	239	480
	Single, not last	2.5% (6)	2.3% (11)
	Last or replicated	2.1% (5)	4.6% (22)
	Any abnormality	4.6% (11)	6.9% (33)
Hematocrit (low)	N	239	481
	Single, not last	0	1.0% (5)
	Last or replicated	0.4% (1)	0.8% (4)
	Any abnormality	0.4% (1)	1.8% (9)
Hematocrit (high)	N	239	481
	Single, not last	0	0
	Last or replicated	0	0.2% (1)

	Any abnormality	0	0.2% (1)
Hemoglobin (low)	N	239	482
	Single, not last	0	1.2% (6)
	Last or replicated	1.7% (4)	2.1% (10)
	Any abnormality	1.7% (4)	3.3% (16)
Lymphocytes (low)	N	239	482
	Single, not last	3.8% (9)	4.8% (23)
	Last or replicated	1.3% (3)	2.1% (10)
	Any abnormality	5.0% (12)	6.8% (33)
Neutrophils (low)	N	239	482
	Single, not last	1.7% (4)	3.9% (19)
	Last or replicated	0	0.6% (3)
	Any abnormality	1.7% (4)	4.5% (22)
Neutrophils (high)	N	239	482
	Single, not last	10.0% (24)	12.9% (62)
	Last or replicated	2.5% (6)	3.5% (17)
	Any abnormality	12.6% (30)	16.4% (79)
Phosphorus (high)	N	239	481
	Single, not last	1.7% (4)	2.3% (11)
	Last or replicated	0	0.4% (2)
	Any abnormality	1.7% (4)	2.7% (13)
RBC (low)	N	239	482
	Single, not last	0.4% (1)	1.2% (6)
	Last or replicated	0.8% (2)	0.2% (1)
	Any abnormality	1.2% (3)	1.5% (7)
Sodium (low)	N	239	481
	Single, not last	0	0.4% (2)
	Last or replicated	0	0
	Any abnormality	0	0.4% (2)
WBC (low)	N	239	482
	Single, not last	2.1% (5)	2.9% (14)
	Last or replicated	0	1.0% (5)
	Any abnormality	2.1% (5)	3.9% (19)

Analysis for transaminase elevations
Lab data from the RMS trials controlled phase and the PPMS trial controlled trial did not suggest an increased risk of transaminase elevations with ocrelizumab. I provide those results below.

Table 23 Post baseline Transaminase elevations MS Trials Controlled Phase

RMS Trials Controlled Phase (Pool A)		
Transaminase elevation cutoff	Interferon beta-1a	Ocrelizumab
AST >3-<=5xULN	3.2% (26/822)	1% (8/818)
>5-<=10xULN	1.0% (8/822)	0
>10-<=20xULN	0.1% (1/822)	0
>=20xULN	0	0
ALT >3-<=5xULN	6.7% (55/823)	1.7% (14/818)
>5-<=10xULN	1.8% (15/823)	0.1% (1/818)
>10-<=20xULN	0.5% (1)	0.1% (1)
>20xULN	0	0
PPMS Trial Controlled Phase	Placebo	Ocrelizumab
AST >3-<=5xULN	0.8% (2/239)	0.6% (3/481)
>5-<=10xULN	0.4% (1/239)	0.2% (1/481)
>10-<=20xULN	0.8% (2/239)	0.2% (1/481)
>=20xULN	0	0
ALT >3-<=5xULN	0.8% (2/239)	2.3% (11/481)
>5-<=10xULN	2.1% (5/239)	0.6% (3/481)
>10-<=20xULN	0	0
>20xULN	0.8% (2/239)	0.2% (1/481)

Analysis for Hy's Law liver injury cases
Genentech identified no cases in the MS trials of ocrelizumab patients with increases in transaminases >=3xULN that were associated with increased total bilirubin.

Lab related AEs
In all MS trials (Pool B) one ocrelizumab patient experienced an SAE under the SOC Investigations (ALT elevated). Subject WA21092-206568-1920921 was a 42 year old male who had a screening ALT of 67U/L (ULN 43U/L). AST and GGT were also just above ULN at screening. On (b) (6), he entered the controlled phase and received ocrelizumab. During controlled phase treatment, ALT fluctuated between upper 60s-low 90s. He completed the controlled phase and continued open label ocrelizumab. On (b) (6) he was hospitalized for evaluation of ALT 141U/L, AST 72 U/L, and total bilirubin 20umol/L. A CT showed diffuse parenchymal changes and HIV and hepatitis tests were negative. He was discharged and continued in the study. Transaminases continued to be mildly elevated.

No AEs under the Investigations SOC led to discontinuation of an ocrelizumab patient in an MS trial.

In the all MS trials (Pool B) laboratory related AEs under the Investigations SOC were not

commonly reported. The AEs reported by at least 5 MS patients were Blood creatine phosphokinase increased (1.1%, n=23), Alanine aminotransferase increased (0.9%, n=19), gamma glutamyl transferase increased (0.7%,n=16), amylase increased (0.5%, n=10), lipase increased (0.4%, n=9), liver function test abnormal (0.4%, n=8), hepatic enzyme increased (0.3%, n=7), transaminases increased (0.3%, n=7), aspartate aminotransferase increased (0.3%, n=6), blood immunoglobulin M decreased (0.2%, n=5), blood triglycerides increased (0.2%, n=5).

In the RMS trials controlled phase (Pool A), the only Investigations AEs that occurred in at least 2 ocrelizumab patients and that occurred more frequently compared to interferon beta-1a were blood glucose increased (interferon beta-1a 0.1%, n=1; ocrelizumab 0.2%, n=2); and blood triglycerides increased (interferon beta-1a 0.1%, n=1; ocrelizumab 0.2%, n=2).

In the PPMS trial controlled phase, several laboratory-related AEs under the Investigation SOC occurred more frequently among ocrelizumab patients compared to placebo, but the differences were small. In the following table I identify Investigations AEs that occurred in at least 2 ocrelizumab patients and that occurred more frequently compared to placebo.

Table 24 Investigations AEs that occurred in at least 2 ocrelizumab patients and that occurred more frequently compared to placebo

Investigation AE	Placebo (n=239)	Ocrelizumab (n=486)
Any	8.4% (20)	11.9% (58)
Alanine aminotransferase increased	0.8% (2)	1.4% (7)
Gamma glutamyl transferase increased	0.8% (2)	1.2% (6)
Blood creatine phosphokinase increased	0.4% (1)	1.2% (6)
Amylase increased	0	1.2% (6)
Liver function test abnormal	0.4% (1)	0.8% (4)
Aspartate aminotransferase increased	0.4% (1)	0.6% (3)
Lipase increased	0	0.8% (4)
Transaminases increased	0.4% (1)	0.6% (3)
Blood testosterone decreased	0	0.6% (3)
White blood cell count decreased	0	0.6% (3)
Eosinophil count increased	0	0.4% (2)
White blood cells urine positive	0	0.4% (2)

Lab Results RA trials

In the RA controlled trials (Pool D), a higher percentage of ocrelizumab patients experienced decreases in neutrophil counts compared with placebo (placebo 1.5%, ocrelizumab 400 mg 3.9%, and ocrelizumab 1000 mg 4.3%). In addition, a higher percentage of ocrelizumab patients experienced decreases in white blood cell counts compared with placebo (placebo 1.0%, OCR 400 mg 4.1%, and OCR 1000 mg 4.3% of patients). For the remaining analytes, lab abnormalities occurred in similar percentages of ocrelizumab and placebo patients. There did not appear to be differences by treatment in the percentages of patients experiencing elevations of AST or ALT.

Analysis for Hy's Law liver injury cases
Genentech identified no cases in the RA trials of ocrelizumab patients with increases in transaminases >=3xULN that were associated with increased total bilirubin.

Submission Specific Laboratory Results
Ocrelizumab causes declines in CD19+ B lymphocytes. Profound mean declines were seen by study week 2. Few patients (0.3-4.3%) repleted their CD19+ lymphocyte counts between infusions. After stopping ocrelizumab treatment, repletion of CD19+ counts was slow and characterization of repletion after stopping was limited by the small number of patients followed.

Ocrelizumab appeared to have minimal effect on CD3+, CD4+, and CD8+ lymphocytes, or NK cells. Ocrelizumab caused declines in immunoglobulins. The greatest decline was seen with IgM, with smaller declines in IgA and IgG.

The effects on CD19+ cells and immunoglobulins are likely responsible for the increased risk for infection in ocrelizumab patients that was seen in MS patients, RA patients, and in patients treated with other approved anti-CD20 monoclonal antibodies.

CD19+ B Lymphocyte Mean change from baseline

RMS Trials Controlled phase (Pool A)
At baseline, the mean CD19+ cell count was similar for the interferon beta-1a (255.8) and ocrelizumab groups (257.6). At study week 2, the mean CD19+ cell count was 223.8 for the interferon beta 1-a group and 0.98 for the ocrelizumab group. For study weeks 12-96, the mean CD19+ cell count for the interferon beta-1a group ranged from 215.4 (week 12) to 283.3 (week 96) and for the ocrelizumab group from 1.74 (week 12) to 12.5 (week 24).

SFU
For patients who entered the SFU after stopping ocrelizumab, mean CD19+ counts increased slowly over time, although these analyses included a small number of patients. Based on 34 patients, the mean CD19+ cell count at SFU week 12 was 28.2. At SFU week 24, the mean CD19+ cell count was 127.2 (n=32), at SFU week 36 was 111.1 (n=22), at SFU week 48 was 173.7 (n=15) and at SFU week 72 was 223.4 (n=5).

PPMS Trial Controlled Phase
Mean change results for CD19+ cell counts similar to those described for RMS trials were seen in the PPMS trials. The placebo group experienced minimal changes in the mean CD19+ cell counts throughout the trial. In the ocrelizumab group, the mean CD19+ cell count was 231.2 at baseline and dropped to 2.7 at week 2. For the remaining time in the controlled phase (study week 120) the mean CD19+ cell count in the ocrelizumab group ranged between 2.38 (week 12) and 10.4 (week 24).

SFU
For patients in PPMS trials who entered the SFU after stopping ocrelizumab, mean CD19+ counts increased slowly over time, with some suggestion of a slower recovery compared to the RMS trials. At SFU week 12 the mean CD19+ cell count was 1.86 (n=7), at SFU week 24 was 6.9 (n=20), at SFU week 36 was 37.8 (n=36), at SFU week 48 was 86.9 (n=33) and at SFU week 72 was 78.3 (n=13), and at SFU week 96 was 44.8 (5).

CD19+ recovery
Despite the notable mean decline in CD19+ cell counts described above, a small proportion of patients repleted their cell counts (defined as CD19+cells >= LLN [80 cells/uL] or baseline levels, whichever is lower) prior to their next infusion. In the RMS trials, the percentage of patients who met the definition of repleted cell counts ranged from 0.3% (week 2) to 4.1% (week 24). In the PPMS trials, the percentage of patients who met the definition of repleted cell counts ranged from 1.1% (week 12) to 3.1% (week 72).

A notable proportion of patients had persistent depression of CD19+ cell counts after stopping ocrelizumab. In RMS trials, during the SFU, 20% of patients hadn't repleted their CD19+ at SFU weeks 48 and 72. In PPMS trials, during the SFU, 51.5% of patients hadn't repleted their CD19+ at SFU week 48 and 61.5% hadn't repleted their CD19+ at SFU week 72. These percentages should be interpreted cautiously because SFU duration was 24 weeks and was only extended further to follow CD19+ repletion in those patients who continued to have low CD19+ counts.

CD3+, CD4+, CD8+ T Lymphocyte Mean Changes

RMS Trials Controlled phase (Pool A)
Mean CD3+, CD4+, and CD8+ T lymphocyte cell counts declined following the first ocrelizumab

infusion and then appeared little changed with subsequent infusions. Interferon patients experienced mean declines in CD3+, CD4+, and CD8+ cell counts that were greater than those seen with ocrelizumab. I provide those mean changes below.

Table 25 RMS Controlled Phase (Pool A) Mean CD3+, CD4+, CD8+ T lymphocyte Counts by Study Week

Study week	T cell population	Interferon	Ocrelizumab
Baseline	CD3+	1411.4	1418.8
	CD4+	928.6	925.8
	CD8+	441.9	448.4
Week 2	CD3+	1322.0	1340.9
	CD4+	864.0	877.6
	CD8+	416.6	424.2
Week 12	CD3+	1217.1	1348.2
	CD4+	821.3	889.1
	CD8+	364.6	423.7
Week 24	CD3+	1153.4	1303.2
	CD4+	787.8	860.7
	CD8+	338.3	408.3
Week 48	CD3+	1116.2	1313.9
	CD4+	794.1	878.3
	CD8+	340.3	406.0
Week 72	CD3+	1155.3	1328.8
	CD4+	795.8	896.0
	CD8+	335.5	405.2
Week 96	CD3+	1177.5	1337.1
	CD4+	815.4	901.8
	CD8+	342.4	412.3

PPMS Trial Controlled Phase
As with RMS trials, ocrelizumab patients in the PPMS trial experienced initial modest declines in CD3+, CD4+, and CD8+ cell counts that appeared to plateau with little additional decline after week 2. In the placebo group, there was a slight mean increase from baseline in these cell counts.

Mean Change NK cells (CD16+56+)
There appeared to be no notable mean changes in NK cells in either the RMS or PPMS ocrelizumab patients. In the RMS trials, interferon beta-1a patients experienced mean decreases in NK lymphocyte counts at Week 12 (baseline 241.8, Week 12 174.4) which then stabilized for the remainder of the controlled treatment period.

Immunoglobulins
RMS Trials Controlled Phase (Pool A)
Genentech reported that at study week 96, ocrelizumab patients experienced a mean decline in IgM of 40% with smaller mean declines in IgA and IgG (3-5%, respectively). Interferon patients experienced negligible changes in immunoglobulin levels.

Mean IgM at baseline for the ocrelizumab group was 1.34g/L and declined to 1.06g/L at week 24 (first on treatment measure) and 0.84g/L at week 96. At week 96, 91% of ocrelizumab patients experienced a decline in IgM of more than 20% from baseline compared to 14% of interferon patients. At week 96, 16.5% (116/703) of ocrelizumab patients had an IgM result that was below the lower limit of normal compared to 0.8% (5/653) of interferon patients.

Mean IgA at baseline for the ocrelizumab group was 2.11g/L and was 2.17g/L at week 24 (first on treatment measure) and 2.06g/L at week 96. At week 96, 12% of ocrelizumab patients experienced a decline in IgA of more than 20% from baseline compared to 2% of interferon patients. At week 96, 2.4% (17/718) of ocrelizumab patients had an IgA result that was below the lower limit of normal compared to 0.8% (5/653) of interferon patients.

Mean IgG at baseline for the ocrelizumab group was 10.52g/L and was 10.51g/L at week 24 (first on treatment measure) and 10.01g/L at week 96. At week 96, 10% of ocrelizumab patients experienced a decline in IgG of more than 20% from baseline compared to 3% of interferon patients. At week 96, 2% (11/719) of ocrelizumab patients had an IgA result that was below the lower limit of normal compared to 0.3% (2/653) of interferon patients.

PPMS Trial Controlled Phase
The declines in immunoglobulins in ocrelizumab patients in PPMS trial were similar to those seen in the RMS trials. At study week 120, ocrelizumab patients experienced a mean decline in IgM of 40% with more modest mean declines in IgA and IgG (6-8%, respectively). Placebo patients experienced negligible changes in immunoglobulin levels.

Mean IgM at baseline for the ocrelizumab group was 1.37g/L and declined to 1.02g/L at week 24 (first on treatment measure) and 0.86g/L at week 120. At week 120, 92% of ocrelizumab patients experienced a decline in IgM of more than 20% from baseline compared to 9% of placebo patients. At week 120, 16% (56/361) of ocrelizumab patients had an IgM result that was below the lower limit of normal compared to 1.2% (2/162) of placebo patients.

Mean IgA at baseline for the ocrelizumab group was 2.17g/L and declined to 2.03g/L at week 24 (first on treatment measure) and was 2.05g/L at week 120. At week 120, 15.5% of ocrelizumab patients experienced a decline in IgA of more than 20% from baseline compared to 3.1% of placebo patients. At week 120, 0.5% (2/369) of ocrelizumab patients had an IgA result that was

below the lower limit of normal compared to 0.6% (1/162) of placebo patients.

Mean IgG at baseline for the ocrelizumab group was 10.68g/L and declined to 10.58g/L at week 24 (first on treatment measure) and was 9.75g/L at week 120. At week 120, 11.4% of ocrelizumab patients experienced a decline in IgG of more than 20% from baseline compared to 8.0% of placebo patients. At week 120, 1.1% (4/371) of ocrelizumab patients had an IgG result that was below the lower limit of normal compared to 1.2% (2/162) of placebo patients.

8.4.7. Vital Signs

Ocrelizumab did not appear to be associated with notable differential effects on vital signs when compared to interferon beta-1a or placebo.

Vital sign mean changes from baseline
In response to a Division request, Genentech provided in a 6/7/16 submission a table of the vital sign mean changes from baseline for non-infusion visits and for infusion visits for the RMS trials (Pool A).

RMS trials, non-infusion visits
At non-infusion visits, mean changes in diastolic blood pressure, systolic blood pressure, heart rate, temperature and respiration were small and generally similar for both the interferon B-1a and ocrelizumab groups. At visit 96, the interferon B-1a group experienced a mean decline in weight of 0.3kg and the ocrelizumab group experienced a mean increase in weight of 0.35kg.

RMS trials, infusion visits
Both ocrelizumab and interferon patients experienced negligible mean changes in respirations and temperature following infusions. Ocrelizumab and interferon patients experienced small mean declines from baseline in systolic and diastolic blood pressure following infusions. Ocrelizumab and interferon patients experienced small mean increases from baseline in heart rate that were generally about 1 bpm higher for ocrelizumab compared to interferon. The greatest mean increase in heart rate was 7.8 bpm and occurred at 3 hours after the first infusion in ocrelizumab patients while at the same time interferon patients experienced a mean increase of 6.0 bpm.

PPMS Trial non-infusion visits
At non-infusion visits, mean changes in diastolic blood pressure, systolic blood pressure, heart rate, temperature and respiration were small and generally similar for both the placebo and ocrelizumab groups.

PPMS Trial, infusion visits
Both ocrelizumab and placebo patients experienced negligible mean changes in respirations

and temperature following infusions. Ocrelizumab and placebo patients generally experienced small mean declines from baseline in systolic and diastolic blood pressure following infusions. Ocrelizumab and placebo patients experienced small mean increases from baseline in heart rate that were generally about 1 bpm higher for ocrelizumab compared to placebo, although there were intervals where the increase was similar or even higher among placebo patients. The greatest mean increase in heart rate was 9.3 bpm and occurred at 3 hours and 30 minutes after the first infusion in ocrelizumab patients, while at the same time placebo patients experienced a mean increase of 7.4 bpm.

Potentially Clinically Significant changes (PCS)
Genentech did not include an analysis of PCS vital sign results in their BLA for ocrelizumab so the Division requested such an analysis in a 7/28/16 IR. Specifically, the Division requested PCS vital sign analyses that used the following criteria:

Post baseline heart rate >120bpm, if pulse was <=120 bpm at baseline, or who had an increase of 20bpm >baseline
Post baseline heart rate <50bpm, if their pulse was >=50 bpm at baseline, or who had a decrease > 20bpm from baseline
Post baseline SBP >180, if SBP was <=180 at baseline or increase in SBP of >40
Post baseline SBP <90, if SBP was >=90 at baseline or decrease in SBP of >30
Post baseline DBP >105, if DBP was <=105 at baseline or increase in DBP of >30
Post baseline DBP <50, if SBP was >=50 at baseline or decrease in DBP of >20

RMS Trials Controlled Phase (Pool A)
The percentages of patients meeting PCS vital sign criteria were generally small and similar for the interferon b-1a and ocrelizumab treatment groups. In the table below, I identify the infusion and results where there was the greatest difference for ocrelizumab compared to interferon beta-1a. These results illustrate that even when selecting the infusion visit with greatest difference in percentage of vital abnormalities, the differences by treatment were relatively small.

Table 26 Infusion with greatest difference in patients meeting PCS criteria for Ocrelizumab compared to interferon beta 1-a, RMS Trials Controlled Phase (Pool A)

Vital sign PCS criteria	Ocrelizumab	Interferon b-1a	Infusion
Post baseline SBP >180, if SBP was <=180 at baseline or increase in SBP of >40	0.6% (5/825)	0	Dose 1 (day 1)
Post baseline SBP	5.1% (37/732)	2.9% (19/663)	Dose 4

<90, if SBP was >=90 at baseline or decrease in SBP of >30			
Post baseline DBP >105, if DBP was <=105 at baseline or increase in DBP of >30	1.4% (11/779)	0.3% (2/751)	Dose 2
Post baseline DBP <50, if SBP was >=50 at baseline or decrease in DBP of >20	8.3% (65/779)	6.0% (45/751)	Dose 2
Post baseline heart rate >120bpm, if pulse was <=120 bpm at baseline, or who had an increase of 20bpm >baseline	15.0% (124/825)	12.4% (102/825)	Dose 1 (day 1)
Post baseline DBP <50, if SBP was >=50 at baseline or decrease in DBP of >20	3.4% (25/732)	2.6% (17/663)	Dose 4

PPMS Trial Controlled Phase
The percentages of patients meeting PCS vital sign criteria were generally small and similar for the placebo and ocrelizumab treatment groups in the PPMS trial. In the table below, I identify the infusion and results where there was the greatest difference for ocrelizumab compared to placebo (through dose 6). These results illustrate that even when selecting the infusion visit with greatest difference in percentage of vital abnormalities, the differences by treatment were relatively small.

Table 27 Infusion with greatest difference in patients meeting PCS criteria for Ocrelizumab compared to placebo, PPMS Trial Controlled Phase

Vital sign PCS criteria	Ocrelizumab	Placebo	Infusion
Post baseline SBP >180, if SBP was <=180 at baseline or increase in SBP of >40	1.1% (5/452)	0.5% (1/216)	Dose 3 (day 1)

Post baseline SBP <90, if SBP was >=90 at baseline or decrease in SBP of >30	4.6% (20/437)	3.8% (8/210)	Dose 3 (day 15)
Post baseline DBP >105, if DBP was <=105 at baseline or increase in DBP of >30	1.9% (9/477)	0.4% (1/235)	Dose 1 (day 15)
Post baseline DBP <50, if SBP was >=50 at baseline or decrease in DBP of >20	7.9% (30/382)	6.3% (10/159)	Dose 6 (day 15)
Post baseline heart rate >120bpm, if pulse was <=120 bpm at baseline, or who had an increase of 20bpm >baseline	22.0% (107/486)	15.5% (37/239)	Dose 1 (day 1)
Post baseline DBP <50, if SBP was >=50 at baseline or decrease in DBP of >20	4.4% (20/452)	2.3% (5/216)	Dose 3 (day 1)

8.4.8. Electrocardiograms (ECGs)

In RMS trials WA21092 and 21093 and the PPMS trial WA25046 ECGs were performed at screening, baseline (prior to first infusion), study week 72, and at the withdrawal of treatment visit. ECGs were reviewed by study site investigators for abnormalities. Abnormalities were reported as AEs. No systematic analysis of ECG intervals was undertaken. This approach is not expected to be a sensitive screen for detecting ECG abnormalities.

All MS trials (Pool B)
From the Investigations SOC and the Cardiac Disorders SOC, ECG related AEs were atrial fibrillation (n=2), bundle branch block left (n=2), bundle branch block right (n=2), defect conduction ventricular (n=2), sinus tachycardia (n=2), supraventricular extrasystoles (n=2), ventricular extrasystoles (n=2), atrial flutter (n=1), atrioventricular block first degree (n=1), electrocardiogram abnormality (n=1), electrocardiogram repolarization abnormality (n=1),

electrocardiogram T wave abnormality (n=1), nodal rhythm (n=1), and supraventricular tachycardia (n=1).

RMS trials controlled phase (Pool A)
No ECG related AE was reported more than once for ocrelizumab patients. The following AEs were reported once for an ocrelizumab patient and not reported for an interferon beta-1a patient: atrial flutter, atrioventricular block first degree, bundle branch block left, bundle branch block right, defect conduction intraventricular, and supraventricular extrasystoles.

PPMS trial
Sinus tachycardia was reported for 0.4% (2/486) ocrelizumab patients and no placebo patients. The following ECG related AEs were reported for one ocrelizumab and no placebo patients: electrocardiogram abnormal, electrocardiogram repolarization abnormality, and ventricular extrasystoles.

8.4.9. QT

Genentech provided a reasonable justification for omitting a formal QT study with ocrelizumab. The development program should have required collection of additional ECGs and formal interval analysis to confirm the absence of a signal requiring additional investigation.

As noted above, ECGs intervals were not systematically measured/assessed in the ocrelizumab development program. In all MS trials (Pool B) no patients had an AE of QT prolongation, although patient WA25046-207348-12602 had an IRR during which a QTc of 615ms was reported (see section 8.5.1, below).

In a 5/13/16 IR, Genentech explained that a thorough QT study was not required for ocrelizumab based on the biologic plausibility, literature review, and nonclinical data supporting the view that ocrelizumab treatment does not have any pro-arrhythmic effect.

Biologic Plausibility
Genentech felt that ocrelizumab is not expected to inhibit the human Ether-à-go-go-Related Gene (hERG) channel or other cardiac ion channels because of its large size, high target specificity and low off-target potential (Rodriguez 2010). Genentech also noted that cardiac cells do not express CD20 antigen, so they felt that is was unlikely that anti-CD20 antibodies can have direct cardiotoxicity.

Literature Review
Genentech cited an FDA study (Schreiber et al. 2014), that found no relevant QT/QTc interval prolongations for the 15 monoclonal antibodies or antibody-drug conjugates (ADCs) evaluated. Therefore, the authors indicated that in their view no dedicated QT assessment is necessary for

monoclonal antibodies, and that clinical ECG monitoring may follow ICH E14 guidelines for agents with a negative thorough QT (TQT) assessment, except for specific monoclonal antibodies where off-target cardiac-related AEs are observed (Schrieber et al. 2014).

In addition, Genentech noted a review of European Public Assessment Reports (EPARs) published by the EMA (Jackson et al. 2015), where PubMed and Embase databases were searched for cases indicative of drug-induced QT prolongation for 28 pre-identified monoclonal antibody drugs authorized in Europe. None of the studies indicated a relevant increase of the risk of QT prolongation. Based on this review, Genentech concluded that there is no evidence that any of the currently marketed monoclonal antibody drugs in Europe increases the risk for QT prolonging effects when used within their approved indications.

Nonclinical Ocrelizumab Data
Genentech also cited results from studies in monkeys that did not find evidence of QT prolongation with ocrelizumab.

8.4.10. Immunogenicity

Development of anti-drug antibodies (ADA) occurred infrequently during MS trials and was similar for ocrelizumab and interferon b-1a and placebo.

RMS Trials Controlled Phase (Pool A)

The baseline prevalence of ocrelizumab anti-drug antibodies (ADA) was <1% in both treatment groups. 0.4% (3/ 807) of patients who received ocrelizumab and had a post baseline ADA result showed positive (treatment-induced and –enhanced) ocrelizumab ADAs. Of these, one patient tested positive for neutralizing antibodies to ocrelizumab. No IRRs or hypersensitivity reactions were observed in the patient who developed neutralizing antibodies. In the IFN group, 0.9% (7/804) tested ADA positive for ocrelizumab post-baseline. Genentech noted that "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."

PPMS Trial Controlled Phase
The baseline prevalence of ocrelizumab ADAs was < 1% in both placebo and ocrelizumab groups. 1.9% (9/481) of patients who received ocrelizumab and had an ADA assay result from a post baseline sample during the controlled treatment period showed positive (treatment-induced and –enhanced) ocrelizumab ADAs. Of these 9, one patient tested positive for neutralizing antibodies to ocrelizumab. The patient who developed neutralizing antibodies did not experience an IRR or hypersensitivity reactions. 3.8% (9/239) of patients in the placebo group tested ADA positive for ocrelizumab post baseline.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Infusion Related Reactions

The class of approved anti-CD20 monoclonal antibodies causes infusion related reactions. For example, the Rituxan labeling includes a boxed warning with the following information:

> Fatal infusion reactions within 24 hours of Rituxan infusion; approximately 80% of fatal reactions occurred with first infusion. Monitor patients and discontinue Rituxan infusion for severe reactions.

The Warnings and Precautions section of Rituxan labeling further describes these reactions as occurring during the first infusion, with time to onset of 30-120 minutes, and with signs and symptoms including urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death. The Rituxan labeling states that patients should be premedicated with an antihistamine and acetaminophen prior to dosing and recommends for RA patients methylprednisolone 100 mg intravenously or its equivalent 30 minutes prior to each infusion. Labeling also recommends that patients experiencing an IRR should receive medical management (e.g. glucocorticoids, epinephrine, bronchodilators, or oxygen) as needed. Labeling notes that temporary or permanent discontinuation of Rituxan may be appropriate, but also suggest that infusion can be resumed at a minimum 50% reduction in rate after symptoms have resolved. Labeling recommends closely monitoring patients with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells (>=25,000/mm^3).

In NHL patients treated with Rituxan, IRRs occurred in 77% of patients following the first dose and decreased with subsequent infusions. IRRs were reported for 32% of Rituxan patients in RA controlled trials.

The labeling for other approved anti-CD20 monoclonal antibodies includes similar information about IRRs. The labeling for the radio-therapeutic agents, ibritumomab (Zevalin) (b) (4) describes IRRs in boxed warnings. Obinutuzumab (Gazyva) and ofatumumab (Arzera) labeling does not have boxed warnings for IRRs, but does describe IRRs in Warnings and Precautions statements.

Given the established relationship between anti-CD20 monoclonal antibodies and IRRs, Genentech required premedication to prevent/mitigate IRRs in ocrelizumab development program trials. For example, in MS trials, all patients received methylprednisolone 100 mg IV by

slow infusion, 30 to 60 minutes prior to each ocrelizumab/placebo infusion. Pre-infusion treatment with an oral analgesic/antipyretic (e.g., acetaminophen/paracetamol [1g]) and an oral antihistamine (e.g., diphenhydramine [50
mg]) was also recommended, but not mandated.

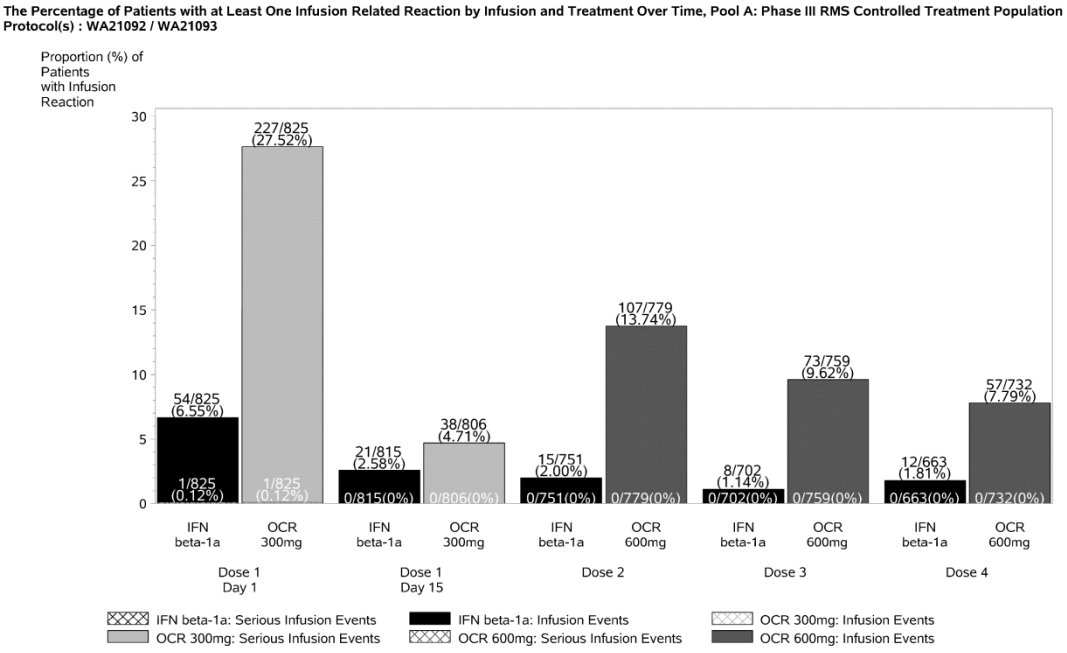
Genentech incorporated into the MS study protocols prospective data collection measures for IRRs. Specifically, IRRs and related symptoms experienced by a patient during the infusion, 1 hour post infusion while the patient was still in the clinic, or within 24 hours after the completion of the infusion while the patient was not in the clinic, were reported on a dedicated IRR CRF form. In addition, investigators were asked to confirm that any event reported on the AE CRF forms with the onset date on the day of an infusion or on the next day after the completion of an infusion did not represent an IRR. Investigators were also asked to confirm that vital signs changes observed during and post-infusion did not represent an IRR.

Note- Genentech purposefully did not present Pool B data due to the different infusion regimens in the RMS and PPMS trials. The IRR frequency results cited for Pool B were derived by this reviewer using the submitted datasets, narratives, and CRFs.

IRR Frequency
For all MS trials (Pool B), 34.2% (734/2147) of ocrelizumab exposed patients experienced 1,474 IRRs.

In the controlled phase of the RMS trials (Pool A) 34.3% (283/825) of ocrelizumab patients experienced an IRR compared to 9.7% (80/826) of Interferon beta-1a patients. The following graph provided by the sponsor demonstrates that IRRs were persistently more common in ocrelizumab patients tan interferon patients, occurred most frequently with the first infusion of ocrelizumab, and declined in frequency, but continued to occur with subsequent doses.

Figure 1 Percentage of Patients with at Least One Infusion Related Reaction by Infusion – Phase III RMS Controlled Treatment Population (Pool A)



Percentages are based on n, number of patients that received the infusion.
Program: /opt/BIOSTAT/prod/cdt3422s/g_ae_irr_inf.sas / Output: /opt/BIOSTAT/prod/cdt3422s/s03422a/reports/g_ae_irr_inf_all_spa.out
24FEB2016 15:05 Page 1 of 1

Note: In the OCR group, Dose 1 was given as two 300-mg infusions on Days 1 and 15. Thereafter, doses were given, as a single 600 mg infusion.

During the controlled phase of the PPMS trial, 39.9% (194/486) of ocrelizumab patients experienced one or more IRR compared to 25.5% (61/239) of placebo patients. Similar to the RMS patients, PPMS ocrelizumab patients experienced IRRs most frequently following the first dose, with decreases in frequency following subsequent doses (Note- in this trial, infusions were given as 2 equally divided doses of 300mg, 2 weeks apart, every 24 weeks).

Timing of IRR with respect to dosing
In the controlled phases of both RMS and PPMS trials, the majority of IRRs in ocrelizumab patients occurred during the infusion, but a notable percentage occurred after leaving the clinic. During the controlled phase of RMS trials, 80.6% (228/283) of the ocrelizumab patients with an IRR experienced the event during the infusion, 11.0% (31/283) after the infusion, but while still in the clinic, and 17.7% (50/283) within 24 hours of infusion, but after leaving the clinic (Note some patients experienced more than 1 IRR, so percentages do not add up to 100%). During the controlled phase of PPMS trials, 61.3% (119/194) of the ocrelizumab patients with an IRR experienced the event during the infusion, 20.1% (39/194) after the infusion but while still in the clinic, and 38.1% (74/283) within 24 hours of infusion, but after leaving the clinic.

IRR Symptoms and Signs

For the controlled phase of RMS trials (Pool A), the symptoms reported by at least 5% of ocrelizumab patients with IRRs and more frequently reported compared to interferon beta-1a patients were pruritus (30.0%, 85/283), rash (30.0%, 85/283), throat irritation (23.7%, 67/283), flushing (15.9% 45/283), urticaria (8.8%, 25/283), and oropharyngeal pain (8.5%, 24/283). In the controlled phase of the PPMS trial, ocrelizumab patients with IRRs experienced similar IRR symptoms at similar frequencies. One notable difference was pyrexia, which was a common IRR symptom for PPMS ocrelizumab patients with IRRs (13.4%, 26/194), but less so for RMS ocrelizumab patients with IRRs (4.2%, 12/283).

In the RMS trials controlled phase (Pool A) vital sign changes were not commonly reported in patients with IRRs, and, except for hypertension, were more common among the interferon beta-1a patients. In the following table I summarize the vital sign AEs associated with IRRs.

Table 28 RMS Trials Controlled Phase (Pool A) Vital sign Abnormalities Associated with IRRs

Vital Sign Abnormality	Interferon beta-1a patients with IRR n=80	Ocrelizumab patients with IRR n=283
Hypotension	7.5% (6)	3.2% (9)
Hypertension	1.3% (1)	1.4% (4)
Tachycardia	17.5% (14)	4.6% (13)
Bradycardia	1.3% (1)	0.4% (1)
Pyrexia	13.8% (11)	4.2% (12)

Most of the above events were grade 1 or 2 severity. There were six grade 3 vital sign AEs associated with IRRs (4 patients) and all were in the ocrelizumab group. These events were hypotension (n=2), hypertension, bradycardia, tachycardia, and pyrexia.

In the following table I summarize the vital sign AEs in patients with IRRs in the PPMS trial controlled phase.

Table 29 PPMS Trials Controlled Phase Vital sign Abnormalities Associated with IRRs

Vital Sign Abnormality	Placebo patients with IRR n=61	Ocrelizumab patients with IRR n=194
Hypotension	9.8% (6)	3.6% (7)
Hypertension	6.6% (4)	4.1% (8)
Tachycardia	4.9% (3)	6.2% (12)
Pyrexia	0	9.8% (13)

The majority of the above events were of grade 1 or 2 intensity. There were 3 cases (2 patients) of Grade 3 vital sign abnormalities, all in the ocrelizumab group (hypotension, hypertension,

pyrexia).

IRR Severity
No deaths were attributed to IRRs in ocrelizumab treated MS patients. For all MS trials (Pool B) 0.3% (7/2,147) ocrelizumab patients experienced IRRs that were classified as SAEs. I summarize those events below.

WA21092-207543-1922844 15 minutes after beginning her first infusion (6mL administered) of ocrelizumab, this 26 year old female developed bronchospasm. The narrative included few details of the actual event. She received glucocorticoid but not antipyretic or antihistamine premedication. She refused hospitalization. The infusion was stopped and she was treated with diphenhydramine and prednisolone. The event was considered resolved the same day and the patient was withdrawn from the study.

WA21493-140993-4051 2 hours and 10 minutes after starting her first infusion (125mL administered), this 24 year old female experienced stuffiness, severe laryngeal/throat irritation (Grade 3), severe throat pain (Grade 3) and mild increase of body temperature (Grade 1; temperature 99.5°F). The infusion was stopped. The patient had received premedication with intravenous methylprednisolone. Approximately 30 minutes later, she also developed life-threatening hypotension (Grade 4; BP 60/0 mmHg, 10 minutes later 80/50mmHg), dizziness (Grade 2), chills, severe laryngeal throat irritation, severe throat pain and mild fever. 90 minutes later her temperature was 98.2°F and blood pressure was 90/60 mmHg. She was hospitalized and was treated with chloropyramine, intravenous dexamethasone, and intravenous prednisolone for one day. Later, the same day, the IRR was assessed as resolved without sequelae. Study drug infusion was permanently discontinued. The patient did not remain in the treatment-free safety follow-up and withdrew from the study.

WA25046-207348-12602 On (b) (6) (Study day 1191, first infusion (b) (6)) approximately 1 hour after starting her infusion, this 42 year old female experienced hypotension, ectopic ventricular beats, paleness and intense asthenia. The patient had received pre-treatment with methylprednisolone. Electrocardiography around that time showed prolonged QTc interval (520 ms, correction formula not reported). Four minutes later, QTc was 450 ms and 3 hours after that, QTc was 615 ms. The patient was sent to the emergency room for overnight observation and ECG showed “Rs complex” 80 bpm with persistence of QTc prolongation. The next day, ((b) (6)), ECG showed Rs complex 60 bpm, QTcB=448ms, QTcF=446ms and QT=441ms. On the same day at 08:17 am, the IRR was considered resolved. No treatment was administered for the event of IRR. A follow up ECG on (b) (6) (study day 1280), showed sinus rhythm of 62bpm, and prolonged QTc (455 in V2, 460ms in D2), interpreted as persistent QTc prolongation (<500msec). It was recommended to maintain potassium and magnesium levels in normal ranges and avoid drugs with electrophysiological effect. Due to the event of serious IRR, on study day 1345 ((b) (6)), treatment with ocrelizumab was permanently discontinued as per

the physician decision and she entered in the treatment-free safety. On the same day she permanently withdrew from the study.

WA25046-208367-30302 One hour after starting his first ocrelizumab infusion (34 mL administered), this 49 year old male developed hyperthermia, and tachycardia (grade 3), hypertension, nausea and hypotension (grade 2), and pruritus and vomiting (grade 1). The patient was hospitalized due to IRR. Prior to the infusion, his temperature was 97.8°F and his highest recorded temperature was 103.5°F (6h 45min after start of infusion). Prior to the infusion, the patient's HR was 74bpm and the highest reported HR was 125bpm (4h15min after infusion start). Prior to starting the infusion the patient had a BP of 140/80mm Hg and the highest and lowest BPs reported during this event were 180/100mmHg (4h15min after infusion start) and 100/50mmHg (9h after infusion start). His ECG was reported to be normal. During hospitalization (from study day 1 to study day 2), he was treated with several medications including antihistamines, glucocorticoids, and paracetamol. The IRR resolved and he was discharged from the hospital. Despite the IRR, the ocrelizumab infusion was completed without intervention He received one additional ocrelizumab infusion on study day 37 without experiencing an IRR. On study day 58 he developed pneumonia and he died on study day 68 (described with deaths, above).

WA25046-208444-37004 This 50 year old male received his first ocrelizumab infusion (b) (6). On (b) (6) (study day 169) he received an infusion of ocrelizumab. On (b) (6) (study day 170), within 24 hours of completion of infusion of study drug, he developed fever (temperature not reported). Later that day his temperature was 104°F, and he developed a flu-like syndrome (asthenia) and psychomotor retardation, resulting in hospitalization. He had received pre-medication with methylprednisolone (100 mg IV), paracetamol and dexchlorpheniramine. He was treated with paracetamol. On (b) (6) (study day 174) the IRR was considered resolved and the patient was discharged from the hospital. No action was taken with ocrelizumab due to the event of IRR. On (b) (6) he was readmitted for gait disturbance which resolved 2 days later and he was then discharged.

WA25046-208688-14402 One hour and 25 minutes after beginning his first infusion of ocrelizumab, this 56 year old male developed fever, rigors and tachycardia, leading to hospitalization (he completed the infusion). His heart rate prior to starting the infusion was 99bpm and his highest heart rate during the event was 128bpm (2h 30min after starting the infusion). His temperature before the infusion was 97.5°F and his highest temperature during the event was 101.1°F (2h 30 min after starting the infusion). He received pre-medication with methylprednisolone, promethazine, and paracetamol. He was treated with paracetamol and promethazine for the IRR. The next day the IRR was considered resolved and he was discharged from the hospital.

WA25046-208787-32311 This 49 year old male received his first ocrelizumab infusion on

(b) (6). On (b) (6), within 24 hours of an infusion, he developed spasticity and was unable to move his legs or get out of his wheelchair. Prior to the infusion he was pre-medicated with chlorpheniramine, methylprednisolone, and paracetamol. On (b) (6), the IRR was considered resolved and he was discharged from the hospital.

In the RMS trials controlled phase (Pool A), 1.3% (11/825) of ocrelizumab patients discontinued for an IRR. All 11 patients were withdrawn after their first infusion. IRR symptoms leading to withdrawal of these 11 patients included rash (6 patients), pruritus (4 patients), and throat irritation (3 patients), dyspnea, nasal congestion, and flushing (all reported in at least 2 patients).

In the PPMS trial controlled phase, 0.2% (2/486) of ocrelizumab patients discontinued for IRRs. One of these patients withdrew following the first dose (dose 1, infusion 1) and the other following Dose 2, Infusion 1. The symptoms for these patients were flushing, hyperhidrosis, and oropharyngeal pain.

When viewed by intensity grade, almost all IRRs from MS trials were graded 1-3. Of the 1,474 IRR events reported in all MS trials (Pool B), 73% (n=1,074) were grade 1; 24% (n=355) were grade 2; 2.6% (n=38) were grade 3; and 0.1% (n=2) were grade 4 (none were grade 5). Both grade 4 events (WA21092-207543-1922844, WA21493-140993-4051, summarized above with SAEs) occurred during the first infusion of ocrelizumab.

IRR management
Some patients who developed IRRs were treated with antihistamines (IV or IM), corticosteroids, non-steroidal anti-inflammatories, bronchodilators, or with other interventions. IRRs were also managed through slowing, interrupting, or discontinuing the infusions.

In the RMS trials controlled phase (Pool A), 65.4% (185/283) of the ocrelizumab patients who experienced an IRR received at least one treatment. Antihistamines were the most commonly administered treatments (46.6%, 132/283). Other commonly administered treatments were corticosteroids, analgesics, and non-steroidal anti-inflammatory medications.

In addition to administered medications, some patients had their infusions modified for IRRs. Modifications included discontinuation, slowing down, or interrupting of an infusion. In the RMS trials controlled phase (Pool A), 54.4% of ocrelizumab patients with an IRR had an infusion modification. Fifteen of these patients had their infusions discontinued while the remainder had infusions that were slowed or interrupted.

In the PPMS trial controlled phase, 47.4% (92/194) of ocrelizumab patients who experienced IRRs received at least one treatment. Antihistamines were the most commonly administered treatments (29.9% 58/194). Other commonly administered treatments were corticosteroids,

analgesics, and non-steroidal anti-inflammatory medications. No ocrelizumab patients with an IRR had their infusion slowed or discontinued and 2.6% (5/193) had their infusion interrupted.

Assessment of Pre-treatment
In the RMS trials controlled phase (Pool A) ocrelizumab patients pretreated with oral antihistamine along with methylprednisolone had at least a 2-fold lower Incidence in IRRs compared with pretreatment with methylprednisolone alone (with the exception of Dose 1, Infusion 2). The addition of analgesics/antipyretics to oral antihistamines did not appear to have additional benefit. For example, on Day 1 dose 1, 49.5% (48/97) patients pre-treated with only methylprednisolone experienced an IRR compared to 19.2% (23/120) pretreated with antihistamine+methylprednisolone, 32.7% (18/55) pretreated with antipyretic+methlprenisolone, and 24.9% (137/551) pretreated with antihistamine+antipyretic+methylprednisolone. The majority of IRRs in patients receiving any additional IRR pretreatment regimen were Grade 1 or 2, and the intensity of the IRR decreased with subsequent dosing, similar to that observed in patients receiving only methylprednisolone. The incidence of Grade 3 IRRs also appeared similar across pre-treatment subgroups.

A similar relationship between IRRs and pretreatment was seen in the PPMS trial controlled phase, although the observed differences by pretreatment were smaller. For example, For Day 1 dose 1, 13.0% (3/23) patients pre-treated with only methylprednisolone experienced an IRR compared to (0/6) pretreated with antihistamine+methylprednisolone, 16.7% (4/24) pretreated with antipyretic+methlprenisolone, and 11.8% (22/186) pretreated with antihistamine+antipyretic+methylprednisolone.

IRRs by Dosing Regimen
There did not appear to be meaningful differences in IRR risk when comparing the dosing regimen across the RMS trials and the PPMS trial, although Genentech did not compare dosing regimens within a trial and therefore there is no direct comparative empirical evidence of IRR risk by dosing regimen. As noted above, 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.

Looking at overall IRR risk, in PPMS trial controlled phase almost 40% of ocrelizumab patients experienced an IRR compared to 34% in RMS trials controlled phase, but the PPMS trial was longer (120 weeks v 96 weeks) and included more infusions (every dose was administered as split infusions). Genentech compared the IRR risks by infusions for these trials. I include that table below.

Table 30 Incidence and Severity of IRRs for Single Infusion versus Divided Dose Regimens for Doses 2, 3, and 4

	RMS Dose 2	**PPMS Dose 2**		**RMS Dose 3**	**PPMS Dose 3**	
	Day 1	Day 1	Day 15	Day 1	Day 1	Day 15
Regimen	600 mg	300 mg	300 mg	600 mg	300 mg	300 mg
Pts with Infusions	779	465	449	759	452	437
Pts with IRRs	107 (13.7%)	54 (11.6%)	23 (5.1%)	73 (9.6%)	52 (11.5%)	22 (5.0%)
Severity Grade 1 Grade 2 Grade 3	 84 (10.8%) 20 (2.6%) 3 (0.4%)	 39 (8.4%) 15 (3.2%) 0	 22 (4.9%) 1 (0.2%) 0	 56 (7.4%) 14 (1.8%) 3 (0.4%)	 39 (8.6%) 13 (2.9%) 0	 19 (4.3%) 3 (0.7%) 0
Most common symptoms >= 10%	pruritus, throat irritation, rash, oropharyngeal pain	pruritus, rash, headache, throat irritation, oropharyngeal pain, pyrexia	pyrexia, flushing	throat irritation, pruritus, rash	pruritus, headache, oropharyn-geal pain, flushing	pruritus, headache, flushing,
Most common symptoms >= 5% < 10%	headache, flushing	fatigue, flashing	dizziness, dysgeusia, throat irritation	flushing	rash, throat irritation, chills, nausea, ear pruritus	fatigue pyrexia

RMS Dose 4	**PPMS Dose 4**	
Day 1	Day 1	Day 15
600 mg	300 mg	300 mg
732	439	430
57 (7.8%)	29 (6.6%)	13 (3.0%)

44 (6.0%) 13 (1.8%) 0	26 (5.9%) 3 (0.7%) 0	12 (2.8%) 1 (0.2%) 0
throat irritation, pruritus, rash, headache	pruritus, flushing, rash, pyrexia, oropharyngeal pain	fatigue, flushing, pyrexia
oropharyngeal pain, flushing	chills, headache	asthenia, chills, headache, dysgeusia, somnolence, nausea

Genentech felt that this analysis supports that from Dose 2 onwards there appears to be no benefit in regard to IRR for PPMS patients in administering ocrelizumab using the divided dose regimen (2 x 300 mg infusions, 14 days apart) and therefore supports an infusion regimen of 600 mg IV infusions every 24 weeks as appropriate for both RMS and PPMS patients; Dose 1 administered as 2 x 300 mg infusions separated by 14 days, and all subsequent doses administered as 1 x 600 mg infusion.

To assess potential differences in IRR risks for split versus combined infusions, the most valid comparison would be PPMS patients dosed 600mg IV every 6 months versus PPMS patient dosed 300mg q 2weeks, every 6 months, which was not done. Genentech's conclusion regarding no benefit in IRR risk for the split dosing regimen assumes that RMS and PPMS patients experience IRRs similarly. Although that may be true, we do not have empirical data to support that assumption.

Genentech updated IRR information in the 90 Day Safety Update. Genentech reported no meaningful changes in IRR frequencies in the RMS or PPMS trials. There were no new IRR SAEs in the RMS or PPMS trials. There were no new reports of IRRs >= Grade 4 in RMS or PPMS trials. No new IRRs of Grade 3 intensity were reported in ocrelizumab patients from RMS trials. Two ocrelizumab patients from the PPMS trial had new Grade 3 IRRs. The symptoms of the IRRs in these 2 patients were headache and flushing (following Dose 1) in a patient from the placebo group who switched to open-label ocrelizumab treatment upon entering the OLE; and pruritus (following Dose 8). No new IRRs led to discontinuation or dose modification in the RMS trials. No patients discontinued from the PPMS trial for IRRs, but one patient did have their dose modified for an IRR of hypotension.

8.5.2. Infections

Summary
Infections were commonly reported in MS trials, and when focusing on the controlled phases, there was a slightly increased risk of overall infection events with ocrelizumab. Ocrelizumab patients appeared to be at greater risk for upper respiratory tract infections, lower respiratory tract infections, and herpes-related infections. When viewed by severity grades, the majority of infections in ocrelizumab patients were grade 1 or 2. In the controlled phases, compared to interferon or placebo, there were more ocrelizumab patients with grade 4 or 5 infections, but the number of such events was small and cannot support definitive conclusions regarding risk. In the controlled phases of MS trials, a higher percentage of comparator patients (interferon, placebo) experienced infection SAEs compared to ocrelizumab patients. Genentech did not identify any opportunistic infections in MS patients treated with ocrelizumab.

Genentech explained that part of the reason for not pursuing approval for a RA treatment indication was an increased incidence of serious and opportunistic infections compared with comparator. The analyses of infections in RA patients demonstrated an increased risk of serious infections that appeared to be dose related and identification of 16 infection events that appeared to be opportunistic infections.
Analysis
Given that ocrelizumab depletes B lymphocytes, Genentech considered infections as events of potential concern and provided in depth analyses of infections in the development program. In considering overall infections, Genentech used 2 pools of events. The first pool included events subsumed under the Infections and Infestations SOC. The second pool included events coded under the Infections and Infestations SOC plus events included under other SOCs, but where a specific pathogen was identified. Results from the broader pool did not meaningfully impact conclusions, so this review will focus on events included under the Infections and Infestations SOC, unless otherwise noted.

Genentech employed “baskets”, or re-groupings, of infections in order to assess potentially related infections that were split into different preferred terms during the coding process. Use of these baskets involved grouping of events based on MedDRA SMQs, when available or based on a prospective categories of preferred terms compiled by Genentech. Genentech provided a listing of preferred terms subsumed under the “basket” terms and the approach seemed generally acceptable. In some instances, it appeared that the re-grouping may have led to lumping of likely unrelated events, but this drawback is minimized by additional available analyses (original MedDRA coding, sponsor baskets, this reviewer’s re-grouping provided above) which provide alternative assessments of infection adverse events.

To analyze serious infections, Genentech considered two groups of events. First, Genentech summarized infection SAEs. In addition, Genentech considered broader pool of events that

included infections that met the criteria for an SAE as well as any non-serious infection that was treated with intravenous antibiotics.

Genentech provided separate analyses of opportunistic infections. Genentech identified potential opportunistic infections using a pre-specified collection of infection event terms. In a 9/7/16 response to an IR, Genentech stated the selection of event terms was based on input from an Infectious Disease specialist. Events identified by these terms were then reviewed by assessment of pathogen, anatomic localization, and endemicity of the infection, duration and type of treatment, and resolution of the infection to determine if they were truly opportunistic infections. Genentech also stated in their response to the Division's IR that the review of the cases was conducted by the medical team at the Sponsor, involving clinical and safety scientists. The medical team first identified those infections that typically occurred in immunocompromised patients, such as aspergillosis, disseminated herpes, pneumocystis jiroveci pneumonia. The second step was a review of the infections in order to identify whether features such as duration, recurrence, outcome, could be indicative of an opportunistic nature. Genentech stated that for the cases reviewed, they considered duration of the infections, their recurrence (especially for the herpetic infections), and their resolution with anti-infectives. Genentech noted that they did not generate a report describing the medical review of these potential opportunistic infections. Genentech's approach to identifying and reviewing potential opportunistic infections appeared reasonable, although documentation in a formal report submitted with the BLA would have allowed for a more transparent and thorough evaluation of their approach.

Infections Overall MS trials (Pool B)
In all MS trials (Pool B), infections were commonly reported (54.4%, 1,169/2,147) and the rate of infections was 77.7/100PYs. Infections were the most commonly reported SOC for SAEs (3.6%, 78/2,147), but only led to discontinuation of 0.3% (7/2,147) of patients.

At the time of the 90 Day Safety Update, 57.3% (1306/2279) of MS patients who received ocrelizumab had one or more infections. The rate of infections was 75.9/100PYs. 4.7% (107/2279) of patients experienced 138 infection SAEs.

RMS Trials Controlled phases (Pool A)
In RMS trials controlled phase (Pool A), a higher proportion of ocrelizumab patients experienced an infection AE (58.4%, 482/825) than interferon patients (interferon b-1a 52.4% 433/826). The results were not meaningfully different when applying the broader definition of infections (ocrelizumab 58.5%; interferon b-1a 53.4%). When considering the number of AEs, there were also more infection events in the ocrelizumab group (n=1,237) compared to the interferon group (n= 966).

When Genentech grouped the infections into baskets, ocrelizumab patients more frequently had upper respiratory tract infections, gastrointestinal tract infections, skin infections, lower respiratory tract infections, herpes infections, and infectious biliary disorders. I provide those results in the following table.

Table 31 Infection Risk by basket terms, RMS trials controlled phase (Pool A)

Infection basket	Interferon b-1a n=826	Ocrelizumab n=825
Patients with at least 1 event	48.5% (401)	54.1% (446)
Upper respiratory tract	33.1% (273)	39.9% (329)
Urinary tract	14.6% (121)	13.8% (114)
Gastrointestinal tract	7.3% (60)	8.4% (69)
Skin	5.9% (49)	7.4% (61)
Lower respiratory tract	5.2% (43)	7.5% (62)
Herpes virus associated	3.6% (30)	6.1% (50)
Biliary	0.5% (4)	0.8% (7)
Sepsis/SIRS (broad)	0.4% (3)	0.1% (1)
Sepsis/SIRS (narrow)	0.4% (3)	0.1% (1)
Central nervous system	0	0

Calculating infections as rates (# infection events under basket terms/person time) did not result in meaningful changes in relative infection risk when comparing the infection risk across treatment arms.

The highest rate of Upper respiratory tract infections among ocrelizumab patients and greatest difference compared to interferon was following the first dose (ocrelizumab 54.5/100PY; interferon 35.5/100PY). Thereafter, the upper respiratory tract infections rates were more similar for ocrelizumab and interferon. Following dose 2, the rate of upper respiratory tract infection for ocrelizumab was 43.6/100PY compared to 36.7/100PY for interferon; following dose 3 the rate for ocrelizumab was 37.9/100PY compared to 35.0/100PY for interferon; and following dose 4 the rate for ocrelizumab was 27.0/100PY compared to 23.3/100PY for interferon.

The highest rate of Herpes infections among ocrelizumab patients and greatest difference compared to interferon was following the first dose (ocrelizumab 6.6/100PY; interferon 3.4/100PY). Thereafter the rates of herpes infections declined, but remained higher among ocrelizumab patients. Following dose 2, the rate of herpes infection for ocrelizumab was 4.7/100PY compared to 2.5/100PY for interferon; following dose 3 the rate for ocrelizumab was 4.2/100PY compared to 2.1/100PY for interferon; and following dose 4 the rate for ocrelizumab was 2.4/100PY compared to 1.3/100PY for interferon.

95% of ocrelizumab infections and 93% of interferon infections were classified as severity grade 1 or 2. Three percent of ocrelizumab patients and 4% of interferon patients had an infection AE with severity grade 3. Two ocrelizumab patients experienced infections of Grade 4 severity, (biliary sepsis and appendicitis). No fatal infections (Grade 5) were reported during the controlled phase of RMS trials.

A higher percentage of interferon patients experienced infection SAEs (2.9%, 24/826) compared to ocrelizumab patients (1.3%, 11/825). When considering serious infections that included SAEs and non-serious infections treated with iv antibiotics, a similar result was seen with 3.8% (31/826) of interferon patients meeting these criteria compared to 1.8% (15/825) of ocrelizumab patients. Pyelonephritis was the only serious infection that occurred in at least 2 ocrelizumab patients and occurred more commonly compared to placebo (ocrelizumab 0.2%, 2/825; placebo 0/826).

PPMS Trial Controlled Phase
In the PPMS trial controlled phase, 71.4% (347/486) of ocrelizumab patients experienced one or more infection AEs compared to 69.9% (167/239) of placebo patients. The number of infection AEs reported (ocrelizumab n=1084, placebo n=502) did not suggest meaningful differences in risk by treatment when considering the 2:1 randomization in this trial.

Analysis of infections in the PPMS trials using “basket” terms showed that PPMS patients, both placebo and ocrelizumab, reported infections more frequently than RMS patients. In the PPMS trials, a higher percentage of ocrelizumab patients reported the following infections compared to placebo patients: upper respiratory tract, skin, lower respiratory tract, and herpes virus associated. I provide the results of the basket term analysis in the following table.

Table 32 Infection Risk by basket terms, PPMS trial controlled phase

Infection basket	Placebo n=239	Ocrelizumab n=486
Patients with at least 1 event	64.0% (153)	67.5% (328)
Upper respiratory tract	42.7% (102)	46.9% (228)
Urinary tract	25.5% (61)	23.0% (112)
Skin	10.0% (24)	12.8% (62)
Gastrointestinal tract	11.3% (27)	9.5% (46)
Lower respiratory tract	7.9% (19)	9.7% (47)
Herpes virus associated	3.3% (8)	4.7% (23)
Sepsis/SIRS (broad)	1.7% (4)	0.8% (4)
Sepsis/SIRS (narrow)	1.7% (4)	0.8% (4)
Biliary	0.4% (1)	0.4% (2)
Central nervous system	0.4% (1)	0

When Genentech calculated infection rates (# infection events under basket terms/person time) only skin infections (ocrelizumab 5.44/100PY, placebo 5.15/100PY) and lower respiratory tract infections (ocrelizumab 4.09/100PY, placebo 3.94/100PY) occurred more frequently with ocrelizumab.

Unlike infection in RMS trials, Genentech did not find a consistent trend in infection rate over time. Overall infection rates for ocrelizumab were 89/100PY following the first dose and 71/100PY following dose 8. The lowest infection rate for ocrelizumab was following dose 6 (67/100PYs).

92% of infections in ocrelizumab patients and 83% of infections in placebo patients were classified as Grade 1 or 2 in severity. Grade 3 infections were reported in 11.5% (n=19) of patients in the placebo group and in 7.5% (n=26) of patients ocrelizumab group. One patient (0.4%) in the placebo group and 8 patients (1.6%) in the ocrelizumab group experienced an infection that was classified as Grade 4. Two ocrelizumab patients experienced Grade 5 events (pneumonia, aspiration pneumonia).

A higher percentage of placebo patients experienced infection SAEs (8.4%, 20/239) compared to ocrelizumab patients (7.0%, 34/486). No additional events were identified when considering serious infections that included SAEs and non-serious infections treated with iv antibiotics. The infection SAEs that occurred in at least 2 ocrelizumab patients and occurred more commonly compared to placebo were cellulitis (ocrelizumab 0.6%, 3/486; placebo 0.4% 1/239), appendicitis (ocrelizumab 0.4%, 2/486; placebo 0/239), bronchitis (ocrelizumab 0.4%, 2/486; placebo 0/239),diverticulitis (ocrelizumab 0.4%, 2/486; placebo 0/239), and pyelonephritis (ocrelizumab 0.4%, 2/486; placebo 0/239).

Opportunistic Infections All MS Trials (Pool B)
Using a broad screening search for potential opportunistic events, Genentech identified 130 patients with events for additional review. The events captured by this search were oral herpes (n=55), herpes zoster, (n=35), herpes simplex (n=14), oral candidiasis (n=8), candida infection (n=6), herpes virus infection (n=5), genital herpes (n=2), ophthalmic herpes simplex (n=2), varicella (n=2), and amebic dysentery, anogenital warts, cervix warts, genital herpes simplex, herpes ophthalmic, keratitis viral, nasal herpes, neutropenic sepsis, oral fungal infection, and urinary tract infection fungal (n=1, each). After Genentech's review of these cases, they considered none to be opportunistic infections.

In the 90 Day Safety Update, Genentech reported an updated total of 162 patients with potential opportunistic infections. The new potential opportunistic infections were oral herpes (n=14), herpes zoster (n=10), candida infection (n=2), genital herpes simplex (n=2), varicella (n=2), varicella zoster virus infection (n=2), and acute hepatitis C, Dengue fever, esophageal candidiasis, genital herpes, keratitis viral, oral candidiasis, oropharyngitis fungal, and pulmonary

tuberculoma, (n=1, each). After Genentech's review of these cases, they considered none to be opportunistic infections.

Genentech identified all ocrelizumab patients who experienced neutropenia during MS trials (n=326). These events were classified as Grade 1 (<LLN -1.5 x 109/L) (n=210), Grade 2 (< 1.5 – 1.0 x 109/L) (n=92), Grade 3(< 1.0 – 0.5 x 109/L) (n=16) and Grade 4 (<0.5 x 109/L) (n=8). For all patients with Grade 2 or higher neutropenia, Genentech looked for infection AEs during or close to the time of neutropenia, and found no association between neutropenia and infections in these patients.

Genentech noted that in MS trials, the levels of IgA and IgG remained stable during treatment with ocrelizumab, while levels of IgM decreased over the course of treatment. The rates of infections per 100PY in patients with decreases in IgAs and IgGs to below the LLN at any time point were similar to the rate in the overall population. In 426 patients with low levels of IgM, the rate of infection (75.2 events per 100PY) was similar to the rate in the overall population (77.7 events per 100PY). Genentech repeated this analysis using serious infections. In 426 patients with low levels of IgM, the rate of serious infection (3.02 events per 100PY, 95% CI 2.12, 4.19) was slightly higher than the rate in the overall population (2.32 events per 100PY, 95% CI 1.90, 2.81), although the 95% confidence intervals overlapped.

Infections in RA Studies
In their Summary of Clinical Safety, Genentech noted that the development program in RA was abandoned due to (b) (4) "an increased incidence of serious and opportunistic infections compared with comparator". Genentech pointed to important differences between RA and MS populations that could result in differential infection when comparing them. RA patients are generally older, with greater comorbid disease burden, and can be exposed to combination immunosuppressive therapy including glucocorticoids, methotrexate, and TNF-α Inhibitors. In the RA trials, ocrelizumab or comparator was added to regimens consisting of methotrexate or leflunomide. Methotrexate labeling includes a boxed warning that describes severe bone marrow suppression and potentially fatal opportunistic infections. Leflunomide has a Warnings and Precautions statement for severe infections (including sepsis), pancytopenia, and agranulocytosis.

In all RA studies (Pool E) 65.9% (1,928/2,926) of ocrelizumab patients experienced 5,677 infections. The rate of infection was 77.5/100PY (95% CI: 75.5, 79.6). The highest rate of infection by PT was upper respiratory tract infection (12.3/100PY, 95% CI: 11.6, 13.2); followed by nasopharyngitis (8.14/100PY, 95% CI: 7.50, 8.82).

In the controlled RA trials, the percentage of patients with an infection was similar between placebo (51.6%; 506 patients) and the ocrelizumab 400 mg (50.8%; 602 patients) treatment groups, and was higher in the ocrelizumab 1000 mg treatment group (55.9%; 529 patients).

There were more AEs of bronchitis in the ocrelizumab 400 mg group (8.2%) compared with the placebo (6.6%) and ocrelizumab 1000 mg (6.1%) groups. The frequency of the other common infection AEs were relatively balanced across groups.

The percentage of patients reporting a serious infection was higher in the ocrelizumab 1000 mg group (5.1% ; n=66) compared with the placebo (3.4%; n=36) and ocrelizumab 400 mg (3.8%; n=52) groups.

For all RA studies (Pool E) Genentech identified 258 ocrelizumab patients (8.8%, 258/2926) with potential opportunistic infections. Herpes zoster (3.8%; 110 patients) was the most commonly reported potential opportunistic infection, followed by oral herpes (2.3%; 66 patients), oral candidiasis (0.8%; 24 patients), herpes simplex (0.6%; 19 patients), candida infection (0.5%; 14 patients), and pneumocystis jirovecii pneumonia (0.2%; 5 patients). Dengue fever, herpes virus infection, and esophageal candidiasis were each reported in 0.1% of patients.

Thirty-one patients (33 infections) that were identified with potentially opportunistic infections had events that were also SAEs and the infections were herpes (herpes zoster, 11 patients and herpes simplex, 1 patient) pneumocystis jirovecii pneumonia (n=5), hepatitis B (one new case and one reactivation), candidiasis (n=2), histoplasmosis (n=2), mycobacterium infection (n=2), and Dengue fever, atypical pneumonia, fungal esophagitis, viral meningoencephalitis, and strongyloidiasis (n= 1, each).

After review of the potentially opportunistic infection cases, Genentech felt that 14 patients (16 infections) were true opportunistic infections. These opportunistic infections were pneumocystis jirovecii pneumonia (n=5), herpes zoster (n=3), herpes zoster oticus, herpes simplex, varicella zoster pneumonia, systemic candida, esophageal candidiasis, mycobacterium abscessus infection, atypical pneumonia, and hepatitis B.

Additional analyses of predictive factors
Genentech analyzed RMS controlled phase data (Pool A) and RA controlled trials data (Pool D) to look for predictive factors for overall infections. Due to the limited number of serious infections in MS patients, Genentech searched for predictive factors for serious infections using only RA trial data. For a discussion of safety analysis by demographics subgroups, please refer to section 8.6 of this review.

Univariate analyses Treatment independent risk factors
For overall infections, in both MS and RA trials, patients in regions other than US/Canada/Australia had lower risks. Other factors that predicted risk of infection were female sex, higher BMI/weight, and history of cardiac disease and previous infections. Higher levels of IgG at baseline decreased the risk of infections, while patients in the lowest group of IgG at baseline (0% <=20%) had a higher infection risk compared with the reference group (IgG > 20%

<= 80%). In MS patients, previous steroid use was associated with a decreased the risk of infections (HR 0.778, 95% CI: 0.645, 0.938) (concomitant steroid use not evaluated). In patients with RA, previous and concomitant steroid use did not seem to have an impact on the risk of infections. In the RA population the dosage of methotrexate at baseline, (> 8 mg) was associated with a higher risk of infections.

Risk factors for serious infections were analyzed in patients with RA. The pattern of risk factors was similar to that described above for all infections. Patients from regions other than the USA/Canada/Australia had a lower risk of infections compared to patients from the USA/Canada/Australia. Patients with higher body weight had an increased risk of infections. Genentech commented that patients in USA/Canada/Australia had higher weights than other regions. A separate analysis showed that within a region the incidence rates of infections in different body weight categories were similar, suggesting that region is a prognostic risk factor while body weight is not.

Univariate analyses Treatment emergent risk factors
No significant interaction with treatment was observed for any of the covariates tested. Genentech identified risk factors with nominal significance for further analyses. For example, an increased dose-dependent risk of all infections and serious infections in RA patients treated with ocrelizumab and recruited in Asia compared with the USA/Canada/Australia. In addition, the risk of all infections and serious infections was increased in Asian RA patients compared with Caucasian RA patients. In RA patients, previous/concomitant use of steroids potentially increased the effect of ocrelizumab on the risk of serious infections at both ocrelizumab 400 mg and ocrelizumab 1000 mg dose levels compared with patients not receiving steroids. Higher levels of IgM at baseline seemed to decrease the effect of ocrelizumab on the incidence of serious infections compared with lower levels of IgM at baseline in RA patients. No treatment interaction with different levels of IgM at baseline was observed for all infections in RA patients. In MS patients, the observed effect was reversed (i.e., low baseline levels of IgM decreased the effect of ocrelizumab on infections compared with higher baseline levels of IgM).

Genentech concluded that their additional analyses support that risk factors for serious infections in RA trials included other comorbidities (ex. heart disease, previous infections), chronic use of immunosuppressants/steroids, and patients from Asia.

8.5.3. Suicide and Depression

There was no imbalance in SAEs or TEAEs in the *Psychiatric disorders* SOC in the controlled trials in RMS or PPMS. However, there was an imbalance in depression, and suicide attempt SAEs that occurred only in ocrelizumab patients and not in comparator patients. Depression TEAEs occurred less frequently in ocrelizumab-treated patients than placebo in the PPMS controlled trial, but occurred slightly more frequently than interferon (8% vs 7%) in the RMS Controlled

Trials (Pool A). Because interferon beta-1a labeling has a warning for depression and suicide, I recommend considering a warning depression and suicide for ocrelizumab.

All MS Trials (Pool B)
Of the 2147 ocrelizumab patients in MS trials, 137 had an AE of depression, 16 had depressed mood, 6 had a suicide attempt, 4 had suicidal ideation, and there was a single case of completed suicide (narrative summarized with the deaths above). In addition there was one AE each of depressive symptom and dysthymic disorder.

Cumulatively through the 90 Day Safety Update, 167 ocrelizumab patients had an AE of depression, 17 had depressed mood, 7 had a suicide attempt, 4 had suicidal ideation, and there was a single case of completed suicide. In addition there was one AE each of adjustment disorder with depressed mood, anhedonia, depressive symptom, dysthymic disorder, and major depression.

RMS Trials Controlled Phase (Pool A)
Depression was reported for 7.8% (64/825) of ocrelizumab patients and 6.5% (54/826) interferon b-1a patients. Except for suicide attempt (ocrelizumab 0.1%, n=1; interferon b-1a n=0) the remaining suicide/depression AEs were reported more frequently by interferon b-1a patients.

Depression/Suicide SAEs
In the following table I summarize the depression and suicide related SAEs from the RMS trials controlled phase experience. There was a small number of events and the risks seemed similar when comparing treatment groups.

SAE	Interferon beta 1-a (n=826)	Ocrelizumab (n=825)
Completed suicide	0.1% (1)	0.1% (1)
Depression	0	0.2% (2)
Depression suicidal	0.2% (2)	0
Suicidal ideation	0.1% (1)	0
Suicide attempt	0	0.1% (1)

PPMS Trial Controlled Phase
Depression was reported by 12.6% (30/239) placebo patients and 9.7% (47/486) ocrelizumab patients. The depression/suicide AEs reported more frequently by ocrelizumab patients were depressed mood (ocrelizumab 1.6%, n=3; placebo 1.3%, n=3), suicide attempt (ocrelizumab 0.4%, n=2; placebo n=0), depression suicidal (ocrelizumab 0.2%, n=1; placebo n=0), and suicidal ideation (ocrelizumab 0.2%, n=1; placebo n=0).

Depression/Suicide SAEs

In the following table I summarize the depression and suicide related SAEs from the PPMS trial controlled phase experience. There was a small number of events, but all occurred in ocrelizumab patients and none in placebo patients.

SAE	Placebo (n=239)	Ocrelizumab (n=486)
Suicide attempt	0	0.4% (2)
Depression suicidal	0	0.2% (1)
Suicidal ideation	0	0.2% (1)

8.5.4. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Using what appeared to be an appropriate approach to identifying potential cases; Genentech did not find any DRESS cases in the ocrelizumab development program.

To identify potential cases of DRESS, Genentech used an approach similar to the SMQ that will soon be available under MedDRA version 19.0. The not yet available SMQ for DRESS has a narrow and a broad basket. The narrow basket consists of two PTs: DRESS and pseudolymphoma. The broad basket consists of 349 PTs grouped in four groups: Skin+Organ (292 PTs), Hematology (44 PTs), Pyrexia (4 PTs), and Lymphadenopathy (9 PTs). The broad basket has an algorithm which requires one PT from the Skin+Organ group plus at least one PT from two of the remaining three groups. Genentech's approach, influenced by above, is provided below:

Step 0: Identify all cases containing either of the two narrow basket PTs (DRESS and pseudolymphoma)

Step 1: Identify all cases from the sub-baskets Hematology, Pyrexia, and Lymphadenopathy of the broad basket by:

- searching for all 57 PTs of the 3 smaller sub-baskets
- and then applying a temporality of maximum 30 days between PTs from each subbasket.

If cases with at least one PT from at least two of the three sub-baskets were identified in Step 1, proceed to Step 2.

Step 2: Check if PTs from the sub-basket of Skin+Organ (292 PTs) were also reported in the cases identified in Step 1 with a temporality of maximum 30 days between PTs from each sub-basket.

If Step 2 was met proceed to Step 3.

Step 3: Perform a medical review of all cases meeting the criteria below to assess the existence of a potential signal:

- Hematology PT and Pyrexia PT and Skin+Organ PT = YES
- Hematology PT and Lymphadenopathy PT and Skin+Organ PT = YES
- Pyrexia PT and Lymphadenopathy PT and Skin+Organ PT = YES

If Step 3 was met, and a signal suspected, the search would be expanded to:

- the controlled treatment periods (Pool A in MS and Pool D in RA)
- abnormal laboratory results that were not reported as AEs (e.g., immunoglobulins, WBC and differentials, platelets).

MS All trials (Pool B)
Genentech identified no cases of DRESS in MS patients in the ISS. The details of the search are summarized below.

Genentech found no events of DRESS or pseudolymphoma (step 0). Genentech identified 3 cases from at least 2 sub-baskets hematology, pyrexia, and lymphadenopathy. One event lacked a resolution date, precluding evaluation of temporal criteria. The remaining 2 cases had events with temporal association of <30 days (step 1). None of the 3 cases identified above also had events from the Skin+Organ basket (Step 2).

No DRESS cases were identified in the 90 Day Safety Update.

RA All Trials (Pool E)
Genentech identified no cases of DRESS in RA patients. The details of the search are summarized below.

Genentech found no events of DRESS or pseudolymphoma (step 0). Genentech identified 4 cases from at least 2 sub-baskets hematology, pyrexia, and lymphadenopathy. Two events were not considered further because they did not meet temporal criteria (i.e., > 30 days apart). The remaining 2 cases lacked a resolution date, precluding evaluation of temporal criteria (step 1). Neither of the 2 cases identified above also had events from the Skin+Organ basket (Step 2).

8.5.5. Anaphylactic Reactions

Genentech did not identify any anaphylaxis cases in the ocrelizumab development program.

Genentech searched for potential cases of anaphylaxis using the SMQ for anaphylactic reaction, by using their predetermined basket of AEs associated with anaphylaxis, and by looking for AEs that are part of Sampson's criteria for anaphylaxis. I include those criteria below.

Sampson's Clinical criteria for diagnosing anaphylaxis
Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING
    a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
    b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
    d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
    a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
    b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

MS All Trials (Pool B)
Genentech identified 4 potential cases of anaphylaxis (circulatory collapseWA25046-231210-11302, asthma WA21093-252185-1932258, dyspneaWA25046-207348-14602, and pruritus allergicWA25046-208440-37004) but upon review determined that none represented anaphylaxis events. I reviewed the datasets and when available narratives and summarize information for these cases below.

The circulatory collapse event was a non-serious AE in a 50 year old male that occurred 60 days after the last dose, had a severity rating of 2, and was listed as occurring during the SFU. The dataset noted that the patient withdrew from double blind treatment prior to this event (reason-consent withdrawn).

The patient with asthma involved a 48 year old female who was hospitalized 97 days after her most recent ocrelizumab infusion. She presented with symptoms of dry cough and diagnosed with asthma.

The dyspnea case involved a 42 year old female. Twenty days after her most recent infusion, she developed dyspnea, mild fever (<37.5C) and muscle fatigue. The dyspnea worsened and she was admitted to a hospital (28 days after last infusion). Lab testing and imaging were negative and she improved and was discharged without a diagnosis, but the narrative did mention "anxious depression status".

The pruritus allergic event involved a 50 year old male. This patient developed pruritus allergic (anatomic site not specified) 125 days after his most recent infusion. His symptoms responded to treatment with topical steroids and antihistamines.

No cases of anaphylaxis were identified in the 90 Day Safety Update.

RA All Trials (Pool E)
After medical review of AEs identified by their search, Genentech identified no cases of anaphylactic reactions in the RA trials.

8.5.6. Autoimmune Disorders

There did not appear to be evidence to support an association between ocrelizumab and autoimmune AEs.

To identify potential autoimmune AEs, Genentech searched for PTs that matched a list approximately 100 terms that was compiled for this purpose. I reviewed the list from the ISS and the 90 Day Safety Update and determined that Genentech's search would likely have captured autoimmune AEs in the development program.

In all MS trials, Genentech identified 12 patients with 13 potential autoimmune disorders (0.6%, 12/2147). The identified events were multiple sclerosis (n=8), autoimmune thyroiditis (n=2), immune thrombocytopenic purpura (n=1), autoimmune uveitis (n=1), and alopecia areata (n=1). Genentech's analysis was based on a search that used an extensive list of potential autoimmune-related preferred terms and would likely have identified a majority of autoimmune AEs.

In the 90 Day Safety Update, Genentech identified 2 additional autoimmune AEs (ITP, autoimmune thyroiditis).

8.6. Safety Analyses by Demographic Subgroups

In their ISS, Genentech examined the RMS trials controlled phase (Pool A) data to look for differences in risk for AEs in demographic subgroups. Genentech also provided demographic

subgroup analyses for MS Pools B and C, but these pools include no comparator groups and so it is not possible to determine if any observed risk differences are due to the demographic factor alone or are due to treatment effects that vary by the demographic factor.

RMS trials controlled phase (Pool A) Demographic data
I summarize data from Genentech's presentations of AE risks by demographic subgroups. There did not appear to be meaningful differences in risk by treatment after stratification by demographic variables. In some cases there were too few events to allow for a robust assessment of risk by demographic variable. Note-Genentech did not provided an analysis stratified by age so I performed the analysis using the sponsor provided datasets.

Table 33 Pool A Trials Select Adverse Events Stratified by Sex

Outcome	Interferon		Ocrelizumab	
	Male 468PYs n=277	Female 931PYs n=549	Male 501PYs n=248	Female 947PYs n=541
AE	255.5/100PY (n=1196)	316.4/100PYs (n=2945)	258.1/100PYs (n=1294)	306.4/100PYs (n=2900)
Death	0.2/100PYs (n=1)	0.1/100PY (n=1)	0.2/100PYs (n=1)	(n=0)
SAE	7.1/100PYs (n=33)	5.9/100PYs (n=55)	6.4/100PYs (n=32)	4.9/100PY (n=46)
Infection	57.3/100PY (n=268)	75.0/100PYs (n=698)	63.8/100PYs (n=320)	96.9/100PYs (n=917)
Malignancy	(n=0)	0.2/100PYs (n=2)	0.4/100PYs (n=2)	0.2/100PY (n=2)

Table 34 Pool A Trials Select Adverse Events Stratified by Age*

Outcome	Interferon		Ocrelizumab	
	Age<=45 1105PYs n=652	Age>45 294PYs n=174	Age<=45 1136PYs n=648	Age>45 312PY n=177
AE	293.7/100PYs (n=3245)	304.8/100PYs (n=896)	298.9/100PYs (n=3395)	256.1/100PYs (n=799)
Death	0.1/100PYs (n=1)	0.3/100PYs (n=1)	0.1/100PYs (n=1)	(n=0)
SAE	5.8/100PYs (n=64)	8.2/100PYs (n=24)	4.6/100PYs (n=52)	8.3/100PYs (n=26)
Infection	70.3/100PYs (n=777)	64.3/100PYs (n=189)	89.3/100PYs (n=1014)	71.5/100PYs (n=223)
Malignancy	(n=0)	0.7/100PYs	0.2/100PYs	0.6/100PYs

		(n=2)	(n=2)	(n=2)

*Genentech did not provide results stratified by age so I conducted these analyses using the Pool A AE and exposure data sets.

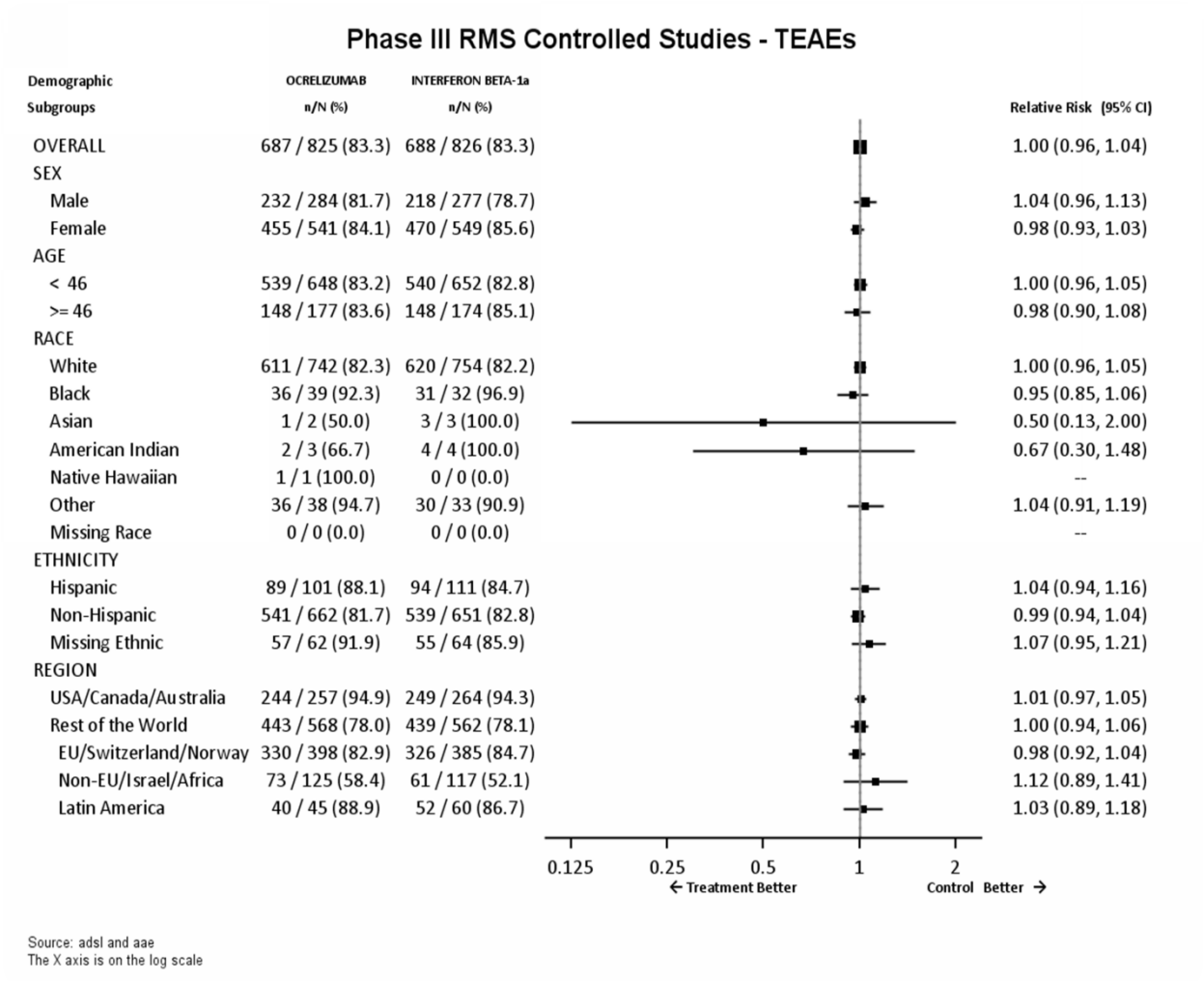
Table 35 Pool A Trials Select Adverse Events Stratified by Race

Outcome	Interferon			Ocrelizumab		
	Black 49PYs (n=32)	White 1284PYs (n=754)	Other 67PYs (n=40)	Black 66PYs (n=39)	White 1302PYs (n=742)	Other 80PYs (n=44)
AE	336/100PYs (n=163)	287/100PYs (n=3689)	433/100PYs (n=289)	379/100PYs (n=251)	283/100PYs (n=3680)	331/100PYs (n=263)
Death	(n=0)	0.2/100PYs (n=2)	(n=0)	(n=0)	0.1/100PYs (n=1)	(n=0)
SAE	12/100PYs (n=6)	6/100PYs (n=75)	10/100PYs (n=7)	15/100PYs (n=10)	5/100PYs (n=63)	6/100PYs (n=5)
Infection	72/100PYs (n=35)	69/100PYs (n=883)	72/100PYs (n=48)	69/100PYs (n=46)	86/100PYs (n=1120)	89/100PYs (n=71)
Malignancy	(n=0)	0.2/100PY (n=2)	(n=0)	(n=0)	0.3/100PYs (n=4)	(n=0)

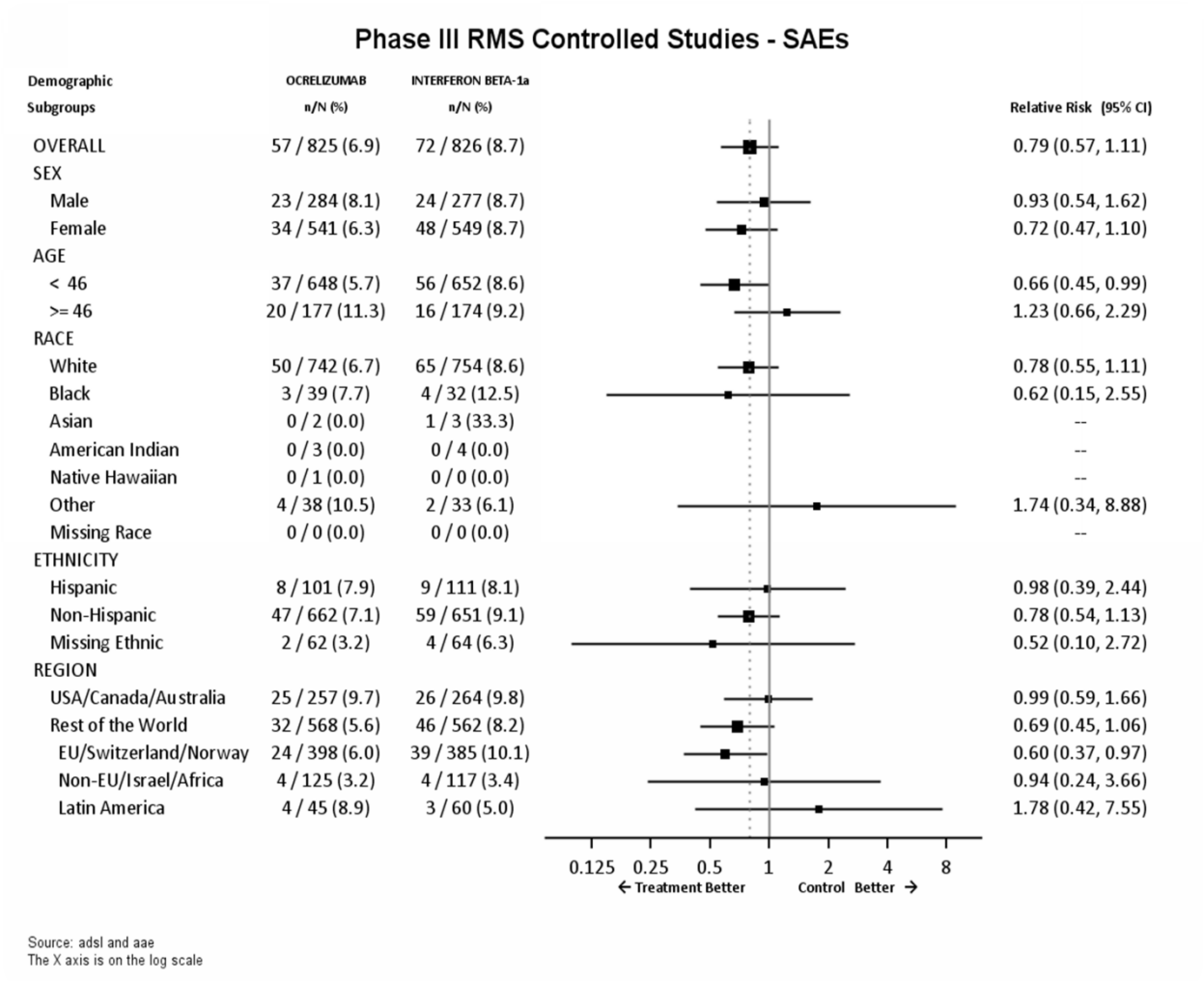
The following table, created from the sponsor provided demographic data sets, summarizes data for the Pool A trials. The table demonstrates that a higher percentage of females than males were enrolled and that distribution of females/males in the treatment groups was similar. The trials included a majority of patients <45 years old. The enrollees were predominantly White (91%). 47% of patients were from EU/Switzerland/Norway, 32% from USA/Canada/Australia, 15% from Non-EU/Israel/Africa, and 6% from Latin America.

Table 7.2.1 Baseline Demographics (saffl='Y')			
Demographic Parameters	**OCRELIZUMAB (N=825) n (%)**	**INTERFERON BETA-1a (N=826) n (%)**	**Total (N=1651) n (%)**
Sex			
Male	284 (34.4)	277 (33.5)	561 (34.0)
Female	541 (65.6)	549 (66.5)	1090 (66.0)
Age			
Mean years (SD)	37.1 (9.2)	37.2 (9.2)	37.2 (9.2)
Median (years)	38	37	37
Min, Max (years)	18, 56	18, 55	18, 56
Age Group			
< 46	648 (78.5)	652 (78.9)	1300 (78.7)
>= 46	177 (21.5)	174 (21.1)	351 (21.3)
Race			
White	742 (89.9)	754 (91.3)	1496 (90.6)
Black or African American	39 (4.7)	32 (3.9)	71 (4.3)
Asian	2 (0.2)	3 (0.4)	5 (0.3)
American Indian or Alaska Native	3 (0.4)	4 (0.5)	7 (0.4)
Native Hawaiian or Other Pacific Islander	1 (0.1)	0 (0.0)	1 (0.1)
Other	38 (4.6)	33 (4.0)	71 (4.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity			
Hispanic or Latino	101 (12.2)	111 (13.4)	212 (12.8)
Not Hispanic or Latino	662 (80.2)	651 (78.8)	1313 (79.5)
Missing	62 (7.5)	64 (7.7)	126 (7.6)
Region			
USA/Canada/Australia	257 (31.2)	264 (32.0)	521 (31.6)
Rest of the World	568 (68.8)	562 (68.0)	1130 (68.4)
EU/Switzerland/Norway	398 (48.2)	385 (46.6)	783 (47.4)
Non-EU/Israel/Africa	125 (15.2)	117 (14.2)	242 (14.7)
Latin America	45 (5.5)	60 (7.3)	105 (6.4)

The following Forest plot of overall AEs in RMS trial controlled phase (Pool A) stratified by demographic variables was created using the Agency provided demographic analysis software. These data do not provide strong evidence of important differences in risk for AEs by the included demographic variables.



The following Forest plot of SAEs stratified by demographic variables was created using the Agency provided demographic analysis software. These data do not suggest important differences in risk for AEs by the included demographic variables.



PPMS Trial

Genentech did not provide in the ISS analyses for the PPMS trial that stratified by demographic variables so the Division requested these analyses. In the tables below, I summarize Genentech's presentations of select AE risks by demographic subgroups that were included in a 9/7/16 IR response.

Table 36 PPMS Trial Select Adverse Events Stratified by Sex

Outcome	Placebo		Ocrelizumab	
	Male 325PYs n=120	Female 335PYs n=119	Male 706PYs n=246	Female 710PYs n=240
AE	256.0/100PY (n=832)	277.8/100PYs (n=930)	260.7/100PYs (n=1842)	260.3/100PYs (n=1848)

Death	0.3/100PYs (n=1)	(n=0)	0.4/100PYs (n=3)	0.1/100PYs (n=1)
SAE	13.2/100PYs (n=43)	10.2/100PYs (n=34)	10.5/100PYs (n=74)	10.0/100PY (n=71)
Infection	68.3/100PY (n=222)	83.6/100PYs (n=280)	69.5/100PYs (n=491)	83.5/100PYs (n=593)
Malignancy	(n=0)	0.6/100PYs (n=2)	0.9/100PYs (n=6)	1.0/100PY (n=7)

Table 37 PPMS Trial Select Adverse Events Stratified by Age*

Outcome	Placebo		Ocrelizumab	
	Age<=45 304PYs n=113	Age>45 356PYs n=126	Age<=45 677PYs n=230	Age>45 739PY n=256
AE	261/100PYs (n=793)	272/100PYs (n=969)	237/100PYs (n=1602)	283/100PYs (n=2088)
Death	0.3/100PYs (n=1)	(n=0)	0.1/100PYs (n=1)	0.4/100PYs (n=3)
SAE	7.9/100PYs (n=24)	14.9/100PYs (n=53)	8.3/100PYs (n=56)	12.0/100PYs (n=89)
Infection	77.3/100PYs (n=235)	75.0/100PYs (n=267)	66.6/100PYs (n=451)	85.7/100PYs (n=633)
Malignancy	(n=0)	0.6/100PYs (n=2)	0.1/100PYs (n=1)	1.6/100PYs (n=12)

Genentech did not provide results stratified by age so I conducted these analyses using the study AE data set. Genentech provided the person time exposure in a 9/12/16 submission.

Table 38 PPMS Trial Select Adverse Events Stratified by Race

Outcome	Placebo			Ocrelizumab		
	Black 9PYs (n=5)	White 640PYs (n=230)	Other 11PYs (n=4)	Black 21PYs (n=9)	White 1329PYs (n=454)	Other 67PYs (n=23)
AE	648/100PYs (n=60)	258/100PYs (n=1650)	494/100PYs (n=52)	251/100PY (n=52)	261/100PYs (n=3462)	263/100PYs (n=176)
Death	(n=0)	0.2/100PYs (n=1)	(n=0)	(n=0)	0.3/100PYs (n=4)	(n=0)
SAE	54/100PYs (n=5)	11/100PYs (n=69)	28/100PYs (n=3)	10/100PYs (n=2)	10/100PYs (n=135)	12/100PYs (n=8)
Infection	13/100PYs	74/100PYs	123/100PYs	48/100PYs	76/100PYs	87/100PYs

	(n=140)	(n=476)	(n=13)	(n=10)	(n=1016)	(n=58)
Malignancy	(n=0)	0.3/100PY (n=2)	(n=0)	(n=0)	1.0/100PYs (n=13)	(n=0)

8.7. Specific Safety Studies/Clinical Trials

N/A

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Summary
During controlled phases of MS trials, a higher percentage of ocrelizumab patients were diagnosed with a malignancy than comparator patients. Fifteen ocrelizumab patients (1.1%, 15/1311) had a malignancy diagnosis (RMS trials 0.5%, 4/825; PPMS 2.8%; 11/486) while 4 patients (0.4%, 4/1065) receiving comparator treatment had a malignancy diagnosis (RMS-IFN b-1a 0.2%, 2/826; PPMS placebo 0.8%, 2/239). In all MS trials (controlled and open label phases) through the 90 day safety update, 1.0% (23/2,279) of ocrelizumab patients were diagnosed with a malignancy and the rate was 0.4/100PY (23/5,711 PYs). For the 23 ocrelizumab patients diagnosed with a malignancy during all MS trials, the time from first infusion to malignancy event ranged from 15-1,303 days and the cumulative ocrelizumab doses ranged from 600-4,800mg.

During controlled phases of ocrelizumab MS trials, the imbalance in breast cancers by treatment was most notable. There were 6 breast cancers in ocrelizumab patients (2 from RMS trials, 4 from PPMS trials) and none in comparator patients. The breast cancer risk in female ocrelizumab patients in MS controlled trials was 0.8% (6/781) compared to 0/668 for female comparator patients. For all MS trials including open label experience, through the 90 day safety update, there were 8 breast cancer cases in female patients exposed to ocrelizumab (0.23/100PYs, 8/3,435PYs). For the 8 breast cancer cases, the time from first ocrelizumab infusion to breast cancer ranged from 378-1298 days and the cumulative dose received ranged from 600-4,600mg. One additional breast cancer case was reported as a late breaking event, after the data cutoff date. Nothing in the narratives for these events could definitively exclude ocrelizumab as a causal/contributory factor.

Genentech acknowledged the imbalance in malignancy risk and attempted to evaluate it further by summarizing the experience in the ocrelizumab RA trials, providing information about breast cancer risk with Rituxan, another anti CD20 monoclonal antibody, and comparing malignancy risk in ocrelizumab trials to external data sources (publications, databases, etc). Genentech felt that incidence rates of malignancies, including breast cancer, in patients treated

with ocrelizumab were within the range of placebo data from clinical trials in MS and epidemiological data and that no conclusion can be made concerning the risk due to the low number of events and the limited follow-up period.

In RA controlled trials, there was no imbalance in overall malignancies or breast cancer, although the controlled phases in RA were shorter in duration than the MS trials. Specifically, there were limited numbers of patients exposed during the time period when many of the breast cancers were reported in the MS controlled phases. For all RA trials, the percentage of patients diagnosed with a malignancy was 3.2% (94/2,926) and the rate was 1.3/100PY (94/7,324PYs). For all RA trials, there were 7 breast cancer diagnoses (0.10/100PYs, 7/7,324PYs). The rate of breast cancers in females was 0.1/100PYs (6/5,792PYs) and in males was .07/100PYs (1/1,532PYs). The percentage of female patients diagnosed with breast cancer during RA trials was 0.3% (6/2,341) and in males was 0.2% (1/585).

Genentech provided post marketing malignancy risk data for another anti CD20 monoclonal antibody, Rituxan. Genentech felt that the cited findings suggest that the breast cancer risk is not elevated with this class member. Our DEPI consultant Dr. Braver reviewed these data and felt that no conclusions on breast cancer risk in relation to Rituximab can be drawn based on the cited analysis. She identified as limitations the lack of analyses by time since initial exposure or cumulative duration of treatment and indications that rheumatoid arthritis (RA) clinical trial participants were at lower cancer risk than other RA patients.

Genentech felt that their comparisons of ocrelizumab clinical trial malignancy risk data to risk data from external sources were reassuring. For example, Genentech noted that the malignancy incidence rates in ocrelizumab treated patients were within the ranges reported in pooled placebo data from other MS clinical trials and published epidemiological data and that the SEER standardized incidence rate of female breast cancer was within the 95% CIs reported for ocrelizumab. Dr. Braver reviewed these analyses and concluded that these comparisons of clinical trial data with external data sources cannot be interpreted due to limitations, most importantly the lack of control for potential confounding factors and the lack of traditional analyses on dose-response and time intervals between exposure and diagnosis.

Consultants from DOP1 and DHP reviewed Genentech's presentations on malignancy risk. The consultants both felt that the data supported a signal, but that there was insufficient information to support conclusions about causality. Both recommended describing the findings in labeling and both acknowledged the need for additional evaluation of this issue.

In accordance with the recommendations of our DOP1 and DHP consultants, malignancy risk, with a focus on breast cancer, should be included in ocrelizumab labeling. Given the currently available evidence, it seems most appropriate to include this information in a Warnings and Precautions statement. In addition, the proposed post marketing study that would capture

malignancies in patients treated with ocrelizumab should be a PMR and should include the changes recommended by our DEPI consultant.

Malignancy Data
All MS Trials (Pool B)
In the ISS, in all MS trials (Pool B), 18 ocrelizumab patients (0.8%, 18/2,147) were diagnosed with one or more malignancies and the rate was 0.40/100PYs (18/4,485PY). Genentech reported 19 patients with malignancies, but the narrative for the squamous cell carcinoma in patient WA21493-141035-5851 noted that the left leg lesion was present prior to the first ocrelizumab infusion, suggesting that this event predated exposure.

In these MS trials 7 female patients were diagnosed with breast cancers (0.5%, 7/1328 females). Aside from basal cell carcinoma* (n=3), no other cancer type was diagnosed more than once. The remaining malignancies were adenocarcinoma of the colon, anaplastic large cell lymphoma, endometrial cancer, malignant fibrous histiocytoma, malignant melanoma, pancreatic carcinoma, papillary thyroid cancer, and renal cancer (<0.1%, 1/2,147, each).

*One ocrelizumab patient had 3 basal cell carcinomas

90 Day Safety Update
In the 90 Day Safety Update, Genentech reported an additional 6 patients with malignancy diagnoses through the data cutoff date. One of the cases was initially reported as an adenocarcinoma, but was subsequently diagnosed as an adenoma (after the cutoff date). Although Genentech included this case in their malignancy total, I will remove it from further consideration, bringing the total to 23 patients with malignancies. The five new malignancy diagnoses were basal cell carcinoma (n=2), breast cancer, malignant melanoma, and keratoacanthoma.

Through the 90 day Safety Update, the updated percentage of MS patients with malignancy was 1.0% (23/2,279) and the updated rate was 0.4/100PYs (23/5,711PYs). The updated percentage of female patients with breast cancer was 0.6% (8/1,398). The rate of breast cancer among females was 0.23/100PY (8/3,435PYs).

One additional case each of breast cancer, basal cell carcinoma, and esophageal cancer were identified as late breaking events reported after the 90 Day Safety Update data cutoff. Without the corresponding exposure data, it is not possible to update risk/incidence calculations that include these cases.

In the table below, I summarize select information for the 23 MS patients with treatment emergent malignancies. I compiled these data from sponsor listings, narrative summaries, and data sets. The time since first dose at diagnosis was estimated in some cases due to missing

data, or evidence supporting that the patients experienced symptoms of the malignancy prior to evaluation.

Table 39 Listing of Malignancies in Ocrelizumab exposed patients from MS trials

Malignancy	Subject ID	Age(years) /Sex	Country	Time (days) since first dose at diagnosis	Cumulative dose at diagnosis
Breast Cancer	WA21092 206629 1920773	54/F	Czech Republic	378	1800mg
Breast Cancer	WA21092 234347 1926392	28/F	USA	463	600mg
Breast Cancer	WA25046 208185 10201	54/F	Germany	451	1800mg
Breast cancer	WA25046 208039 47403	54/F	France	882	3600mg
Breast cancer	WA25046 208661 21006	47/F	Poland	737	3000mg
Breast cancer	WA25046 208787 32301	52/F	UK	917	3600mg
Breast cancer	WA21493 140954 1052	43/F	Bulgaria	748	4600mg
Breast cancer+	WA21092 207258 1920875	49/F	Czech Republic	1298	4200mg
Basal cell carcinoma	WA25046 232161 33801	50/M	USA	15	600mg
Basal cell carcinoma	WA25046 232161 33804	41/M	USA	224	1200mg
Basal cell carcinoma*	WA25046 232432 36701	52/M	USA	596	2400mg
Basal cell carcinoma+	WA21093 209753 1930893	50/F	Canada	1052	4200mg
Basal cell carcinoma+	WA21093 234130 1937531	54/F	USA	500	1200mg
Melanoma	WA21093 209753 1930896	45/M	Canada	643	2400mg
Melanoma+	WA21092 235418 1927417	48/F	USA	370	1800mg
Adenocarcinoma colon	WA21092 236548 1928222	43/F	USA	300	1200mg

Renal cell carcinoma	WA21092 206601 1920611	48/M	Bulgaria	582	2400mg
Papillary Thyroid carcinoma	WA21092 207258 1920873	47/F	Czech Republic	972	3600mg
Malignant fibrous histiocytoma	WA25046 208269 12001	50/F	Greece	1303	4800mg
Pancreatic carcinoma	WA25046 208392 21404	48/F	Poland	1247	4500mg
Endometrial carcinoma	WA25046 232175 35603	55/F	USA	265	1200mg
Anaplastic large cell lymphoma	WA25046 249488 32601	51/M	UK	451	1800mg
Keratoacanthoma +	WA25046 232180 35902	47/F	USA	1000	3900mg

*This subject had 2 basal cell carcinomas on study day 596 and a third diagnosed on study day 1079, when his cumulative dose was 4,200mg.
+Reported in the 90 Day Safety Update

Given the number of breast cancers in MS patients and the imbalance in the controlled phases of MS trials, I summarize details from the narratives for these events below.

Summary of Narratives for MS ocrelizumab patients with breast cancers in the ISS
Six of the seven women (WA21092 206629 1920773, WA25046 208039 47403, WA25046 208185 10201, WA25046 208661 21006, WA25046 208787 32301, WA21493 140954 1052) diagnosed with breast cancer had similar ages (43, 47, 52, 54, 54, and 54 years). They were exposed to cumulative ocrelizumab doses of 1,800mg, 1,800mg, 3,000mg, 3,600mg, 3,600mg, and 4,600mg. Their durations between first ocrelizumab exposure and breast cancer symptoms/diagnosis were 393, 451, 737, 748, 882, and 917 days. These 6 women were from the Czech Republic, France, Germany, Poland, United Kingdom, and Bulgaria. I provide details from their narratives below.

Subject WA21092 206629 1920773 was a 54 year old female from the Czech Republic. On study day 378 she underwent an ultrasound to evaluate pain and inflammation in her right breast. The study found a 2.5 x 3 cm solid and immobile mass was found in the right retromammary space. After treatment with antibiotics and a follow up ultrasound, she underwent a biopsy. She was diagnosed with invasive ductal breast carcinoma (Nottingham classification score 8). MIB-1 proliferation index was 60 to 80% with positive E-Cadherin expression. ER negative, PR negative, MIB-1 proliferation index: 60 to 80%, with positive E-Cadherin expression. The HER2-neu expression test was positive and the tumor was scored as 3. Tumor markers included CA15-3: 13.6; CEA: 0.4. The left axilla and supraclavicular fossa were without any pathological findings. She underwent right wedge resection of the breast with removal of axillary lymph (14

lymph nodes) and an axillary fatty body (9 x 7 x 6 cm). Histology of the extracted breast tissue with lymph node, showed invasive ductal carcinoma (Grade 3, Nottingham classification 8-9, M8500/33, PT4(2)N3AMX). The cancer cells were invading the surrounding fatty tissue through the lymph capsules. A total of 5 additional metastatic foci were found outside the lymph node. She was treated with IV paclitaxel, IV anthracycline and IV cyclophosphamide, and IV trastuzumab (Herceptin).

Subject WA25046 208039 47403 was a 54 year old female from France. On study day 882, a mammogram was performed to evaluate a right breast nodule and pain. On study day 884, a biopsy confirmed the diagnosis of right breast invasive ductal carcinoma. She underwent a right partial mastectomy with homolateral axillary dissection and sentinel node. The extemporaneous examination confirmed the diagnosis of infiltrating carcinoma with macroscopically healthy margins; the sentinel node was obtained and sliced and it was concluded that the tumor was nonmetastatic (0N/1N). The microscopic examination confirmed an invasive ductal carcinoma Elston-Ellis grade III (3+3+2) – MSBR 4. Additional prognostic factors showed ER 90% 3+ intensity, PR 85% 3+ intensity and HER" status negative. The invasive ductal carcinoma stage was confirmed as pT1cN0M0. She received radiotherapy.

Subject WA25046 208185 10201 was a 54 year old female from Germany. She underwent a routine mammogram which showed a right breast mass and (3cm from the nipple in the right breast) and microcalcifications in the left breast (6 cm from the nipple). The mass was clinically palpable. On study day 451, a biopsy and pathological examination of the resected tumor confirmed the diagnosis of invasive breast carcinoma (approximately 1.1 cm; pT1c, pN0 (0/2), pM0, G2), which was HER2/neu negative. Immunohistochemical evaluation showed ER+ (>80%), PR+ (70%) and ki-67 25%. On study day 471 ((b) (6)), she underwent right mastectomy and sentinel lymph node excision and histological examination showed normal axillary lymph nodes and the patient was discharged from the hospital. On study day 513 (b) (6) , the patient was started on hormonal therapy with letrozole (2.5 mg IV QD) which stopped on study day 537 (b) (6) due to side effects (hot flushes, difficulty to sleep and joint pain). It was reported that currently, the patient was not receiving any treatment.

Subject WA25046 208661 21006 was a 47 year old female from Poland. On study day 737, she underwent an ultrasound to evaluate a lump in her breast. The ultrasound showed a 20x16 mm hypogenic tumor of the left breast. A mammogram performed on study day 762 showed a 20 x 20 mm irregular shadow. On study day 782 a core needle biopsy of the left breast tumor was performed. Histopathology results from the core needle biopsy revealed left breast tumor R-4. The patho-morphologic diagnosis was invasive breast carcinoma (NST), subtype luminal B, HER2 positive; MIB-1 (positive) about 5% cells; Receptors: ER (3+) 90% cells total score 8/8 positive; PgR (3+) 70% cells Total score 7/8 positive; HER (2+) questionable. Positive for HER2 gene amplification HER2 (FISH test) result was ambiguous. She underwent radical mastectomy of left breast. Post-surgery histopathology results confirmed the diagnosis of invasive breast

carcinoma with staging pT2N2aM0. She was treated with fluorouracil, doxorubicin, cyclophosphamide, and trastuzumab.

Subject WA25046 208787 32301 was a 52 year old female from the UK. On study day 917, an ultrasound guided breast core biopsy was performed to evaluate a lump detected by routine mammography. Microscopic core biopsies showed infiltrating Grade 2 right breast ductal carcinoma which was provisional Grade 1 (T2, P2, M1) in the tissue and associated areas of stromal desmoplasia with focal elastosis were also observed. Focal admixed intermediate grade ductal carcinoma in-situ (DCIS) of comedo type was noted. Also focal vascular invasion was reported. A hormone receptor (estrogen) status report with strong intensity (3) staining showed 67-100%(5) proportion of positive cells and a modified quick score of 8. A Her2 status report showed a result of negative score 0. Surgery was recommended. On study day 1012, radiotherapy and treatment with tamoxifen (20 mg, QD, PO) were started. At the time of last report the event of invasive ductal breast carcinoma was reported to be ongoing.

Subject WA21493 140954 1052 was a 43 year old female from Bulgaria with a history of bilateral fibrocystic mastopathy, and left breast partial resection for fibroadenoma. On study day 748 she developed palpable indurated lump in the lateral side of her left breast with intermittent blood secretion from the nipple. On Study Day 773 (b) (6)), she underwent resection of her left breast with axiallary lymph node dissection. The histological examination revealed Grade 2, invasive ductal carcinoma (2.5 cm), Stage III clinical group 3, ICD: C 50+1. 3 of 9 lymph nodes examined showed metastasis (0.24 cm) without capsule infiltration, PN1B receptor to estradiol:214 and receptor to progesterone:114. Immunohistochemical examination showed HER2 (-), ER and PR. On Study Day 836 ((b) (6) she was started on unspecified chemotherapy.

Subject WA21092 2234347 1926392 was a 28 year old female from the United States who received a single dose of ocrelizumab (600mg cumulative dose) and developed a urinary tract infection that led to withdrawal on study day 84. She enrolled in SFU and started treatment with dimethyl fumarate. 463 days after her last infusion she was diagnosed with breast cancer. Her mother and maternal aunt had been diagnosed with breast cancer but no other risk factors were identified.

90 Day Safety Update
An additional breast cancer case was reported in the 90 Day Safety Update.
Subject WA21092-207258-1920875 was a 49 year old female from the Czech Republic who received ocrelizumab during the controlled phase of the trial. She completed the controlled phase and entered the open label phase. 98 days after her most recent open label infusion (Study day 1298), a mammogram was performed and the patient was diagnosed with right breast cancer (TNM stage: T1bN0MX). She underwent partial mastectomy (extirpation of the right axillary nodes, resection of the right pectoral muscle). The histology test showed Grade 1

cancer with no special type (NST), with estrogen receptor 90%, progesterone receptor 90%, Erb 0 and Ki-67 10% and she started on treatment with tamoxifen.

I provide a summary of the late breaking breast cancer case below.
Subject WA21093 234091 1937354 was a 41 year old from the United States who completed interferon b-1a in the controlled phase and received her first dose of open label ocrelizumab on study day 700. During the controlled phase, on study day 467 (prior to starting ocrelizumab), she underwent mammogram digital screening with tomosynthesis which showed bilateral nodules, possibly cysts (BI-RAD-0). She underwent bilateral breast ultrasound on study day 485 (b) (6)), which showed numerous cysts bilaterally, ranging up to 3.1 cm on the right and 3.7 cm on the left. She also had small nodules bilaterally with benign features and no suspicious findings (BI-RAD- 2 – Benign findings) and she was recommended to undergo routine sonogram in one year. Two months after her first ocrelizumab infusion she underwent a mammogram and ultrasound to evaluate an inverted nipple and the results were negative. 636 days after her first ocrelizumab infusion (cumulative dose 2400mg) she was evaluated for left nipple pain and following a suspicious mammogram and ultrasound she underwent a biopsy that showed a well differentiated invasive ductal cell carcinoma with microcalcifications. Axillary nodes were positive. She underwent right simple mastectomy, left axilla lymph node excision, left breast modified radical mastectomy (11/23 nodes with metastasis with focal extranodal extension). On study day 1,414, she started chemotherapy with cyclophosphamide and Adriamycin.

Reviewer Comment: Nothing in the narrative summaries would exclude a possible causal/contributory role of ocrelizumab in these cases.

RMS Trials Controlled Phase (Pool A)
During the controlled phases of RMS trials, there was a 2.5-fold increase in overall malignancy risk among ocrelizumab patients compared to interferon beta-1a patients. Four ocrelizumab patients (0.5%, 4/825) had a malignancy compared to 2 interferon beta-1a patients (0.2%, 2/826). The malignancy rate for ocrelizumab patients was 0.28/100PY (4/1,447.9PY) compared to 0.14/100PY (2/1,399.0PY) in interferon b-1a patients.

Two female ocrelizumab patients (0.4%, 2/541) and no interferon beta-1a female patients (0/549) were diagnosed with breast cancers. The remaining malignancy diagnoses in ocrelizumab patients were malignant melanoma and renal cancer. The malignancy diagnoses for interferon beta-1a patients were mantle cell lymphoma and squamous cell carcinoma.

PPMS Trial Controlled Phase
There was a 2.9 fold increase in malignancy risk among ocrelizumab patients compared to placebo patients in the PPMS trial. Eleven ocrelizumab patients (2.3%, 11/486) had a malignancy AE compared to 2 placebo patients (0.8%, 2/239). The malignancy rate for

ocrelizumab patients was 0.78/100PY (11/1416.4PY) compared to 0.30/100PY (2/659.8PY) in placebo patients.

Four female ocrelizumab patients (1.7%, 4/240) and no female placebo patients (0/119) were diagnosed with breast cancer. The remaining malignancy diagnoses in ocrelizumab patients were basal cell carcinoma (n=3), anaplastic large cell lymphoma, endometrial cancer, malignant fibrous histiocytoma, and pancreatic carcinoma metastatic. The malignancy diagnoses for placebo patients were basal cell carcinoma and adenocarcinoma of the cervix.

All RA Trials (Pool E)
In all RA trials (Pool E), 94 ocrelizumab patients (3.2%, 94/2926) were diagnosed with one or more malignancies and the rate of malignancies was 1.28/100 PY (94/7,323.9PY). This total included 7 patients diagnosed with breast cancers (6 female, 1 male). The rate of breast cancers in females was 0.1/100PYs (6/5,792PYs) and in males was .07/100PYs (1/1,532PYs). The percentage of female patients diagnosed with breast cancer during RA trials was 0.3% (6/2,341) and of males was 0.2% (1/585). The following table lists the malignancies diagnosed more than once during RA trials.

Table 40 Malignancies in Ocrelizumab exposed patients, ALL RA Trials (Pool E)

MedDRA SOC MedDRA Preferred Term	Ocrelizumab n=2926, 7323.9PY
Neoplasms benign, malignant, and unspecified	
Total number of patients with at least 1 event	3.2% (94)
Number of events	121
Basal cell carcinoma	0.9% (26)
Malignant melanoma	0.2% (6)
Prostate cancer	0.2% (6)
Squamous cell carcinoma of the skin	0.2% (6)
Breast cancer	0.2% (5)
Bowen's disease	0.1% (4)
Squamous cell carcinoma	0.1% (4)
B-cell lymphoma	0.1% (3)
Gastric cancer	0.1% (3)
Squamous cell carcinoma of the lung	0.1% (3)
Bladder transitional cell carcinoma	<0.1% (2)
Cervix carcinoma stage 0	<0.1% (2)
Colon cancer	<0.1% (2)
Diffuse large B-cell lymphoma	<0.1% (2)
Intraductal proliferative breast lesion	<0.1% (2)
Lung adenocarcinoma	<0.1% (2)

Lung neoplasm malignant	<0.1% (2)
Non-Hodgkin's lymphoma	<0.1% (2)

The malignancies diagnosed once were: Anaplastic large cell lymphoma, Bladder cancer, Bladder transitional cell carcinoma recurrent, Bronchial carcinoma, Carcinoma in situ of skin, Chronic myeloid leukemia, Extranodal marginal zone B-cell lymphoma, gastrointestinal carcinoma, Inflammatory carcinoma of the breast, Intestinal adenocarcinoma, Laryngeal squamous cell carcinoma, lung adenocarcinoma metastatic, Lymphoma, Malignant melanoma in situ, Metastases to liver, metastatic gastric cancer, Metastatic renal cell carcinoma, Mycosis fungoides, Myxoid liposarcoma, Ovarian cancer, Ovarian cancer metastatic, Ovarian epithelial cancer, Plasma cell myeloma, Plasmacytoma, Rectal cancer, Rectosigmoid cancer metastatic, Renal cell carcinoma, Skin cancer, And T-cell lymphoma.

As noted above, the 7 ocrelizumab RA breast cancers included one diagnosis in a male. Patient WA20495-141462-90803, a 67 year old Japanese male previously treated with infliximab, was diagnosed with breast cancer one year after the start of the treatment with ocrelizumab 200 mg.
Reviewer comment- the background incidence of male breast cancer in Japan was estimated as 0.18/100,000 man years, making this an unexpected event given that there were 585 males with 1,532 man years exposure to ocrelizumab in RA trials.[2]

RA Trials Controlled phases (Pool D)
In RA controlled trials, the risk for malignancies was similar for the placebo (1.0%; 10/981), ocrelizumab 400 mg (0.7%; 8/1186), and ocrelizumab 1000 mg (1.2%; 11/947) treatment groups. The malignancy rate for placebo patients was 1.1/100PY (10/902.7PY), for ocrelizumab 400 mg was 0.80/100PY (8/1,004.1PY) and for ocrelizumab 1000 mg was 1.2/100PY (11/906.3PY) groups.

One placebo patient and no ocrelizumab patients were diagnosed with breast cancer in these studies. In the following table I summarize the malignancies from the Pool D studies.

Table 41 Malignancies RA Controlled Trials (Pool D)

MedDRA SOC MedDRA Preferred Term	Placebo (n=981, 903 PY)	ocrelizumab 400mg (n=1186, 1004PY)	ocrelizumab 1000mg (N=947, 906PY)
Neoplasms benign, malignant, and unspecified			
Total number of patients with at	1.0% (10)	0.7% (8)	1.2% (11)

[2] Ly,D; Forman, D; Ferlay, J; Brinton, LA; Cook, MB. An International Comparison of Male and Female Breast Cancer Incidence Rates. International J Cancer. 2013 Apr 15;132(8):1918-26.

least 1 event			
Number of events	10	9	12
Basal cell carcinoma	0.2% (2)	0.2% (2)	0.3% (3)
Squamous cell carcinoma skin	0.1% (1)	<0.1% (1)	0.1% (1)
Adenocarcinoma of colon	0.2% (2)	0	0
Bowen's disease	0	0.2% (2)	0
Breast cancer	0.1% (1)	0	0
Diffuse large B-cell lymphoma	0.1% (1)	<0.1%(1)	0
Lung neoplasm malignant	0.1% (1)	0	0.1% (1)
B-cell lymphoma	0	0	0.1% (1)
Bladder transitional cell carcinoma	0	<0.1% (1)	0
Bronchial carcinoma	0	0	0.1% (1)
Carcinoma in situ skin	0	<0.1% (1)	0
Lung adenocarcinoma	0	0	0.1% (1)
Lymphoma	0.1% (1)	0	0
Malignant melanoma	0	0	0.1% (1)
Ovarian cancer	0	0	0.1% (1)
Prostate cancer	0.1% (1)	0	0
Rectal cancer	0	<0.1% (1)	0
Squamous cell carcinoma lung	0	0	0.1% (1)
Uterine cancer	0	0	0.1% (1)

Limitations of RA controlled phase data
The controlled phase data for the RA trials are not directly comparable to the data from the MS trials because of the shorter trial duration of the RA controlled trials. In MS trials, Genentech reported that 1,140 patients were exposed for >95 weeks, with 716 patients exposed in the RMS trial controlled phases and 424 patients exposed in the PPMS trial controlled phase. In the RA controlled trials, exposure to ocrelizumab for at least 96 weeks was only 104 patients (57 patients at 400mg, 47 patients at 1000mg). This is especially important if one looks to the RA trial data for breast cancer risk comparisons because the earliest breast cancer diagnosis in the controlled phases of MS trials occurred after 393 days and 4/6 breast cancers occurred after 95 weeks. Therefore, in RA trials there was limited experience at the duration of treatment when many of the breast cancers occurred in the MS trials.

Comparisons to external data sources malignancy rates

MS Data
Genentech provided a table that compared the malignancy rate in all MS trials (Pool B) to the comparators from the controlled phases of these trials (placebo, interferon beta-1a) and to 3

different external data sources. The first external data source was a Laser-Analytic report that included malignancy rates compiled from placebo comparator groups in MS trials that were identified by searching published trials. These data are intended to represent a rate for patients enrolled in MS trials but not exposed to investigational drugs. The second data source was from a Danish MS registry (Neilsen et al, 2006) and the third data source was from a Canadian MS registry (Kingwell et al 2012).

Genentech's comparisons reflect the ocrelizumab clinical trial malignancy rate imbalances described above, where ocrelizumab patients had higher rates of malignancies and breast cancer compared to interferon beta-1a and placebo. Genentech's comparisons to external data sources suggest that the overall malignancy rate with ocrelizumab was similar to rates seen in placebo patients in published MS trials and in MS registries although ocrelizumab patients did have higher breast cancer rates than those found in the external data sources. I provide those results below.

Table 42 Comparison of Malignancy risk from Ocrelizumab MS trial to Outside Data Sources (rates/100PY) *

	Ocrelizumab Pool B	Comparator (IFN and PBO)[a]	MS Trial Placebo[b]	MS Registry
Malignancies	0.425 (0.256-0.664)	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) 0.37	0.097 (0.012, 0.352)	0.33 (0.20-0.50)	(0.32-0.43)[d]
Breast cancer (female)	0.261 (0.105-0.538)	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)	0.097 (0.012-0.352)	0.097 (0.012, 0.352)	0.19 (0.15-0.24)[d]

*Through the ISS cutoff date. Does not include data from the 90 Day Safety Update
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 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).
a Combined from Phase III RMS (Pool A; IFN) and Phase III PPMS (placebo) controlled treatment populations.
b [redacted] (b) (4) 2016, age range mostly 18-55 years
c Nielsen et al. 2006, Denmark MS Registry
d Kingwell et al. 2012, British Columbia, Canada MS Registry

In addition to the comparisons above, Genentech also compared ocrelizumab malignancy rates to National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) data. For this analysis, the Genentech standardized ocrelizumab incidence rates to the US population. The

sponsor used both 5 year and 10 year age groupings and presented comparisons of overall malignancy rates (excluding NMSC) and breast cancer rates overall and by sex.
There appeared to be little difference in the overall malignancy rate when comparing the ocrelizumab US standardized rate (0.286/100PY, 95% CI 0.155, 0.968) and SEER rate (0.268 95% CI 0.268, 0.269) using 10 year age groupings. For female breast cancer, the US standardized rate for ocrelizumab was 0.281/100 PY (95% CI 0.104, 0.666) and for SEER was 0.124/100PY (95% CI 0.124, 0.125). Genentech noted that "these comparisons should be interpreted with caution because of the low number of malignancies reported in the MS program."

Genentech wrote the following regarding their comparisons:

> The incidence rates per 100PY of breast cancer within the MS program was higher in female patients treated with ocrelizumab (0.261; 95% CI: 0.105, 0.538) relative to comparator (0.0; 95% CI: 0, 0.293). However, the incidence rates per 100PY in ocrelizumab treated patients were within the ranges reported in pooled placebo data from MS clinical trials (0.16; 95% CI: 0.06, 0.32) and published epidemiological data (Kingwell et al. 2012 [0.21; 95% CI: 0.18, 0.23] and also Nielsen et al. 2006; [0.14 per 100PY; 0.11, 0.16]). The SEER standardized incidence rate per 100PY of female breast cancer (0.124; 95% CI: 0.124, 0.125) was within the 95% CIs reported for ocrelizumab (0.281; 95% CI: 0.104, 0.666).

RA Data
Despite the absence of an increased malignancy risk signal from RA trials, Genentech provided comparisons of malignancy rates to external data sources. For example, Genentech compared the overall malignancy incidence rate (excluding NMSC) for ocrelizumab in RA trials (0.903/100PY; 95% CI: 0.697, 1.151), to rates reported in US (1.30/100PY; 95% CI: 1.19, 1.41; Wolfe et al. 2007) and Danish (1.27/100PY; 95% CI:1.21, 1.33; Mellemkjaer et al. 1996) RA patients.

In addition, Genentech provided comparisons of the incidence rate of breast cancer in ocrelizumab patients compared with epidemiological data. The overall rate of breast cancer in RA trial patients who received ocrelizumab (males and females) was 0.111/100PY (95% CI: 0.048, 0.219) which was consistent with rates reported in RA patient registries (0.13/100PY; 95% CI: 0.10, 0.15; Mellemkjaer et al. 1996). The incidence rate of breast cancer in female RA patients exposed to ocrelizumab was 0.122/100PY (95% CI: 0.049, 0.252), and was similar to a rate reported by Mercer et al. 2013 (0.31/100PY; 95% CI: 0.21, 0.45).

Consult Responses
Given the malignancy risk imbalance, and Genentech's assessments, DNP consulted Division of Oncology Products 1 (DOP1), Division of Hematology Products (DHP), and Division of Epidemiology 1 (DEPI1) to assist in evaluating this issue.

Dr. Gwynn Ison from DOP1 and Dr. Bindu Kanapuru from DHP provided responses to the same set of questions and I summarize those responses below.

DNP asked: In describing the malignancy risk in the controlled trials, is it appropriate to consider all diagnosed cancers, regardless of cell type, or should the assessment focus only on the cluster of breast cases?

Both Dr. Ison and Dr. Kanapuru felt that all malignancies should be considered in the evaluation of cancer risk with ocrelizumab. Dr. Kananpuru also noted that given the imbalance in breast cancer cases, it is also appropriate to focus assessment on malignancy risk from breast cancer alone.

DNP asked: Considering the low number of events and limited follow up cited by Genentech, do you view the imbalance in breast cancer diagnoses (6 vs. 0) in these controlled trials as concerning?

Dr. Ison responded that "Although it is difficult to make any conclusions about whether there is cause for concern, with respect to the imbalance in cases diagnosed in ocrelizumab treated patients, a potential safety signal should not be ruled out, at this time." Dr. Kananpuru wrote "Yes. The imbalance of breast cancer cases in the ocrelizumab group and combined placebo and interferon group at this stage of follow-up is concerning. Longer follow-up is recommended to further characterize this finding."

DNP asked: Do you find Genentech's comparison to outside databases reassuring, despite the observed imbalance from within the controlled trials?

Neither Dr. Ison nor Dr. Kanapuru found these comparisons reassuring, and both deferred to DEPI/OSE's assessment of the cited databases. Dr. Kanapuru also cited a publication evaluating impact of disease-modifying treatments and cancer risk in 7,418 MS patients gathered from nine French MS centers (Lebrun C 2008). Dr. Kanapuru noted that the review concluded that MS patients have a decreased overall risk of cancer; however an increased risk for breast cancer was noted in women with MS treated with immunosuppressive therapy.

DNP asked: If you agree with Genentech that no conclusion on malignancy can be made, do you think it is appropriate to further evaluate this signal in the post marketing period as proposed?

Dr. Ison wrote that this signal warrants further evaluation, including collection of information on newly diagnosed malignancies. Dr. Ison recommended that Genentech collect the following information for new malignancies: the pathological cancer diagnosis, stage at diagnosis, time on therapy with ocrelizumab at the time of cancer diagnosis and action taken with ocrelizumab

therapy (continue vs. discontinue). For breast cancer cases, the sponsor should collect stage at diagnosis and hormonal status of the tumor (to include ER/PR status and HER2 status). Dr. Ison felt that it is difficult to make a conclusion about whether causality can be attributed to ocrelizumab in any of the cancer cases identified, but that a relationship should not be ruled out at this time. Dr. Ison recommended including the information about potential malignancy risk in the product labeling and noted that other products such as olaparib (Lynparza) and alemtuzumab (Lemtrada) include information on cases of malignancy in the label and have malignancy risk as a section in Warnings and Precautions. In addition, the Lemtrada label contains a boxed warning describing the risk of malignancy. Dr. Kanapuru agreed that (b) (4) as proposed by the Sponsor is necessary but also recommended that the results from the controlled trials of imbalance in breast cancer diagnoses (6 vs. 0) should be included in the proposed labeling for ocrelizumab. Dr. Kanapuru felt that this recommendation was consistent with the alemtuzumab labeling and other products.

Dr. Elisa Braver from DEPI 1 responded to questions from DNP regarding the external databases used for malignancy risk comparisons and for comment on Genentech's post marketing study proposal for further evaluating the malignancy risk.

DNP asked for an evaluation of the evidence presented by Genentech that another anti-CD20 monoclonal antibody, Rituxan, was not associated with increased breast cancer risk. Genentech reported that in 2016, a specific assessment for the risk of breast cancer observed in the Swedish registry ARTIS confirmed the results of the exhaustive review conducted in 2014 and no increased risk was seen with rituximab for female breast cancer (Frisell 2016; ARTIS coordinator; communication to Sponsor). DNP requested an evaluation of the two sources cited by Genentech (PBER, Frisell, ARTIS assessment) which they claim found no additional risk of malignancy with Rituxan.

Dr. Braver felt that no conclusions on breast cancer risk in relation to rituximab can be drawn based on the analysis by Frisell (2016), which did not control for potential confounding factors. Dr. Braver noted that the "data sources cited in PBER suggest no increased cancer risk from use of Rituxan; however, the findings are inconclusive due to the lack of analyses by time since initial exposure or cumulative duration of treatment and indications that rheumatoid arthritis (RA) clinical trial participants were at lower cancer risk than other RA patients."

DNP asked: To assess the imbalance in malignancy risk in the ocrelizumab MS clinical trials, Genentech made comparisons of the cancer rates in the clinical trials to rates from placebo data from clinical trials in MS ((b) (4) Report 2016), rates from population-based epidemiological data (Nielsen et al. 2006) and SEER data. We request an evaluation of these external data sources used as comparative data by Genentech. Specifically, we request an evaluation of the strengths and weaknesses of using these data sources to assess the malignancy risk observed in the ocrelizumab MS controlled trials.

Dr. Braver responded," Using the MS and RA data sources for safety data is useful; however, the statistical analyses that were done were inadequate to account for the latency period for cancers to develop and also did not examine potential confounding factors. Using the Surveillance, Epidemiology, and End Results (SEER) database is not useful because of potential differences in cancer risk, confounding factors, and cancer screening rates between MS patients and the general population."

In a follow up email dated August 1, 2016, Dr. Braver also noted the following:

> As was the case with the comparisons with placebo/comparator drug groups, there were inadequate analyses of malignancy incidence rates in comparisons with Kingwell, Neilsen, and (b) (4) data. Data were not presented by cumulative doses or by time intervals since first dose of OCR. Furthermore, no adjustments were made for age or other factors associated with breast cancer, such as body mass index, family history of breast cancer, age at first birth, alcohol consumption, or use of hormone treatments during menopause. Another limitation was that regional differences between the locations of the MS clinical trials and the MS registries (Kingwell, Neilsen, (b) (4)) were not addressed by the analyses.
>
> The sponsor stated that the increased incidence rate of breast cancer observed among OCR-treated MS patients fell within the 95% confidence intervals of comparators, pooled placebo data, and epidemiologic data. As a result, the sponsor concluded that "No conclusion can be made to date concerning the risk due to the low number of events and the limited follow-up period." However, overlapping confidence intervals do not necessarily indicate that a safety signal is inconclusive or due to chance; they may reflect small numbers in individual trials that led to wide confidence intervals. Also, there may be statistically significant differences even in when confidence intervals overlap.
>
> Aside from the failure to adjust for age or other confounding factors, there are other limitations of the sponsor's comparisons with the MS registry in British Columbia, Canada (Kingwell) and the MS registry in Denmark (Neilsen). One is that there are major regional differences between the British Columbia MS registry, which observed no increased breast cancer risk in the MS patients compared with the local female population, versus the Danish MS registry, which observed significantly increased risks of breast cancer among MS patients compared with the Danish female population.
>
> Also, there are questions about the numbers cited by the sponsor. The sponsor made an error in the text, but not Table 105, when describing the British Columbia study (Kingwell). DEPI calculated that the breast cancer incidence rate for the British Columbia, Canada registry reported on by Kingwell was 0.14 (95% CI: 0.11-0.16), rather

than 0.21 (95% CI: 0.18-0.23), which was reported in the Integrated Safety Summary (page 285). DEPI could not reproduce the breast cancer incidence rate reported by the sponsor from the Danish MS registry because insufficient information was included in the published paper.

In conclusion, the Sponsor went to a great deal of effort to gather relevant safety data from external data sources. However, the Sponsor's comparisons of clinical trial data on malignancy risk with external data sources cannot be interpreted due to limitations in their analyses, most importantly the lack of control for potential confounding factors and the lack of traditional analyses on dose-response and time intervals between exposure and diagnosis.

Dr. Braver requested additional analyses of malignancies including incidences over time, by cumulative dose, and stratified by age. In a summary of these results provided in an email dated 9/12/16, Dr. Braver noted that the overall malignancy rate was higher in ocrelizumab patients >=45 (7800/10,000PY) than those <45 years old (800/10,000PY). Similarly, breast cancer incidence was higher among ocrelizumab treated females >=45 (49.8/10,000PY) compared to those <45 years old (9/10,000PYs). Dr. Braver also noted that of the 9 breast cancer cases, 1 was diagnosed at Stage IV (invasive ductal breast cancer); 2 were diagnosed at Stage III (breast cancer) or IIIA (invasive ductal breast carcinoma); 4 were diagnosed at Stage I or Stage IA (breast cancer or invasive ductal breast carcinoma); and 2 were missing information on stage. Dr. Braver commented that the breast cancers diagnosed at Stage III or Stage IV likely were developing before the patients entered the clinical trials. If OCR acts solely by initiating the first stage of tumor development, then these cancers would not be related to OCR exposure. Dr. Braver summarized the breast cancer cases by cumulative dose as follows: 1 breast cancer (age <45) after receiving 1st 600 mg dose of OCR; 2 breast cancers (ages 45+) after 3rd dose; 1 breast cancer (age 45+) after 5th dose; 2 breast cancers (ages 45+) after 6th dose; 1 breast cancer (age <45) after 7th dose; and1 breast cancer (age 45+) after 8th dose.

DNP asked: Genentech proposed (b) (4) . We request an evaluation of the sponsor's proposal for their post marketing assessment of malignancy risk with ocrelizumab. (b) (4)

Dr. Braver felt that Genentech's proposal was inadequate. She recommended (b) (4) and requesting that

Genentech propose [redacted] (b) (4)

8.8.2. Human Reproduction and Pregnancy

The ocrelizumab development program included a small number of pregnancies, with few adverse outcomes. The data are insufficient to support conclusions about effects of ocrelizumab on human reproduction and pregnancy.

Background
In all clinical trials with ocrelizumab, double-barrier contraception was mandatory. A mandatory urine pregnancy test was performed as a minimum prior to each infusion. If the pregnancy test was positive treatment with ocrelizumab was to be withheld.

Genentech explained that no relevant transportation of immunoglobulins (and therefore ocrelizumab) through the placenta occurs during the 1st trimester of pregnancy. Based on this understanding, and considering ocrelizumab's half-life, Genentech used the following criteria to determine whether the embryo/fetus was believed to be transplacentally exposed:

> Embryo/fetus not expected to be transplacentally exposed to ocrelizumab if ocrelizumab was last administered 3 or more months before conception. Genentech did note that in these cases an embryo/fetus may still be affected indirectly by the ocrelizumab induced B-cell depletion in the pregnant mother.
>
> Embryo/fetus potentially transplacentally exposed to ocrelizumab if ocrelizumab was last administered less than 3 months before conception, during pregnancy, or exact ocrelizumab exposure unknown. Applying a conservative rule, an embryo/fetus is considered exposed even if the last ocrelizumab infusion was administered before the start of the 2nd trimester, or if the exposure time is missing.

Pregnancies
Genentech provided a Drug Safety Report that identified and summarized 51 pregnancy related AEs involving 49 pregnancies in 46 women, where the mother received ocrelizumab in clinical trials (cutoff date 9/14/15). The age of the 46 pregnant mothers ranged from 17 years to 42 years, and the mean age was 30.3 years. Genentech noted that 26 of the identified pregnancy related AEs in mothers who received ocrelizumab came from MS trials and 35 from trials of other indications (13 SLE/LN, 22 RA).

Pregnancies with Live Births
From all trial indications there were 49 pregnancy reports with 24 live births (5 from MS trials, 19 from other indication trials). I summarize those events below.
MS trials

There were 5 live births from pregnancies in MS trials, four of which were normal babies born at full term. I provide a summary of the remaining case below.

A preterm birth was reported for a baby with benign nasopharyngeal neoplasm, jaundice, respiratory distress, and low birth weight. The nasopharyngeal neoplasm was classified as a structural malformation, but no histopathological report was provided complicating assessment. The last ocrelizumab infusion was administered to this mother approximately 6 months prior to conception. Genentech noted that the FDA's reviewer guidance regarding evaluating the risks of drug exposure in human pregnancies identifies the sensitive period in human development for the palate as from the end of the 6th week to the end of the 9th gestational week. Genentech applied the conservative time window described above for fetal exposure to ocrelizumab in utero and concluded that the embryo/fetus would not have been exposed ocrelizumab during this period, because the last infusion was more than 3 months prior to conception. Respiratory distress was secondary to the large nasopharyngeal mass, exaggerated by the preterm birth at 34 weeks gestation. Genentech felt that the jaundice and low birth weight were related to the preterm delivery.

Trials for other indications
There were 19 live births from pregnancies in ocrelizumab trials for indications other than MS. 12 of these babies were normal (11 were full term, 1 unknown gestational week). Of the 7 remaining live births, 2 were considered to have structural malformations. I summarize those events below.

AER 606368: Congenital positional feet contracture and limited hips abduction (both classified as structural malformation), as well as neonatal rash were noted on the day of birth and hyperbilirubinemia on day three of life. The mother had concomitantly taken methotrexate for RA, a known teratogen, up to four months prior to the conception. Based on the time period between the last doses of ocrelizumab and methotrexate and the estimated date of conception, Genentech felt it unlikely that either drug played a causative role in the development of the reported abnormal findings. Genentech noted that I was unclear from the report if the feet contracture/limited hip abduction abnormalities were structural or functional abnormalities. Genentech also noted that the last ocrelizumab infusion was administered 12.5 weeks prior to conception and therefore felt the embryo was not transplacentally exposed to ocrelizumab.

AER 1110613: The baby delivered by a mother with nephritis due to SLE had a small right renal cyst (9 mm), which was not considered to be of clinical significance. Ocrelizumab had been stopped 3 years (152 weeks) prior to conception. Azathioprine was stopped 6 weeks after conception.

Using the above 2 cases, Genentech felt the congenital malformation rate in this non-MS

dataset (5.7%, 2/35 pregnancies) was comparable to the 6.5% reported in the literature. Four of the remaining 5 live births with abnormalities were pre-term. The last case was low birth weight. I summarize those cases below.

For the 4 pre-term deliveries, the maternal age ranged from 23 – 37 years. Two mothers were from trials for nephritis due to SLE, and two from RA trials. Two babies were reported as healthy. The other 2 pre-term babies had abnormal findings diagnosed and I summarize those cases below.

AER 687303: A Cesarean section was done at 32 weeks gestation due to antiphospholipid syndrome secondary to SLE diagnosed in the pregnant mother four days prior to delivery. The preterm newborn was reportedly in good condition, however received management as low birth weight preterm (birth weight: 1.16 kg, and length 40.4 cm). At 4 months age, the baby showed gradual and normal growth (weight 2.14 kg) without remarkable complication. The last ocrelizumab infusion was administered approximately 4 months before conception, while mycophenolate, irbesartan, rabeprazole and prednisolone were stopped 18 days after conception.

AER 715989: A Cesarean section was performed at 36 weeks gestation for gestational hypertension complicated by pre-eclampsia (reportedly lung maturation was performed). The baby was small for gestational age (1.53 kg, 39 cm), APGAR score was 9 at 10 minutes and the baby suffered from respiratory distress (requiring oxygen therapy for 5 days). During the hospitalization the baby experienced sepsis, hypertension, retinopathy of prematurity, hyperbilirubinemia, and neonatal anemia. At the time of discharge (4 weeks after birth), the baby's weight was 2.005 kg, and the length 41.5 cm. The mother with nephritis due to SLE had the following relevant medical history: hypertension, hypothyroidism, and glucocorticosteroid therapy, which are risk factors for prematurity and small for date babies. Concomitant medications mycophenolate mofetil and enalapril are known teratogens; and enalapril was administered in the first trimester of pregnancy. The last ocrelizumab infusion had been administered approximately 10 months (40 weeks) before conception. Since conception occurred nearly 10 months after the last OCR dose, Genentech noted that this fetus is not considered to have been transplacentally exposed to ocrelizumab. Genentech did not have information regarding B-cell count and immunoglobulin status in the newborn at delivery. In the mother, CD19+ B-cell counts were normal four weeks before conception (92 cells/µL) and during gestational week six (100 cells/µL), while they were 57 cells/µL, i.e. below the lower limit of normal (LLN, 80 cells/µL) in gestational week 20. The maternal B-cell count on the day of delivery at 36 weeks gestation was not known.

Genentech noted that the rate of premature delivery in non-MS patients (11.4%, 4/35) was lower than the rate of premature delivery in the literature for patients with RA (28%). The last live birth case from a trial for other indications (AER 620295) was a case assessed as

growth alteration because of low birth weight (5.1 lbs, length 19 inches, at 39 weeks gestation, born to a mother of 50 kg weight).

Pregnancies without live births
There were 25 pregnancies not resulting in live births including outcomes of spontaneous abortions, missed abortions, fetal death, elective terminations, lost to follow up, and ongoing pregnancies at the time of the data cutoff.

MS trials
There were no pregnancies resulting in spontaneous or missed abortions or fetal death in MS trials.

There were 7 pregnancies in MS trials that were electively terminated (1 due to patient's decision, 6 with no reason provided). None of the reports of the 7 elective terminations included evidence of embryo/fetal malformation. Genentech noted the rate of elective terminations in MS trials (44%, 7/16) was higher than a rate for pregnancies in MS patients reported in the literature (27%). Genentech also noted that 5/7 elective terminations were from Eastern European countries, where elective termination rates have been reported to be as high as 50%.

There were 4 pregnancies from MS trials that were ongoing at the time of the data cutoff for this report.

Trials for other indications
There were 11 pregnancies in trials of other indications resulting in spontaneous or missed abortions or fetal death. None of the 11 had evidence of embryo/fetal abnormalities. One of these cases was a fetal death in a mother that died from a pulmonary embolism during the 7th month of pregnancy.

Two pregnancies from trials of other indications were electively terminated. One of the elective terminations was due to prolonged use of methotrexate and the report for the other did not identify a reason. Neither report indicated embryo/fetal malformations.

The outcome for one pregnancy was not known because of loss to follow-up.

Based on the information presented in their report, Genentech concluded that there was "no evidence for an increased risk of ocrelizumab for spontaneous/missed abortion, fetal death, induced abortion, premature birth, structural malformations, functional deficits, or growth abnormalities". Genentech also noted that "B-cell levels and immune globulin counts in human neonates following maternal exposure to OCR have not been studied in clinical trials and the effect of OCR on the immune system of the newborn and its development and maturation

during the first months of the infants live is unknown."
In the 90 Day Safety Update, Genentech provided follow up information for the 4 pregnancies that were ongoing at the time of the ISS and 6 newly identified pregnancies. All 4 follow up reports described live births of normal babies at full term. Four of the six new pregnancies were ongoing at the time of the 90 Day Safety Update submission. Of the remaining 2 pregnancies, one patient (Patient WA25046-208541-30602) delivered a normal baby. The other (Patient WA21093-209771-1930433) had a stillbirth at an unknown gestational week with minimal information available about the conception and pregnancy.

8.8.3. Pediatrics and Assessment of Effects on Growth

Pediatric patients were not exposed to ocrelizumab during the development program. Patients below 16 years of age were excluded from the LN study and patients below 18 years of age were excluded from the remaining trials.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Ocrelizumab is administered as an infusion and therefore is not subject to overdose by patient intent or mistake. There were no reports of investigation site administered overdose infusions. The highest ocrelizumab dose studied in clinical trials was 2000mg.

To look for events suggestive of drug abuse, Genentech examined the list of PTs for both MS and RA All Exposure pools (Pool B and Pool E) mapping to the SOC of Psychiatric Disorders and Nervous System Disorders. A review of additional terms such as abnormal dreams, clumsiness, lethargy, delirium, confusional state was also assessed. Genentech did not find evidence of ocrelizumab related drug abuse.

Genentech searched MS Pools B and RA Pool E for "Drug Withdrawal" in the SOC of General Disorders and Administration Site Disorders, and two patients were identified with drug withdrawals related to treatments other than ocrelizumab (clonazepam and narcotic). Genentech's review of the clinical cases in MS and RA did not identify any withdrawal event terms related to ocrelizumab.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

N/A

8.9.2. Expectations on Safety in the Postmarket Setting

During the post marketing experience, it is expected that there will be cases of infections due to the suppressive effects of ocrelizumab on the immune system (CD19+ cells, immunoglobulins). Post marketing reports should monitor for infections with emphasis on serious infections and opportunistic infections, with specific focus on identifying cases of Progressive Multifocal Leukoencephalopathy, and cases of Hepatitis B reactivation. PML and Hepatitis B reactivation are included in the labeling for approved antiC20 monoclonal antibodies but were not reported in MS patients in the ocrelizumab BLA.

IRRs will occur and be reported during the post marketing period. Post marketing reports should characterize the IRR events as well as establish whether pretreatment was used, if treatment of IRR was required, and if any potential predictive characteristics were suspected in the patient.

The relationship between ocrelizumab and malignancy, cholecystitis/cholelithiasis, and pancreatitis are not clear at the time of approval and should be monitored in the post marketing period.

8.10. Additional Safety Issues From Other Disciplines

At the time of the completion of this review I am unaware of any safety issues from other disciplines.

8.11. Integrated Assessment of Safety

1. Malignancy
Malignancy risk with ocrelizumab is an area of uncertainty with significant implications. Genentech designated malignancies as events of interest in the MS development program. During the controlled phases of the 3 Phase III MS trials, a higher percentage of ocrelizumab patients were diagnosed with a malignancy compared to interferon or placebo patients. Although many of these malignancy types were single events, there was a cluster of 6 breast cancers in ocrelizumab patients and none in patients receiving comparator treatment.

Evidence supporting an association
The evidence supporting an association between ocrelizumab and increased overall malignancy risk and breast cancer risk is the quantitative difference in risk observed during randomized controlled trials. Overall, in controlled trials 1.1%, of ocrelizumab patients and 0.4% of comparator patients had a malignancy diagnosis. In addition, although the numbers become small, there is some suggestion of replication of this finding when considering separately the results of the RMS trials (Pool A) and the PPMS trial. The main argument against this evidence is that it is too limited, with a small number of events and inadequate follow up to support conclusions about causality. There was no argument made that cases were diagnosed

inappropriately, inappropriately classified by treatment, that there was systematic bias, or that there were any other alternative explanations for the imbalance in malignancies.

Although the risk of breast cancer was not increased with ocrelizumab in the RA controlled trials (see below), one of the ocrelizumab breast cancer cases was diagnosed in a male patient. Given the low background rate of such an event (0.18/100,000 man years), it is unexpected to see a case of male breast cancer in a database that included only 585 male ocrelizumab patients with 1,532 man years exposure.

Evidence against an association
Genentech made comparisons of the malignancy risk in the ocrelizumab program to data collected from sources outside of the clinical trial (published data from other MS clinical trials, MS registries, and SEER data). Based on these comparisons, the malignancy risks did not appear markedly increased in ocrelizumab exposed clinical trial patients. In comments regarding the value of these comparisons, our DEPI consultant did not feel they were reliable because of limitations in the clinical trial data analyses as well as limitations in the data used for the comparisons.

Genentech noted that a pooled analysis of the RA development controlled trials did not suggest an imbalance in malignancy risk when comparing ocrelizumab patients to placebo. Although true, an important caveat is that the exposure duration of the RA controlled trials was shorter than the MS controlled trials. The RA trials included few patients observed during the period when malignancies were diagnosed in ocrelizumab patients in the MS trials. It is therefore possible that the RA trials missed the period of increased risk because they were too short in duration. When comparing the malignancy rates from controlled and open label experience for MS and RA trials the overall malignancy rate in MS trials was 0.4/100PYs compared to 1.3/100PYs in the RA trials. The female breast cancer rate from controlled and open label experience for MS trials was 0.23/100PYs compared to 0.10/100PYs in RA trials.

Aside from Bexxar, a CD20-directed radiotherapeutic antibody, malignancy is not recognized as a risk in the labeling for the approved antiCD20 monoclonal antibodies. Bexxar labeling includes a Warnings and Precautions statement that describes the risk for secondary malignancies.

Consultant Opinions
Consultants from DOP1 and DHP both suggested that the ocrelizumab data were a signal for concern but that the data were inadequate to support conclusions about malignancy risk. Both consultants recommended additional evaluation of this signal and both recommended including information about the observed malignancy risk in ocrelizumab labeling. The consultants provided examples of labeling describing malignancy risk including alemtuzumab and olaparib. Alemtuzumab, an antiCD-52 monoclonal antibody indicated for the treatment of MS, has a boxed warning that includes language regarding malignancies (thyroid cancer,

melanoma, and lymphoproliferative disorders). Olaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for a subset of ovarian cancer patients, includes a Warnings and Precautions statement for myelodysplastic syndrome/acute myeloid leukemia.

Genentech felt no conclusion regarding malignancy risk could be made due to the small number of events and limited follow up and they did not propose labeling language regarding the malignancy findings. Genentech committed to monitoring malignancies in the post marketing period. Genentech proposed a post marketing study that would capture malignancies. Our DEPI consultant reviewed the proposal and made recommendations for increasing the size and duration of the study.

In accordance with our DOP1 and DHP consultants, I agree that malignancy risk, with a focus on breast cancer, should be described in ocrelizumab labeling. Given the currently available evidence, it seems most appropriate to include this information in a Warnings and Precautions statement. In addition, the proposed post marketing study that would capture malignancies in patients treated with ocrelizumab should be a PMR and should include the changes recommended by our DEPI consultant.

2. Infections
Infections are a well-established adverse effect with anti-CD20 monoclonal antibodies, including ocrelizumab. Ocrelizumab depletes B lymphocytes and decreases immunoglobulins. Genentech stated that the increased risk of infections in ocrelizumab treated patients in RA trials was one reason that they abandoned the RA indication. In RA trials, there appeared to be an increased risk of death due to infection, an increased risk of infection SAEs, and a number of opportunistic infections in ocrelizumab exposed patients.

In the MS controlled trials, a higher percentage of ocrelizumab patients experienced infection AEs compared to interferon patients or placebo patients. Ocrelizumab patients were at greater risk for upper respiratory tract infections, lower respiratory tract infections, and herpes-related infections. The majority of infections in ocrelizumab patients were grade 1 or 2 in severity. In the controlled phases of MS trials, compared to interferon or placebo, more ocrelizumab patients had grade 4 or 5 infections, but the number of such events was small. In the controlled phases of RMS trials, a higher percentage of interferon patients experienced infection SAEs compared to ocrelizumab patients but in the PPMS trial, a higher percentage of ocrelizumab patients experienced infection SAEs compared to placebo patients. There were no identified opportunistic infections in the MS trials. Two MS trial deaths appeared to be due to infection, although the precise role of ocrelizumab in these events is not clear.

Infection risk should be described in labeling in a Warnings and Precautions statement and Genentech has proposed such language.

3. Infusion related reactions
IRRs are well-established adverse effects with anti-CD20 monoclonal antibodies, including ocrelizumab. Approved anti-CD20 monoclonal antibodies have either boxed warnings or Warnings and Precautions statements that describe life threatening IRRs. Prior to infusion, all MS patients were required to receive pretreatment with corticosteroids, and pretreatment with antihistamines and antipyretics was encouraged.

In MS controlled trials 34-40% of ocrelizumab patients experienced one or more IRR. The IRRs observed most commonly during MS clinical trials were pruritus, rash, throat irritation, flushing, urticaria, and oropharyngeal pain. No patients died due to an IRR, 7 patients experienced IRR SAEs and 13 patients withdrew from ocrelizumab treatment for IRRs. Patients treated with ocrelizumab were at highest risk for an IRR with the first infusion. Four of the 7 IRR SAEs and 12/13 withdrawals for IRRs occurred with the first infusion. The majority of IRRs occurred during the infusion with smaller percentages of events occurring after the infusion and while still in the clinic, or within 24 hours after the infusion but after leaving the clinic. Post hoc analysis suggested that patients who received antihistamines in addition to corticosteroids as pretreatment less frequently experienced an IRR.

Patients who experienced IRRs were treated with antihistamines (IV or IM), corticosteroids, non-steroidal anti-inflammatories, bronchodilators, or with other interventions. IRRs were also managed through slowing, interrupting, or discontinuing the infusions.

IRRs should be described in labeling in a Warnings and Precautions statement and Genentech has proposed such language.

4. Depression/Suicide
There was an imbalance in depression, and suicide attempt SAEs that occurred only in ocrelizumab patients and not in comparator patients in the MS controlled trials. Although depression TEAEs occurred less frequently in ocrelizumab-treated patients than placebo in the PPMS controlled trial, they occurred slightly more frequently than interferon (8% vs 7%) in the RMS Controlled Trials (Pool A). Because interferon beta-1a labeling has a warning for depression and suicide, it seems appropriate to recommend a similar warning for ocrelizumab.

5. Gall bladder related AEs
Cholelithiasis/cholecystitis risk with ocrelizumab is an area of uncertainty with significant implications. When viewed together, cholelithiasis and cholecystitis were among the most commonly reported SAEs in the MS clinical trials. During the controlled phases of RMS trials, 0.7% (n=6) of ocrelizumab had a cholelithiasis/cholecystitis SAE compared to 0.2% (n=2) of interferon patients. In the controlled phase of the PPMS trial, 0.6% (n=3) ocrelizumab patients and 0.4% (n=1) placebo patients experienced a cholelithiasis/cholecystitis SAE. Similar imbalances in these events by treatment were not observed in the RA controlled trials. The

labeling for the approved antiCD20 monocloncal antibodies does not include language about cholelithiasis/cholecystitis events.

The available evidence does not support inclusion of these events in labeling but post marketing reports should be monitored for these events. Although there were numerical imbalances for these events, the number events and magnitude of imbalances were small and not supported by data from the RA treatment population, or by data from other members of the antiCD20 monoclonal antibody class.

6. Pancreatitis
There were 5 SAEs of pancreatitis in MS ocrelizumab patients. Two cases occurred in patients with documented cholelithiasis, one case was attributed to hypertriglyceridemia, and 2 cases did not have an identified cause. The divergent etiologies for these cases do not suggest a clear relationship to ocrelizumab and therefore do not support inclusion of this event in labeling at this time. Post marketing reports should be monitored for additional cases.

9 Advisory Committee Meeting and Other External Consultations

N/A

10 Labeling Recommendations

10.1. Prescribing Information

All safety related sections will be reviewed and edited to comply with Agency labeling formatting requirements.

The Warnings and Precautions section on Infusion reactions will be edited to use the term Infusion reactions rather than (b) (4). The reason for the change is that the approved antiCD20 monoclonal antibodies as well as other MS infused drugs in our Division use the term Infusion reactions. The section will also be streamlined.

I will propose deleting the Warnings and Precautions section on (b) (4)

I will propose adding a section that explains the malignancy/breast cancer imbalance observed

in the MS development program.

The Warnings and Precautions section on Infections will be revised to include information about the infections more commonly seen with ocrelizumab in the MS trials and to state that although no cases were seen, PML and Hepatitis B reactivation are anticipated based on the experience with the approved antiCD20 monoclonal antibodies.

I will propose a Warnings and Precautions statement for depression and suicide.

I will propose using separate tables to identify the common treatment emergent AEs from RMS and PPMS trials. The tables should include all TEAEs and not just those felt to be related to ocrelizumab.

10.2. Patient Labeling

A Medication Guide was submitted and will be reviewed. Final decisions on language and content are pending completion of the review and negotiation of labeling.

10.3. Nonprescription Labeling

N/A

11 Risk Evaluation and Mitigation Strategies (REMS)

11.1. Safety Issue(s) that Warrant Consideration of a REMS

11.2. Conditions of Use to Address Safety Issue(s)

11.3. Recommendations on REMS

A REMS is not required for safe use of ocrelizumab. Labeling can adequately explain the risk of IRRs and will include information regarding IRR symptoms, pre-treatment, management, and recommendations for discontinuation. Labeling can also describe the potential risk for infection in patients treated with ocrelizumab. Labeling can provide information regarding the observed malignancy risk imbalance. There are no identified safety issues where a REMS would be

expected to mitigated identified risks.

12 Postmarketing Requirements and Commitments

Genentech proposed (b) (4) The study should be a PMR, particularly since it will be important in evaluating the breast malignancy signal that arose from an imbalance in MS controlled trials.

13 Appendices

13.1. References

13.2. Financial Disclosure

Refer to the Clinical Review

Covered Clinical Study (Name and/or Number):

Was a list of clinical investigators provided:	Yes ☐	No ☐ (Request list from Applicant)
Total number of investigators identified: _____		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): _____		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): _		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S		

Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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/s/

GERARD A BOEHM
09/14/2016

SALLY U YASUDA
09/14/2016

Medical Officer Review of Consult
Division of Oncology Products-1

BLA #	761053
Drug(s)	Ocrelizumab
BLA Sponsor	Genentech
Consulting Division	Division of Neurology Products, Nahleen Lopez, RPM
Primary Reviewer	Gwynn Ison, MD
Team Leader	Laleh Amiri, MD
Consult Due Date	7/8/16

Background:
According to the Sponsor, given the evidence of B-cell involvement in the pathophysiology of MS, they undertook the ocrelizumab development program (described by this clinical overview), which 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 or plasma. Ocrelizumab selectively depletes CD20-expressing B cells by mechanisms such as antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cell-mediate cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and apoptosis (Kappos et al. 2011), the capacity for B-cell reconstitution and pre-existing humoral immunity are preserved (Martin and Chan 2006; DiLillo et al. 2008).

The precise mechanisms through which ocrelizumab is thought to exert its therapeutic clinical effects in MS are not fully elucidated, but involve immunomodulation through reduction in the number and function of B cells. These changes are thought to be responsible for the consequent improvement in the disease course of MS (Avivi et al. 2013).

On 4/28/16, Genentech submitted a BLA for ocrelizumab to the Division of Neurology Products. Ocrelizumab is an anti-CD20 recombinant humanized monoclonal antibody to be used for the treatment of relapsing and primary progressive forms of multiple sclerosis (MS). Two pivotal trials included studies WA21092 and WA21093, which were identically designed, randomized, active comparator (IFN-B-1a) trials. An additional trial in primary progressive MS was study WA25046 (placebo comparator). Data from 9 additional trials in other indications (including 2926 patients) were also part of the database. One study, WA21493, was a Phase II placebo controlled dose finding study of ocrelizumab vs. placebo in patients with RRMS.

In the clinical trial data, a higher rate of malignancy was observed among patients receiving ocrelizumab, compared to IFN-B-1a or placebo. The majority of cancers were isolated types, but there was a cluster of breast cancer cases. In controlled trials, there were 7 patients receiving ocrelizumab who were diagnosed with breast cancer, compared with no cases in the comparator groups (which included IFN or placebo).

Questions for DOP1:

1. In describing the malignancy risk in the controlled trials, is it appropriate to consider all diagnosed cancers, regardless of cell type, or should the assessment focus only on the cluster of breast cases?

   DOP1 response:
   In attempting to determine malignancy risk potentially related to ocrelizumab, it is important to consider all cancers diagnosed and identified in the BLA database. This should include all documented cases of malignancy in any patient who received ocrelizumab, regardless of whether the drug was received on a controlled trial or not, and regardless of whether the treatment was received during the randomized or open-label portion of the trial. Based upon the limited assessment performed (including reading summaries and narratives provided by the Sponsor), it appears that the Sponsor's report of 19 cases of malignancy in ocrelizumab treated patients may be accurate, but an exhaustive review of the datasets should be performed to confirm this. See response to Question 2, with regard to the breast cancer cases.

2. Considering the low number of events and limited follow up cited by Genentech, do you view the imbalance in breast cancer diagnoses (6 vs. 0) in these controlled trials as concerning?

   DOP1 response: Based upon our review of the narratives submitted, there appear to be 7 cases of breast cancer diagnosed in patients who received ocrelizumab (not 6, as noted by the Sponsor). The study and ID numbers for these patients are as follows:
   1) **WA21092-206629-1920773**
   2) **WA21092-234347-2926392**
   3) **WA25046-208039-47403**
   4) **WA25046-208185-10201**
   5) **WA25046-208661-21006**
   6) **WA25046-20878-32301**
   7) **WA21493-140954-1052**

   There do not appear to have been any breast cancer cases diagnosed in the placebo or comparator (IFN) arms of the trials conducted. The narratives for each of the above cases were reviewed and assessed for details, including age of the patient at cancer diagnosis, number of days on therapy with ocrelizumab, presence of family history of breast or other cancers, and pertinent pathological tumor characteristics and stage at diagnosis. Unfortunately, details of stage and subtype (ER/PR status, HER2 status) were not provided for most of the breast cancer cases described. It was interesting that some of the patients continued on therapy with ocrelizumab, despite cancer diagnosis, where as some of the patients had therapy

discontinued by the investigator, since the cancer was thought (by the investigator) to possibly be related to therapy with ocrelizumab, in those cases. Although it is difficult to make any conclusions about whether there is cause for concern, with respect to the imbalance in cases diagnosed in ocrelizumab treated patients, a potential safety signal should not be ruled out, at this time. See also response to Question 4.

3. Do you find Genentech's comparison to outside databases reassuring, despite the observed imbalance from within the controlled trials?

   DOP1 response: No, but we defer to OSE's assessment of this aspect of the Sponsor's account, with regard to the validity of these databases, as well as the role of the comparison of data within controlled trials to these outside databases.

4. If you agree with Genentech that no conclusion on malignancy can be made, do you think it is appropriate to further evaluate this signal in the post-marketing period as proposed?

   DOP1 response: We do not agree that no conclusion on malignancy can be made. The signal identified within the trials in the ocrelizumab does warrant further evaluation, and should include collection of information on newly diagnosed malignancies, in general. Specific guidance should be given to the Sponsor on the information collected going forward, but should include, at a minimum, the pathological cancer diagnosis, stage at diagnosis, time on therapy with ocrelizumab at the time of cancer diagnosis, and action taken with ocrelizumab therapy at that point (continue vs. discontinue). For breast cancer cases, specifically, details collected should include stage at diagnosis and hormonal status of the tumor (to include ER/PR status and HER2 status).

   Although it is difficult to make a conclusion about whether causality can be attributed to ocrelizumab in any of the cancer cases identified, a relationship should not be ruled out, at this time. We think that there is precedent for including the information about potential malignancy risk in the product labeling. For example, other products such as olaparib (Lynparza) and alemtuzumab (Lemtrada) include information on cases of malignancy in the label and have malignancy risk as a section in Warnings and Precautions. The Lemtrada label also contains a box warning describing the risk of malignancy. Using these examples, it is warranted to have further discussions with the Sponsor regarding the need to include this information in the label.

Breast cancer cases table:

#	Study	Patient ID/ Age/ sex	Underlying disease	Cancer diagnosed	Treatment arm and dose	Days on study drug (Sponsor derived)	Time from last dose study drug to cancer in days (Sponsor derived)	Narrative info- study day of event, outcome if available
1	WA21092	206629-1920773/ 54 y/o white female Czech	MS	Invasive ductal carcinoma (breast)	Ocre 600	840	57	Event diagnosed Study day 393, G4 AE- study drug stopped as result of dx. Withdrawn from study D 421.
2	WA21092	234347-1926392 29 y/o female US	MS	Invasive ductal carcinoma (breast)	Ocre 600	502	463	Event diagnosed study day 463, but narrative states she was only on drug for 84 days- d/c due to UTI.
3	WA25046	208039-47403 54 y/o female France	MS	Invasive ductal carcinoma (breast)	Ocre 600	968	47	Last infusion Ocre D856. D882 mammo performed. Subsequent biopsy revealed invasive ductal carcinoma. Underwent surgery with mastectomy and ALND. No other info given.
4	WA25046	208185-10201 54 y/o female Germany	MS	Breast cancer	Ocre 600	886	115	Last infusion of ocre was Day 351. Narrative states she had breast biopsy D451 with malignant cells and had R mastectomy D471. Investigator attributed breast cancer to be related to ocrelizumab.
5	WA25046	208661-21006 47 y/o female Poland	MS	Invasive breast cancer	Ocre 600	832	58	According to the narrative, on study day 737 she had U/S L breast which revelaed hypogenic tumor. Study D811 she was diagnosed with invasive breast carcinoma. Ocrelizumab was discontinued. She had radical mastectomy, but diagnosis was deemed unrelated to study drug by investigator.
6	WA25046	208787-32301 52 y/o female US	MS	Invasive ductal carcinoma-breast	Ocre 600	1273	92	Narrative states that she stopped therapy with ocrelizumab on D 854. On study day 917, patient had a R breast biopsy, which revealed infiltrating ductal carcinoma. She began radiation therapy and tamoxifen on study day 1012. Investigator attributed diagnosis as related to study drug.
7	WA21493	140954-1052 45 y/o female Bulgaria	MS	Breast cancer	Ocre 1000	1291	258	Narrative states that patient had h/o bilateral breast fibroaednomas treated with partial breast resection in 2005. Began ocrelizumab 2009. On study day 491,

								completed treatment phase. On D748 she developed L breast induration with palpable mass. On D773 had subtotal mastectomy and axillary lymph node dissection. She had Stage III invasive ductal cancer- ER+ PR+, HER2-. On D836 she started unspecified chemotherapy.

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/s/

GWYNN ISON
06/28/2016

LALEH AMIRI KORDESTANI
06/28/2016