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APPLICATION NUMBER:

761053Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

BLA Number	761053
Link to EDR	\\CDSESUB1\evsprod\BLA761053\0000
Initial Submission Date	4/28/2016
Submission Type	Priority
Brand Name	OCREVUS
Generic Name	Ocrelizumab
Dosage Form and Strength	IV solution, 300 mg/10 ml (30 mg/mL) in a single-use vial
Route of Administration	Intravenous Infusion
Proposed Indication	Treatment of relapsing forms of multiple sclerosis (MS) and primary progressive MS
Applicant	Genentech
Associated IND	IND 100593
OCP Review Team	Jagan Parepally, Angela Men, Xiaofeng Wang, Kevin Krudys
OCP Final Signatory	Mehul Mehta, PhD Division Director Division of Clinical Pharmacology I

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1. EXECUTIVE SUMMARY

The sponsor is seeking the approval for ocrelizumab, a recombinant, humanized monoclonal antibody that selectively targets CD20-expressing B cells to treat primary progressive(PPMS) and relapsing forms (RMS) of multiple sclerosis. The proposed dosing regimen is 600 mg dose IV (b) (4) administered every 6 months. The efficacy and safety of ocrelizumab in multiple sclerosis patients was supported by three pivotal Phase III randomized, double-blind, parallel group, active comparator controlled / placebo controlled, multicenter trials in RMS patients and PPMS patients. The 600 mg dose was selected for Phase 3 studies based on Phase 2 dose ranging study.

In addition, the sponsor submitted 7 clinical pharmacology studies conducted in rheumatoid arthritis (RA) patients to support the pharmacokinetics (PK) and pharmacodynamics (PD) of ocrelizumab following IV administration. Population PK and PK/PD analyses were performed to evaluate the potential impact of covariates on PK and PD. A two compartment pharmacokinetic model describes concentration-time course of ocrelizumab. Pharmacodynamic measures included evaluation of CD19+ B cells, T-Cells and NK-cells in blood. Ocrelizumab treatment led to rapid and complete depletion of B cells in blood which was sustained throughout treatment.

From a clinical pharmacology perspective, the proposed 600 mg dose every 6 months supported the indication in multiple sclerosis. Since a single dose, 600 mg, was studied in Phase 3 studies, exposure-response relationships for efficacy and safety could not be established from the data and thus cannot be used to support an alternative dose or dosing regimen that could result in a better benefit/risk profile than the currently proposed one. The incidence of immunogenicity was approximately 1%. Patients with neutralizing antibodies showed faster clearance of ocrelizumab and faster B-cell repletion. There was no impact on safety and efficacy in all the patients with of treatment-emergent anti-drug antibodies (ADAs).

The primary focus of the review is harmonization of dosing regimen between the RMS and PPMS indications.

1.1 Recommendations

The Office of Clinical Pharmacology Divisions of Clinical Pharmacology I and Pharmacometrics have reviewed the information contained in BLA 761,053. The review team recommends approval of this BLA from a clinical pharmacology perspective. The key review issues with specific recommendations /comments are summarized below:

Review Issue	Recommendations and Comments
Supportive evidence of effectiveness	The primary evidence of effectiveness comes from, two Phase 3 studies in RMS patients (study WA21092 and WA21093) and Phase 3 study in PPMS (WA25046). Supportive evidence comes for a phase 2 dose ranging

	study (study WA21493). Dose-response in B-cell depletion and repletion in the Phase 1/2 study (study ACT2847g) and the B-cell count profiles in the Phase 3 studies WA21092, WA21093, and WA25046 provide supportive mechanistic evidence for effectiveness.
General dosing instructions	The proposed initial 600 mg dose administered as two separate IV infusions; first as a 300 mg infusion followed 2 weeks later by a second 300 mg infusion. Followed by 600 mg dose is administered as a single IV infusion every 6 months is acceptable from clinical pharmacology perspective. In Phase III pivotal RMS and PPMS trials, two different infusion regimens were used (see Section 3.3.3 for further details): 600 mg vs. 2x300mg. The overall exposure (AUC per 600 mg dose over the 24 week dosing interval) was identical between the single 600 mg infusion and the double (2 x 300 mg) infusion regimens. The B-cell depletion (a pharmacodynamic marker) was comparable for both regimens. The pattern of transient B-cell repletion between the ocrelizumab doses was the same in the RMS and PPMS trials, independent of the infusion regimens. Although the Cmax was approximately 50% higher, the rate and severity of infusion related reactions (IRRs) were comparable. There were no obvious safety differences between these two dosing regimens.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose individualization is recommended based on intrinsic and extrinsic factors. Body weight based dosing is not required (see section 2.2.1)
Labeling	Generally acceptable. The review team has specific content and formatting change recommendations.
Bridge between the to-be-marketed and clinical trial formulations	Not applicable. To-be-marketed formulation was used in clinical trials.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Ocrelizumab is a recombinant humanized monoclonal antibody that selectively targets CD20-expressing B cells. CD20 is a cell surface antigen found on pre-B cells, mature and memory B cells but not expressed on lymphoid stem cells and plasma cells. The capacity of B-cell reconstitution and preexisting humoral immunity are preserved. The precise mechanisms through which ocrelizumab exerts its therapeutic clinical effects in MS are not fully elucidated but involve immunomodulation through the reduction in the number and function of B cells. Treatment with ocrelizumab leads to depletion of CD19+ B-cells in blood by 14 days post-treatment (first time-point of assessment). For the B-cell counts, CD19 is used as a marker since the presence of ocrelizumab interferes with the recognition of CD20 by the assay.

The following is a summary of the clinical pharmacokinetics of ocrelizumab:

Pharmacokinetics in the MS patients follow a two compartment model with time dependent clearance (typical for an IgG1 monoclonal antibody). The pharmacokinetics of ocrelizumab was essentially linear and dose proportional between 400 mg and 2000 mg.

Absorption: Ocrelizumab is administered as an IV infusion. There have been no studies performed with other routes of administration.

Distribution: The estimated volume of distribution for the central compartment was 2.78 L. Peripheral volume and inter-compartment clearance were estimated at 2.68 L and 0.294 L/day, respectively by population pharmacokinetics.

Metabolism: Not studied. In general antibodies are cleared by catabolism.

Elimination: The initial time-dependent clearance was 0.0489 L/day which declined with a half-life of 33 weeks. The terminal elimination half-life was 26 days.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The applicant proposes 600 mg ocrelizumab dose administered every 6 months. The first dose is administered as a divided dose of two IV infusions consisting of 300 mg each administered two weeks apart. The second and subsequent doses of ocrelizumab are administered as a single 600 mg IV infusion every 6 months.

A dosing interval of 24 weeks was selected based on signs of B cell repletion by 6 months post-dose at doses of 400 mg and above. This dosing regimen of administration every 6 months was to ensure continuous depletion of peripheral blood B-cells throughout treatment.

Infusion Regimen Harmonization

In Phase III pivotal RMS and PPMS trials, the initial dose was administered as two 300 mg infusions given 14 days apart. In the RMS Studies WA21092 and WA21093 subsequent doses were administered as single 600 mg infusions, whereas in the PPMS Phase III Study WA25046 administration of ocrelizumab continued as an infusion regimen of 2 x 300 mg through the entire treatment period.

The initial results from the first 24 weeks in this RA study suggested that the double ocrelizumab infusion of 2 x 200 mg might result in better efficacy outcomes compared to the single.

The Cmax was approximately 50% different between 300 mg and 600 mg infusions, the rate and severity of IRRs was comparable between the double infusion regimen in the PPMS trial and the single infusion regimen in the RMS trials. The overall exposure (AUC per 600 mg dose over the 24 week dosing interval) was identical between the single 600 mg infusion and the double (2 x 300 mg) infusion regimens. The B-cell depletion as the pharmacodynamic marker was comparable for both regimens, including immediate B-cell depletion in blood following the first infusion and continued depletion with all subsequent doses. The pattern of transient B-cell repletion between the ocrelizumab doses was the same in the RMS and PPMS trials, independent of the single 600 mg or 2 x 300 mg dosing regimen. There were no obvious safety differences between these two dosing regimens.

Based on these supporting data, it is acceptable to harmonize infusion regimen of 600 mg IV infusions every 6 months for both RMS and PPMS patients; Dose 1 administered as 2 x 300 mg infusions separated by 2 weeks, and all subsequent doses administered as 1 x 600 mg infusion.

2.2.2 Therapeutic individualization

At this time therapeutic individualization is not recommended. The only factor of interest from an individualization perspective was the impact of body weight on dosing which is described below.

Fixed Dose vs Body Weight Based Dosing: Although body weight was identified as a significant covariate in the population pharmacokinetic analysis, the effect of body weight on ocrelizumab pharmacokinetics was relatively small. Specifically, Cmax values were estimated to be 19% higher for RMS patients weighing < 60 kg and 13% lower for patients weighing >90 kg compared with the 60-90 kg weight group. $AUC_{\tau,ss}$ values were 26% higher for patients weighing < 60 kg and 21% lower for patients weighing > 90 kg compared with the 60-90 kg weight group. The similar pattern was observed in PPMS patients. The reviewer evaluated the applicant's proposed fixed dosing of 600 mg and the potential body weight-based dosing of 8 mg/kg by comparing the predicted steady state AUC under the two different dosing regimens. The results show that no or limited benefit from the PK perspective can be expected by switching from fixed dosing of 600 mg to body weight-based dosing of 8 mg/kg (for further details see section 3.3.6*).*

In addition, subgroup analyses of primary and secondary efficacy endpoints regarding body weight were conducted by the applicant. In study WA25046 for PPMS, consistent treatment effect favoring ocrelizumab in the subgroups of patients with baseline body weight < 75 kg and those with baseline body weight ≥ 75 kg were observed for both the primary efficacy endpoint of time to onset of 12-week CDP (HR 0.76 [95% CI: 0.54, 1.07] for <75 kg vs. HR 0.76 [95% CI: 0.52, 1.12] for ≥ 75 kg) and secondary efficacy endpoint of time to onset of 24-week CDP (HR 0.78 [95% CI: 0.55, 1.11] for <75 kg vs. HR 0.73 [95% CI: 0.49, 1.10] for ≥ 75 kg). In studies WA21092 and WA21093 for RMS, although the secondary endpoint analysis results show that the subgroup of patients with baseline body weight < 75 kg showed a greater reduction of 12-week CDP on ocrelizumab versus interferon beta-1a (HR 0.36 [95% CI: 0.18, 0.72] in study WA21092 and HR 0.43 [95% CI: 0.24, 0.79] in study WA21093) compared with patients with baseline body weight ≥ 75 kg (HR 0.85 [95% CI: 0.46, 1.56] in the study WA21093 and HR 0.90 [95% CI: 0.53, 1.53] in the study WA21093), no treatment difference between the two body weight subgroups was observed for the primary endpoint of ARR (HR 0.51 [95% CI: 0.33, 0.77] for <75 kg vs. HR 0.50 [95% CI: 0.33, 0.76] for ≥ 75 kg in study WA21092; HR 0.47 [95% CI: 0.32, 0.70] for <75 kg vs. HR 0.60 [95% CI: 0.39, 0.94] for ≥ 75 kg in study WA21093).

Therefore, based on the pharmacokinetic and efficacy data discussed above, as well as consideration of clinical convenience, the proposed fixed dosing of 600 mg is considered to be appropriate and no alternative dose or dosing regimen for different body weight subgroups is necessary.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

In general the applicant proposed labeling statements are acceptable. However, the Office of Clinical Pharmacology recommends the following labeling concepts to be included in the final package insert:

The section 7 should be formatted to be consistent with previous BLA labeling language (eg., rituximab USPI). The sections 8.5, Geriatric Use, 8.6, Hepatic Impairment, 8.7, Renal Impairment should be deleted since no formal studies have been conducted in these population and this information is covered in section 12.3 Pharmacokinetics. The section 12.2 should be edited to remove potential promotional language related to the (b) (4) and section 12.3 the PK parameters following two different dosing regimens used in Phase 3 studies are recommended to be revised to clearly describe PK parameters following two different dosing regimens used in Phase 3 studies. The immunogenicity information is described in the section 12.4 we recommend that this information should be moved to section 6.3 to be consistent with the other applications.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

OCREVUS is provided in glass vials as a sterile single use solution for IV infusion. 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) mM sodium acetate at pH 5.3, with [redacted] (b) (4) mM trehalose dihydrate and 0.02% polysorbate 20.

The proposed indication of ocrelizumab is for the treatment of relapsing multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS). There are no approved therapies for PPMS which have shown significant effect on slowing progression of disability. OCREVUS has shown a clinically meaningful effect on slowing the progression of disability and reduction in deterioration of walking speed in patients with PPMS. Based on the results from the pivotal Study WA25046 in patients with PPMS, the Agency granted priority review designation for this BLA.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Ocrelizumab is a recombinant humanized monoclonal antibody that selectively targets CD20-expressing B-cells. The exact mechanism by which ocrelizumab exerts its therapeutic clinical effects in MS are not fully understood. The purported mechanism involves immunomodulation through the reduction in the number and function of CD20-expressing B-cells. Following cell surface binding, ocrelizumab selectively depletes CD20-expressing B cells through antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and apoptosis.
General Information	

Bioanalysis	Serum ocrelizumab concentrations were measured in serum by a validated Enzyme-Linked Immunosorbent Assay (ELISA). The assay used goat anti-ocrelizumab CDR antibodies to capture ocrelizumab from serum samples. Bound ocrelizumab was detected with a goat F(ab')2 anti-human IgG (Fc-gamma fragment) conjugated to horseradish peroxidase (HRP), and a peroxidase substrate (tetramethyl benzidine) was used for color development. The lower limit of detection (LLOQ) in human serum was 1.56 ng/mL. Analytical reports were submitted and QC reports were summarized for the use of the method for each study. Analytical methods for detection of anti-drug antibodies (ADAs) in serum were validated and demonstrated adequate sensitivity and drug tolerance for detection of ADA responses in human serum. In the pivotal studies (WA21092, WA21093 and WA25046), samples that were positive for the presence of ADA were then further analyzed for anti-drug NAbs. Pharmacodynamic assays: CD19+, T-cells and NK cells were measured with flow cytometry. All assays were validated and reports were submitted (see appendix 4.1 for further details)
Healthy Volunteers vs Patients	No studies were conducted in healthy subjects.
Drug exposure at steady state following the therapeutic dosing regimen	The overall exposure at the steady state (AUC over the 24 weeks dosing interval) of ocrelizumab was 3510 µg.hr/mL.
Dose Proportionality	The pharmacokinetics of ocrelizumab was essentially linear and dose proportional between 400 mg and 2000 mg. Additional information related to dose proportionality was supported by studies conducted in RA population.
Variability	Intra-subject variability was 18.6% Inter-individual variability in clearance was 19%, in central volume of distribution 14%, and in peripheral volume of distribution 16%. Overall inter-patient variability for all PK parameters in MS patients was up to 30% (coefficient of variation [CV]) for all the PK parameters.
ADME	
Absorption	Ocrelizumab was administered as an IV infusion. No studies were performed with other routes of administration.
Distribution	The estimated volume of distribution for the central compartment was 2.78 L. Peripheral volume and inter-compartment clearance were estimated at 2.68 L and 0.294 L/day, respectively from population pharmacokinetics.
Metabolism	Not studied. In general antibodies are expected to be metabolized into peptides and amino acids via catabolic pathway.
Elimination	The initial time-dependent clearance was 0.0489 L/day which declined with a half-life of 33 weeks. The terminal elimination half-life was 26 days.
IMMUNOGENICITY	

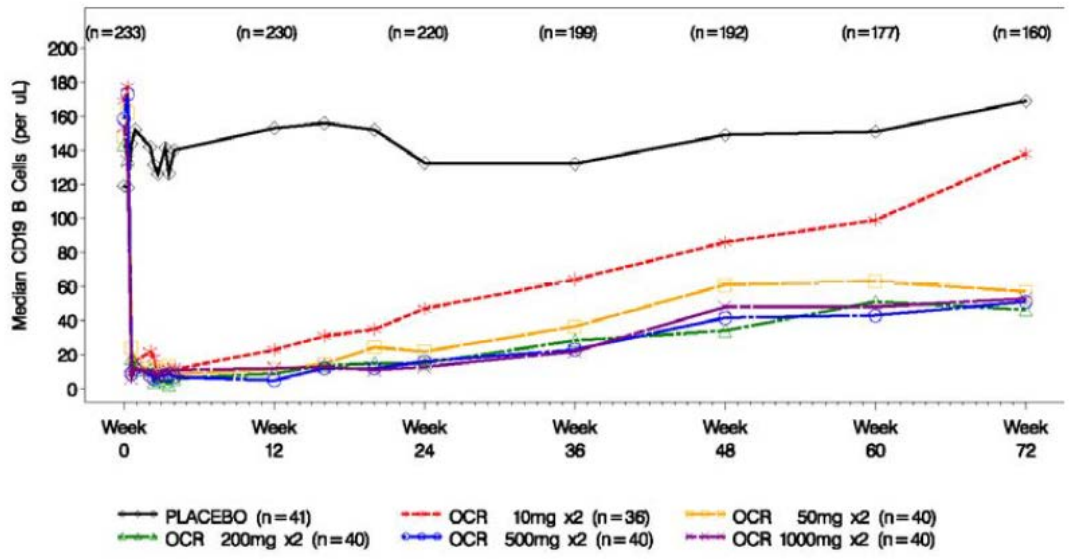
Immunogenicity	The incidence of immunogenicity was approximately 1%. Out of 1311 patients treated with ocrelizumab, 12 (~1%) tested positive for treatment-emergent ADAs, of which 2 patients tested positive for neutralizing antibodies. Patients with neutralizing antibodies showed faster clearance of ocrelizumab and faster B-cell repletion in 2 patients. There was no impact on safety and efficacy in all the patients with of treatment-emergent ADAs.

3.3 Clinical Pharmacology Review Questions

3.3.1 Does the clinical pharmacology information provide supportive evidence of effectiveness?

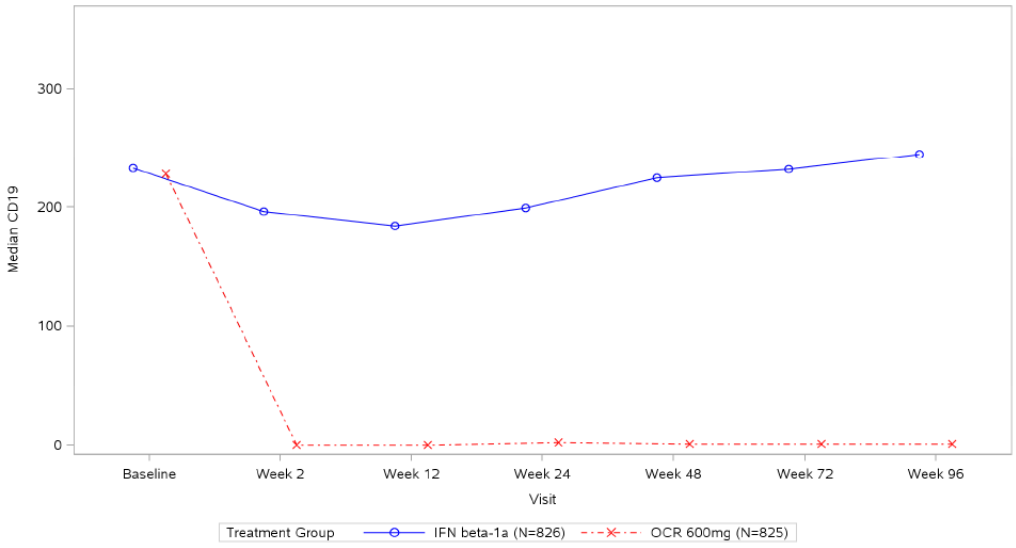
Yes. The dose-response relationship for B-cell depletion and repletion in the Phase 1/2 study ACT2847g and the B-cell count profiles in the Phase 3 studies WA21092, WA21093, and WA25046 provide supportive mechanistic evidence for effectiveness. Ocrelizumab selectively targets CD20-expressing B cells and the presumed mechanism of action for ocrelizumab to treat MS is to involve immunomodulation through the reduction in the number and function of CD20-expressing B-cells. Study ACT2847g was a randomized, placebo-controlled, multicenter, blinded Phase I/II study of the safety of escalating doses of ocrelizumab in subjects with moderate to severe rheumatoid arthritis (RA) receiving stable doses of concomitant methotrexate, in which subjects received two IV infusions of ocrelizumab or placebo on days 1 and 15 at 2x10, 2x50, 2x200, 2x500, and 2x1000 mg dose levels. As shown in **Figure 1**, B-cell depletion was achieved at all doses immediately after the initial infusion and a dose-dependent trend for B-cell repletion in the 2x10 and 2x50-mg dose groups over time was observed, but no obvious difference was observed across the 2x200, 2x500, and 2x1000-mg dose groups through week 72, suggesting that a relative maximum of B-cell depletion was reached at the 2x200-mg dose. In addition, rapid and sustained B-cell depletions in blood were also observed in the RMS Phase 3 studies WA21092 and WA21093 (shown in **Figure 2**) and in the PPMS Phase 3 study WA25026 (shown in **Figure 3**) and were maintained with continued treatment.

Figure 1: Median Peripheral Blood B-Cell Profiles following IV Ocrelizumab Administration in Subjects with RA in Study ACT2847g



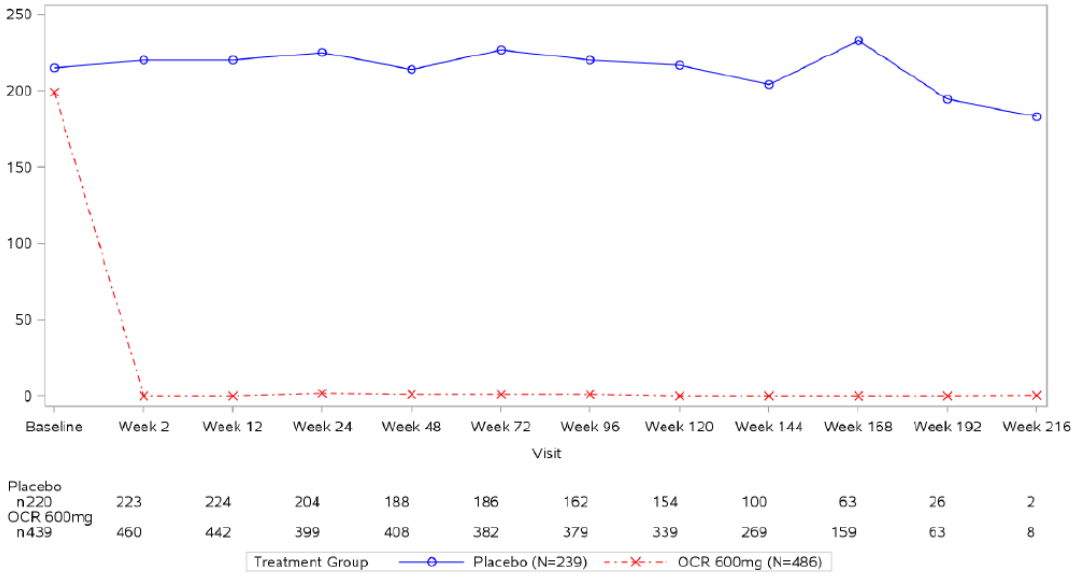
Source: CSR ACT2847g Figure 4 on page 65

Figure 2: Median B-Cell Count Profile in Studies WA21092 and WA21093 (pooled; RMS)



Source: Summary of Clinical Pharmacology Studies Figure 9 on page 46

Figure 3: Median B-Cell Count in Study WA25046 (PPMS)



Source: Summary of Clinical Pharmacology Studies Figure 19 on page 64

In RA, Phase III studies, efficacy was demonstrated by doses of 400 mg and 1000 mg. However, clinical outcomes were maximally improved by the 1000 mg dose, despite peripheral blood B cell depletion with all doses. Based on these findings, 600 mg and 2000 mg were selected for assessment in the Phase II dose finding study of ocrelizumab in patients with RMS, WA21493. The 600 mg dose was selected for the pivotal phase III studies in RMS and PPMS, since no clear differences in efficacy were observed between the two doses from the analysis of the primary outcome (number of T1 Gd-enhancing lesions at weeks 12, 16, 20 and 24). Both ocrelizumab doses demonstrated statistically significant reductions in ARR compared with placebo.

The following schematic represents an overview of Phase III clinical studies in MS.

Figure 4: Study Schematic: Overview of MS clinical studies

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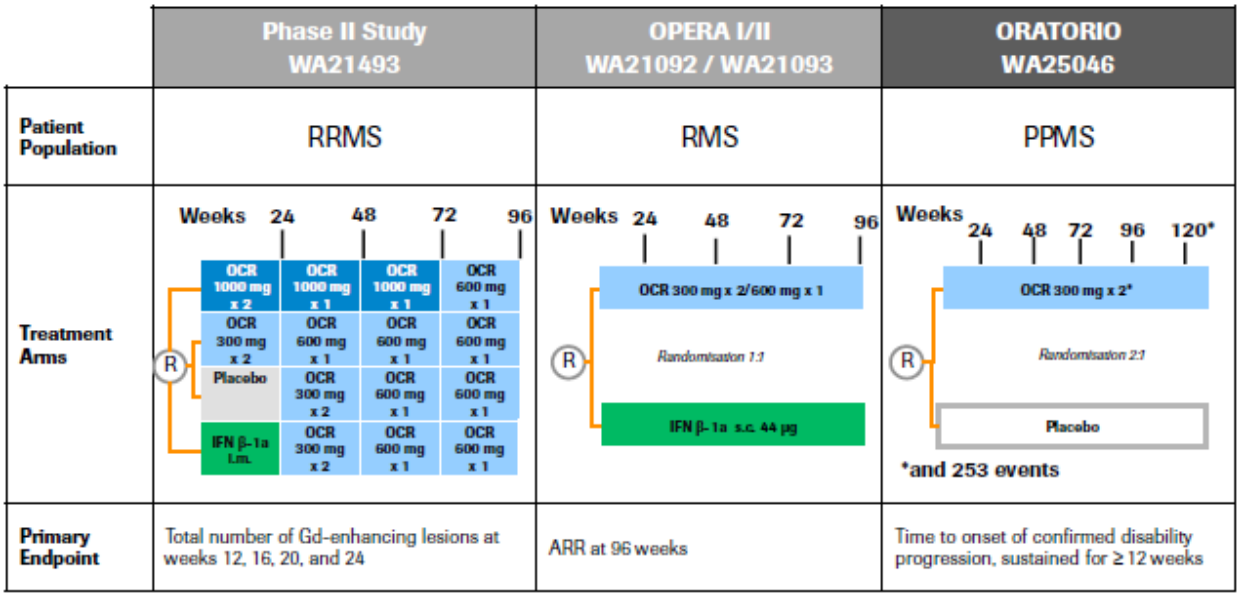


ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; Gd = gadolinium; IFN = Interferon; OCR = ocrelizumab; PPMS = primary progressive MS

Studies WA21092 and WA21093 are two identically designed Phase 3 trials to evaluate the efficacy and safety of ocrelizumab compared with interferon beta-1a in patients with RMS and both trials met the pre-specified primary efficacy endpoint of reduction in annualized relapse rate (ARR). Study WA25046 is the Phase 3 trial to evaluate the efficacy and safety of ocrelizumab compared with placebo in patients with PPMS and it met the pre-specified primary efficacy endpoint of reduction in time to onset of 12-week clinical disability progression (CDP). (*Please refer to the statistical review by Dr. Sharon Yan and clinical efficacy review by Dr. Lawrence Rodichok for details about results of the pivotal efficacy trials.*)

3.3.2 Is the proposed general dose and dosing regimen appropriate?

Yes. The proposed general dose and dosing regimen for the proposed indications in RMS and PPMS are appropriate.

Dose Selection

Based on clinical outcome measure in RA studies, 600 mg and 2000 mg were selected for assessment in the Phase II dose finding study of ocrelizumab in patients with RMS, WA21493. Since there was no clear differences in efficacy observed between the two doses from the analysis of the primary outcome (number of T1 Gd-enhancing lesions at weeks 12, 16, 20 and 24) and both ocrelizumab doses demonstrated statistically significant reductions in ARR compared with placebo. The 600 mg dose was selected for the pivotal phase III studies in RMS and PPMS. The Agency agreed that 600 mg was a reasonable dose but encouraged the Sponsor to evaluate a second lower dose between 600 mg and doses that produce high rate of antibody formation. However, the sponsor conducted Phase 3 studies at a single 600 mg dose.

A dosing interval of 24 weeks was selected based on signs of repletion by 6 months post-dose at doses of 400 mg and above. This dosing regimen of administration every 6 months was to ensure continuous depletion of peripheral blood B-cells throughout treatment. Evidence of effectiveness and safety of 600 mg is supported by two identical pivotal Phase III studies in RMS patients and a single pivotal Phase III study in PPMS patients (see section 3.3.1).

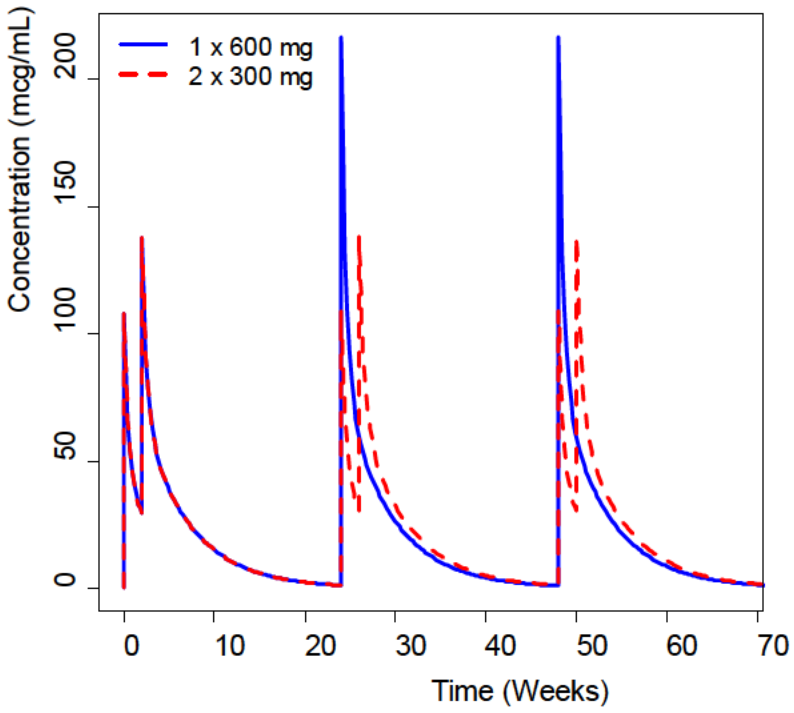
Harmonization of Dosing Regimens for RMS and PPMS Indications

The PK, PD, and safety data support a harmonized infusion regimen of 600 mg IV infusions every 6 months (Dose 1 administered as 2 x 300 mg infusions separated by 2 weeks, and all subsequent doses administered as 1 x 600 mg infusion for both RMS and PPMS patients. The applicant's original rationale for selecting dual infusion regimen in the PPMS phase 3 study and supportive evidence for harmonization are described below.

Applicant's rationale for selecting dual infusion regimen in the PPMS study: The rationale for selecting the dual-infusion regimen in the PPMS study WA25046 was based on early data from a Phase 3 study in rheumatoid arthritis (RA), study WA20496, in which the efficacy and safety of 400 mg ocrelizumab given as a single Infusion (400 mg x 1) or dual infusion (200 mg x 2) in patients with active rheumatoid arthritis (RA) were evaluated. The selection of two different infusion regimens was based on previous phase 2 study results which showed similar clinical efficacy accompanied by acceptable tolerability profiles and with reasonably low human anti-human antibody (HAHA) rates. Thus, both dose regimens were selected in study WA20496 to compare the two regimens on the basis efficacy, safety, PK and PD. Early data from the first 24-week treatment period showed that administration of ocrelizumab via dual infusion (200 mg x 2) appeared to be associated with a numerically better clinical response as measured as ACR20 response compared to ocrelizumab single infusion (400 mg x 1). However, analyses of data from the second 24-week treatment period suggested that the efficacy achieved after an initial dosing with dual infusion of ocrelizumab (200 mg x 2) during the first period could be maintained at similar levels by either an 400 mg single infusion or by an 200 mg x2 dual infusion as a second treatment. (See section 4.6 for detailed study design and results for study WA20496.) At the time the WA25046 study design was being finalized, only the 24-weekd data from study WA20496 was available, and therefore, the dual infusion regimen (300 mg x 2) was selected for the PPMS study WA25046. However, when the two RMS studies WA21092 and WA21093 were initiated, the final data and conclusion of the RA study WA20496 became available, thus the single infusion regimen was selected for the RMS studies.

Pharmacokinetics: The two different regimens resulted in similar AUC and Ctrough while a single 600 mg infusion resulted in ~50% increase in Cmax compared to two 300 mg infusions (***Figure 5***). Such an increase in Cmax is not considered clinically significant since the exposure-safety relationship shows no obvious increase in safety findings with increased exposure within the exposure range at 600 mg dose level.

Figure 5: Comparison of PK Profiles between the Two Regimens



Pharmacodynamics: The two regimens resulted in comparable B-cell count profiles, as shown in ***Figure 6***. In addition, the distributions of B-cell counts are comparable between the two regimens at various time points including week 24, 48, 72, and 96 (***Figure 7*** shows the result at week 24 for illustration; the same trend is observed at the other time points as shown in section 4.6). Moreover, the percentage of patients with B-cell repletion (defined as B cells repleted to above the lower limit of normal (LLN) or baseline value whichever was lower) is also comparable between the two regimens at various time points, as shown in ***Table 1***.

Figure 6: Comparison of Absolute B-Cell Count Profiles between the Two Regimens

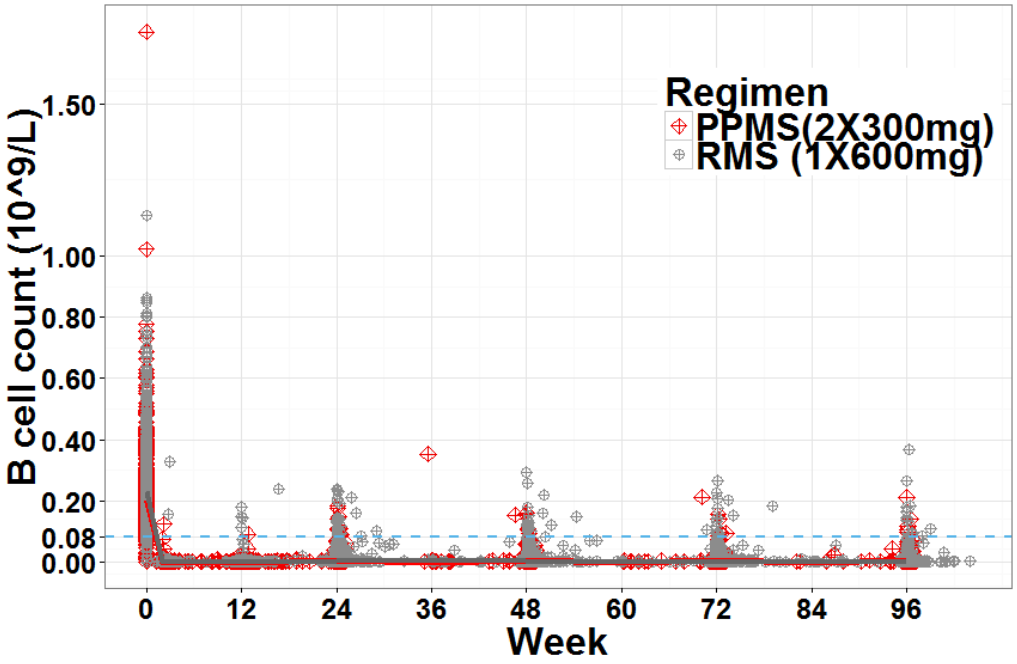


Figure 7: Comparison of B-Cell Count Distribution between the Two Regimens

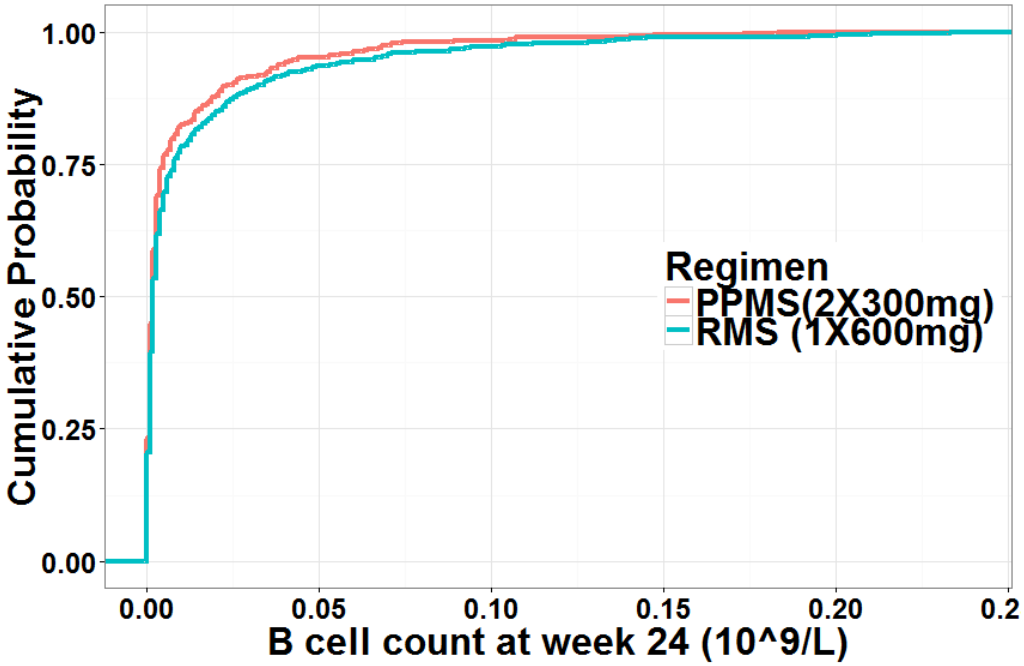


Table 1: Comparable % Patients with B-Cell Repletion between the Two Regimens

Week	% Patients Repleted	
	RMS (single 600 mg infusion)	PPMS (double 300 mg infusions)

	(WA21092, WA21093)	(WA25046)
24	4.1	3.3
48	3.3	2.7
72	2.2	3.1
86	2.6	1.8

Safety: There was no obvious difference in the pattern of infusion related reactions (IRR) between the single 600 infusion regimen in the RMS studies and the double 300 mg infusion regimen in the PPMS study, as shown in ***Table 2***. The incidence, severity and symptoms of IRRs were similar between the two regimens. Therefore, from the safety perspective, there appears to be no benefit for PPMS patients to receive double infusion regimen from dose 2. Moreover, harmonizing the dosing regimen for RMS and PPMS could potentially reduce dosing errors.

Table 2: Incidence and Severity of IRRs for Single versus Double Infusions for Doses 2, 3, and 4

	RMS Dose 2	PPMS Dose 2		RMS Dose 3	PPMS Dose 3		RMS Dose 4	PMS 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	107 (13.7%)	54 (11.6%)	23 (5.1%)	73 (9.6%)	52 (11.5%)	22 (5.0%)	57 (7.8%)	29 (6.6%)	13 (3.0%)
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	44 (6.0%) 13 (1.8%) 0	26 (5.9%) 3 (0.7%) 0	12 (2.8%) 1 (0.2%) 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, oropharyngeal pain, flushing	pruritus, headache, flushing, fatigue, pyrexia	throat irritation, pruritus, rash, headache	pruritus, flushing, rash, pyrexia, oropharyngeal pain	fatigue, flushing, pyrexia
Most common symptoms ≥ 5% < 10%	headache, flushing	fatigue, flashing	dizziness, dysgeusia throat irritation	flushing	rash, throat irritation, chills, nausea, ear pruritus	none	oropharyngeal pain, flushing	chills, headache	asthenia, chills, headache, dysgeusia, somnolescence, nausea

Source: Summary of Clinical Pharmacology Table 22 on page 84

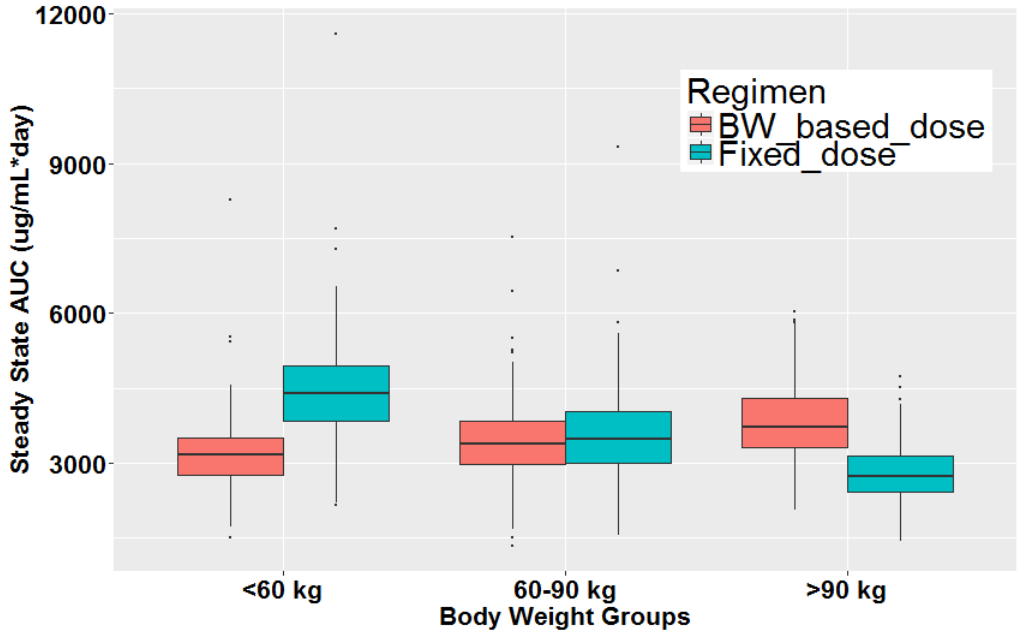
Therefore, the PK, PD, and safety data support a harmonized infusion regimen of 600 mg IV infusions every 6 months (Dose 1 administered as 2 x 300 mg infusions separated by 2 weeks, and all subsequent doses administered as 1 x 600 mg infusion) for both RMS and PPMS patients.

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

No. There is no need for alternative dose or dosing regimen for subpopulation based on the intrinsic factors as described below. The fixed 600 mg dose every six months is appropriate given the non-clinically relevant effect of covariates on PK and convenience in clinical setting.

Body Weight: Although body weight was identified as a significant covariate in the population pharmacokinetic analysis, the effect of body weight on ocrelizumab pharmacokinetics was relatively small. Specifically, Cmax values were estimated to be 19% higher for RMS patients weighing < 60 kg and 13% lower for patients weighing >90 kg compared with the 60-90 kg weight group. $AUC_{\tau,ss}$ values were 26% higher for patients weighing < 60 kg and 21% lower for patients weighing > 90 kg compared with the 60-90 kg weight group. The similar pattern was observed in PPMS patients. The reviewer evaluated the applicant's proposed fixed dosing of 600 mg and the potential body weight-based dosing of 8 mg/kg by comparing the predicted steady state AUC under the two different dosing regimens. The results show that no or limited benefit from the PK perspective can be expected by switching from fixed dosing of 600 mg to body weight-based dosing of 8 mg/kg (shown in ***Figure 8***).

Figure 8: PK Comparison between Fixed dosing of 600 mg and Body Weight-based dosing of 8 mg/day



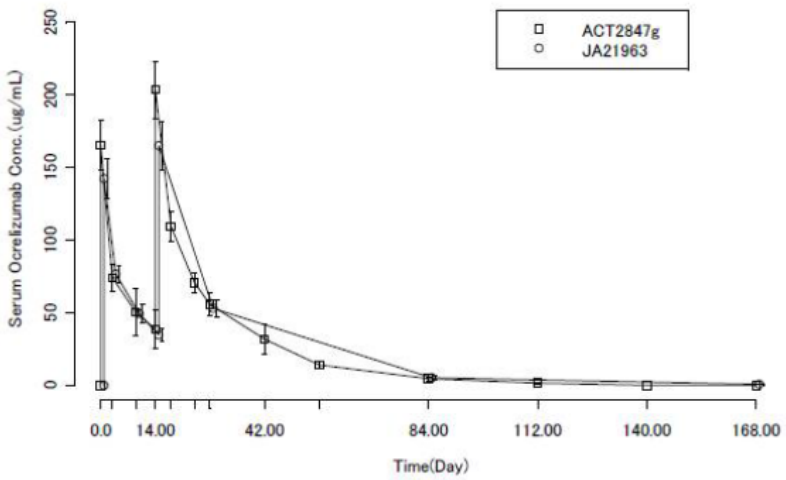
In addition, subgroup analyses of primary and secondary efficacy endpoints regarding body weight were conducted by the applicant. In study WA25046 for PPMS, consistent treatment

effect favoring ocrelizumab in the subgroups of patients with baseline body weight < 75 kg and those with baseline body weight ≥ 75 kg were observed for both the primary efficacy endpoint of time to onset of 12-week CDP (HR 0.76 [95% CI: 0.54, 1.07] for <75 kg vs. HR 0.76 [95% CI: 0.52, 1.12] for ≥ 75 kg) and secondary efficacy endpoint of time to onset of 24-week CDP (HR 0.78 [95% CI: 0.55, 1.11] for <75 kg vs. HR 0.73 [95% CI: 0.49, 1.10] for ≥ 75 kg). In studies WA21092 and WA21093 for RMS, although the secondary endpoint analysis results show that the subgroup of patients with baseline body weight < 75 kg showed a greater reduction of 12-week CDP on ocrelizumab versus interferon beta-1a (HR 0.36 [95% CI: 0.18, 0.72] in study WA21092 and HR 0.43 [95% CI: 0.24, 0.79] in study WA21093) compared with patients with baseline body weight ≥ 75 kg (HR 0.85 [95% CI: 0.46, 1.56] in the study WA21093 and HR 0.90 [95% CI: 0.53, 1.53] in the study WA21093), no treatment difference between the two body weight subgroups was observed for the primary endpoint of ARR (HR 0.51 [95% CI: 0.33, 0.77] for <75 kg vs. HR 0.50 [95% CI: 0.33, 0.76] for ≥ 75 kg in study WA21092; HR 0.47 [95% CI: 0.32, 0.70] for <75 kg vs. HR 0.60 [95% CI: 0.39, 0.94] for ≥ 75 kg in study WA21093).

Therefore, based on the pharmacokinetic and efficacy data discussed above, as well as consideration of clinical convenience, the proposed fixed dosing of 600 mg is considered to be appropriate and no alternative dose or dosing regimen for different body weight subgroups is necessary.

Race and Ethnicity: Based on population PK analysis of the MS trial data sets, there was no effect of ethnicity and race on the pharmacokinetics of ocrelizumab. Based on a PK study conducted in Japanese population a cross study comparison resulted in no significant differences in the pharmacokinetics of ocrelizumab between Japanese and non-Japanese RA patients (Figure 9).

Figure 9: Mean Ocrelizumab Concentration versus Time for ACT2847g versus JA21963 (Ocrelizumab 500 mg x 2)



Gender: Gender had a relatively small effect on central volume of distribution. Males showed <12% greater central volume when compared to females.

Renal and Hepatic Impairment: There were no dedicated studies conducted in patients with renal or hepatic impairment since PK of monoclonal antibodies are not known to be effected by renal or hepatic impairment. There was no change in pharmacokinetics observed in patients with mild renal impairment, or in patients with elevated liver enzymes.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Since ocrelizumab is administered by IV infusion, food-drug interactions are not anticipated or applicable. Drug-drug interactions are not expected based on the CYPs, other metabolizing enzymes, or transporters, since ocrelizumab is a monoclonal antibody. Therefore, no drug-drug interaction studies were conducted in vitro or in vivo.

4. APPENDICES

Appendix 4.1: Summary of Bioanalytical Method Validation and Performance

4.1.1 How are the active moieties identified and measured in the clinical pharmacology and biopharmaceutics studies?

Serum ocrelizumab concentrations were measured in plasma by a validated Enzyme-Linked Immunosorbent Assay (ELISA). The assay used goat anti-ocrelizumab CDR antibodies to capture ocrelizumab from serum samples. Bound ocrelizumab was detected with a goat F(ab')2 anti-human IgG (Fc-gamma fragment) conjugated to horseradish peroxidase (HRP), and a peroxidase substrate (tetramethyl benzidine) was used for color development. The lower limit of quantitation (LLOQ) in human serum was 1.56 ng/mL. Analytical reports were submitted and QC reports were summarized for the use of the method for each study

Analytical methods for detection of anti-drug antibodies (ADAs) in serum were validated and demonstrated adequate sensitivity and drug tolerance for detection of ADA responses in human serum. In the pivotal studies (WA21092, WA21093 and WA25046), samples that were positive for the presence of ADA were then further analyzed for anti-drug neutralizing anti-bodies (Nabs).

Pharmacodynamic assays: CD19+ was measured with flow cytometry. All assays were validated and reports were submitted.

4.1.2 What bioanalytical methods are used to assess ocrelizumab concentrations? Briefly describe the methods and summarize the assay performance.

Serum Ocrelizumab concentrations were measured in plasma by a validated ELISA. See section above. The accuracy, precision, and other relevant parameters for the assay are described in Table below. This is sufficient to meet the requirements of the submitted studies.

Summary of Assay Validation Report

Analyte	rhuMAb 2H7, ocrelizumab
Matrix	Human normal, rheumatoid arthritis, non-Hodgkin's lymphoma, multiple sclerosis, and lupus sera
Reference or Analytical Standard	Source: 2H7 Genentech, Inc. reference material, Lot 2H7203-1; at 19.8 mg/mL
Minimum Dilution	1/100
Limit of Detection	0.75 ng/mL
LLOQ	1.56 ng/mL
ULOQ	100 ng/mL
MQC	250 ng/mL
Accuracy (% Bias)	LLOQ: Low: 15.6 %, Mid: 0%, High: 8.8%, ULOQ: 17.8%

Inter-Batch Precision (%CV)	LLOQ: 16.0%, Low: 12.5%, Mid: 8.0%, High: 18.7%, ULOQ: 21.5%
Intra-Batch Precision (%CV)	LLOQ: 12.0%, Low: 9.4 %, Mid: 7.3%, High: 17.6%, ULOQ: 19.1%
Hook Effect	No hook effect observed up to 500 μg/mL
Accuracy in Normal Human Serum Sample (% Recovery)	Low (700 ng/mL): 105% to 111%, Mid (1500 ng/mL): 103% to 112%, High (7500 ng/mL): 96% to 111%
Linearity in Normal Human Serum Sample (% Difference from Preceding Dilution)	≤20% for 6 of 6 low, mid, and high samples acceptable
Recovery in Rheumatoid Arthritis Human Serum Sample (% Recovery)	Low (700 ng/mL): 87% to 109%, Mid (1500 ng/mL): 80% to 117%, High (7500 ng/mL): 89% to 112% for 5 of 5 samples acceptable
Linearity in Rheumatoid Arthritis Human Serum Sample (% Difference from Preceding Dilution)	≤20% for 5 of 5 low, mid, and high samples acceptable
Recovery in Multiple Sclerosis Serum Sample (% Recovery)	Low (700 ng/mL): 84% to 148% for 10 of 12 samples acceptable Mid (1500 ng/mL): 89% to 108%, High (7500 ng/mL): 85% to 105% for 12 of 12 samples acceptable
Linearity in Multiple Sclerosis Serum Sample (% Difference from Preceding Dilutions)	≤20% for 10 of 12 mid and high samples acceptable
Cross-Reactivity	Cross-reactivity: rituximab
Interference	Interfering: anti-ocrelizumab polyclonal antibodies and rituximab Non-Interfering: infliximab, adalimumab, and etanercept, rheumatoid factor, hemoglobin, and lipids
Analyte Stability	Neat: 32 days at 2 °C -8 °C, 4 hours at room temperature, and 8 freeze/thaw cycles. Diluted: 7 Days At 2◦C -8°C
Long-Term Stability	4 years at -60 °C, 13 months at -20 °C
Dilution Integrity	upto 100000 ng/mL. The plate acceptance criteria for dilutional linearity are ±30% Bias for Low and High QC; for Mid QC ± 20% bias.

4.1.3 What is the range of the standard curve? How does it relate to the requirements for clinical studies?

The range of the standard curve used for clinical sample analysis was from 1.56 to 200 ng/mL. The assay range combined with the validated dilution methods are acceptable based on serum ocrelizumab concentrations observed in the studies.

4.1.4 What is the QC sample plan?

Quality Control (QC) samples were freshly prepared on each analysis day by spiking the respective working solutions into human serum. The run acceptance criteria was %CV ≤ 20%, % Bias ± 20% for 320 ng/mL (LQC), 1500 ng/mL (MQC) and 7500 ng/mL (HQC).

4.1.5 What bioanalytical methods are used to assess the formation of the antiproduct antibodies? Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference and matrix, etc.

Anti-drug antibodies in human serum samples were detected using Bridging Antibody Electro chemiluminescent Assay (ECLA). Goat anti-ocrelizumab affinity purified anti-CDR an antibody in normal human serum was used as the positive titer control and positive screen control.

All ADA positive serum samples were screened using antibody-dependent cellular cytotoxicity (ADCC) assay. The assay measures lysis of Calcein AM pre-labeled human CD20+ B lymphoma cells MEC-2, by engineered human natural killer (NK) effector cells in the presence of ocrelizumab. When the target cell is lysed, fluorescent Calcein is released and the fluorescent signal is measured. Refer to the CMC/OBP immunogenicity review for further details on the assays.

Appendix 4.2: Immunogenicity

4.2.1 What is the incidence (rate) of the formation of the anti-drug antibodies (ADAs), the rate of ADAs formation following the treatment and adequacy of the sampling schedule?

Patients were tested for anti-drug antibodies (ADAs) in all clinical MS trials (Study RMS-1, Study RMS-2, and Study PPMS-1). Anti-drug antibodies in human serum samples were detected using Bridging Antibody Electro chemiluminescent Assay (ECLA). Goat anti-ocrelizumab affinity purified anti-CDR antibodies in normal human serum were used as the positive titer control and positive screen control. All ADA positive serum samples were screened using antibody-dependent cellular cytotoxicity (ADCC) assay. The assay measures lysis of Calcein AM pre-labeled human CD20+ B lymphoma cells MEC-2, by engineered human natural killer (NK) effector cells in the presence of ocrelizumab. When the target cell is lysed, fluorescent Calcein is released and the fluorescent signal is measured.

The blood samples were tested at multiple time points (baseline and every 6 months post treatment for the duration of the trial). Out of 1311 patients treated with ocrelizumab, 12 (~1%) tested positive for treatment-emergent ADAs, of which 2 patients tested positive for neutralizing antibodies. Patients with neutralizing antibodies showed faster clearance of ocrelizumab and faster B-cell repletion in 2 patients. There was no impact on safety and efficacy in all the patients with of treatment-emergent ADAs.

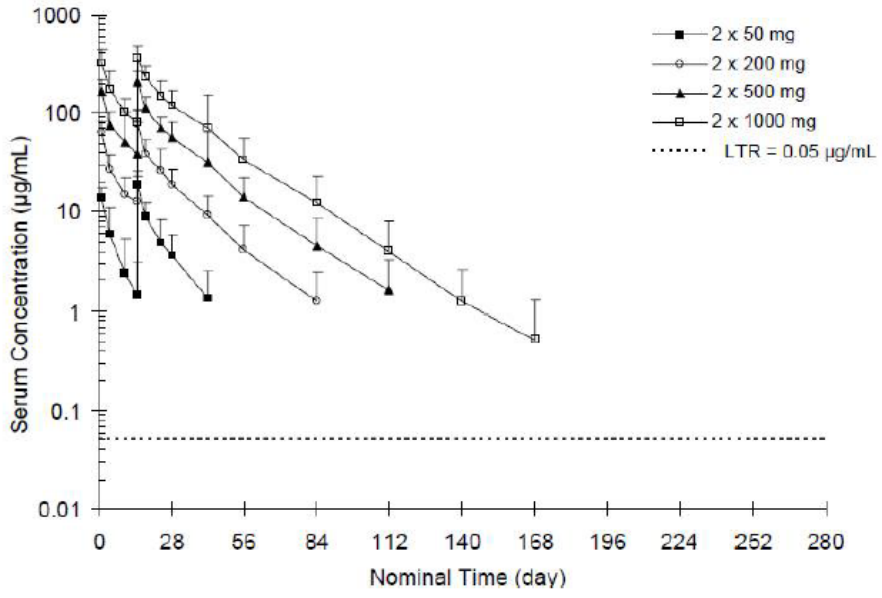
Appendix 4.3: Pharmacokinetics

Single-Dose:
Single-dose PK characteristics of ocrelizumab were evaluated in Studies ACT2847g, WA18230 and JA21963 in patients with RA [see Individual Study Summaries Appendix 4.6 for more detail].

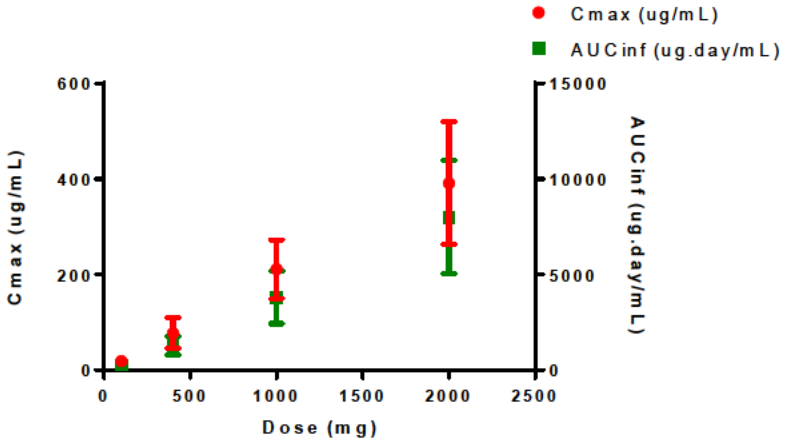
Studies ACT2847g: This was the first-in-human study in patients with moderate-to-severe RA receiving concomitant methotrexate (MTX). A single dose of ocrelizumab or placebo was administered as two IV infusions 14 days apart (on Day 1 and Day 15) in a dose-escalating manner: 20 mg (2 x 10 mg), 100 mg (2 x 50 mg), 400 mg (2 x 200 mg), 1000 mg (2 x 500 mg), and 2000 mg (2 x 1000 mg).

Representative serum ocrelizumab concentration-time profiles following single IV infusions from Study ACT2847g are illustrated in figure below.

Figure 10: Ocrelizumab Concentration versus Time



Ocrelizumab Cmax and AUCinf following administration of single IV infusions from Study ACT2847g are illustrated in figure below.



Study WA18230: The primary objective of this Phase I/II study was to evaluate the safety and tolerability of escalating single IV doses of ocrelizumab in combination with methotrexate. In Part 1, 8 patients each received 400 mg, 1000 mg, 1500 mg, or 2000 mg ocrelizumab as an IV infusion on Day 1.

Following table represents PK parameters following single iv infusions from Study WA18230.

Table 3: Ocrelizumab PK Parameters from Study WA18230

Dose (mg)	$t_{1/2}$ (day)	C_{max} (µg/mL)	AUC_{inf} (µg • day/mL)	CL (L/day)
400 (n=35)	17.7 ± 4.51	116 ± 28	1403 ± 355	0.31 ± 0.09
1000 (n=38)	19.9 ± 5.62	327 ± 92	4173 ± 1226	0.28 ± 0.10
1500 (n=38)	21.1 ± 4.17	487 ± 130	6551 ± 2402	0.26 ± 0.11
2000 (n=9)	20.0 ± 4.95	648 ± 132	9331 ± 2143	0.22 ± 0.07

Mean ± standard deviation.

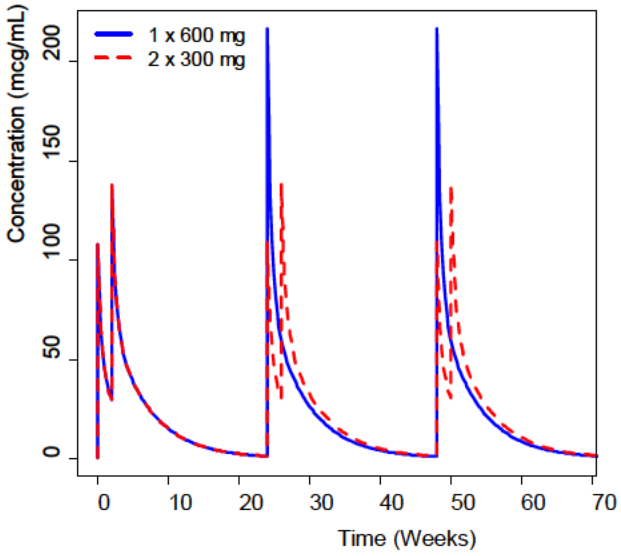
The clearance of ocrelizumab was non-linear below 400 mg; higher clearance at lower doses is likely due to target-mediated drug disposition, a characteristic of monoclonal antibodies. The mean terminal elimination half-life ranged from 11.7 to 17.4 days. The pharmacokinetics of ocrelizumab was essentially linear and dose proportional between 400 mg and 2000 mg.

Multiple-Dose:
Population PK (popPK) analysis was conducted to describe the multiple-dose (600 mg iv infusion, once every 6 months) ocrelizumab PK characteristics in MS patients, for the following studies [see Appendix 4.3 for more detail]:

- Pooled data from the 2 pivotal Phase III studies WA21092 and WA21093 in RMS patients, plus the Phase II study WA21493 in RRMS patients
- Phase III study WA25046 in PPMS patients

The popPK model was developed based on the RMS data which was used to predict the PPMS PK profiles. Following figure represents serum ocrelizumab concentration-time profiles after multiple *i.v* infusions.

Figure 11: Plasma concentration time profiles from Phase 3 studies. Solid blue line represents RMS studies and dotted red line for PPMS study.



The concentration-time course of ocrelizumab was described by a two compartment pharmacokinetic model.

Ocrelizumab total clearance was described as the sum of a constant clearance and a time-dependent clearance that decreased slowly and stabilized with continued time. Ocrelizumab constant clearance and central volume were estimated at 0.17 L/day (95%CI: 0.166-0.174 L/day) and 2.78 L (95% CI: 2.71-2.85 L), peripheral volume and inter-compartment clearance were 2.68 L (95% CI: 2.53-2.82 L) and 0.294 L/day (95%CI: 0.251-0.337 L/day). Initial time-dependent clearance (additional to the constant clearance) was estimated at 0.0489 L/day (95%CI: 0.0464-0.0514 L/day), which comprises 20% of the total initial clearance, and declined with a half-life of 33 weeks.

Table 4: Summary of Key Pharmacokinetic Parameters of Ocrelizumab Following Multiple IV Infusions Every 6 Months (Studies WA21092, WA21093 and WA21493).

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

Table 5: Summary of Key Pharmacokinetic Parameters of Ocrelizumab Following Multiple IV Infusions Every 6 Months (Study WA25046)

	Statistics	Dosing Period (Weeks)				
		1 (0-24)	2 (24-48)	3 (48-72)	4 (72-96)	5 (96-120)
N		482	482	482	482	482
C_{max} (µg/mL)	Mean (SD)	136.4 (27.8)	138.9 (28.2)	140.4 (28.4)	141.4 (28.6)	142 (28.7)
	Median (Range)	134.3 (7.8-245.6)	136.6 (7.9-249.8)	137.9 (7.9-252.3)	139.7 (8-253.9)	140.2 (8-255)
	Geometric Mean (CV)	133.2 (0.24)	135.6 (0.24)	137.1 (0.24)	138.1 (0.24)	138.7 (0.24)
C_{trough} (µg/mL)	Mean (SD)	0.6 (0.5)	0.8 (0.7)	1 (0.9)	1.2 (1)	1.3 (1.1)
	Median (Range)	0.5 (0-3.9)	0.7 (0-5.5)	0.8 (0-6.9)	1 (0-7.8)	1 (0-8.4)
	Geometric Mean (CV)	0.4 (0.96)	0.6 (0.93)	0.7 (0.91)	0.9 (0.9)	0.9 (0.9)
AUC_τ (µg/mL • day)	Mean (SD)	2892 (820)	3185 (904)	3383 (960)	3516 (1000)	3601 (1027)
	Median (Range)	2836 (369-6430)	3116 (381-7331)	3314 (384-7926)	3447 (385-8332)	3534 (386-8602)
	Geometric Mean (CV)	2771 (0.3)	3053 (0.3)	3244 (0.3)	3371 (0.3)	3453 (0.3)
Cumulative AUC (µg/mL • day)	Mean (SD)	2892 (820)	6076 (1723)	9459 (2680)	12975 (3675)	16576 (4697)
	Median (Range)	2836 (369-6430)	5954 (750-13761)	9256 (1134-21687)	12711 (1519-30019)	16246 (1905-38621)
	Geometric Mean (CV)	2771 (0.3)	5824 (0.3)	9069 (0.3)	12442 (0.3)	15896 (0.3)

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4.4 Pharmacometrics Assessment: Population PK Analyses

4.4.1 Applicant's Population PK analysis for RMS

A population PK analysis was conducted by the applicant to characterize ocrelizumab pharmacokinetics following intravenous administration in patients with RMS, to identify covariate factors that could influence ocrelizumab disposition, and to compute individual exposure estimates for subsequent exposure-response analyses.

Data from one Phase 2 study (WA21493) and two Phase 3 studies (WA21092 and WA21093) were included in the analysis. PK samples were collected 5-30 minutes pre-dose (prior to the methylprednisolone infusion) on Day 1, Day 15, and Day 169, 30 (± 10) minutes after completion of the ocrelizumab infusion on Day 1 and Day 15, and on Days 29, 57, 85, 113, and 141 in study WA21493. In studies WA21092 and WA21093, PK samples were drawn pre-dose (5-30 minutes prior to the methylprednisolone infusion) at weeks 1, 24, 48, and 72, 30 (± 10) minutes after completion of the ocrelizumab infusion at week 72, 84, and 96, and also on the withdrawal from the study visit in case of early withdrawal. The population PK dataset contains a total of 4901 ocrelizumab PK samples from 941 patients on ocrelizumab treatment. Of the 4901 samples, 122 (2.5%) data points were excluded from the analysis (43 samples were collected before start of treatment or from patients in the comparator arms; 79 data points showed unexpectedly low/high or inconsistent values). BQL concentrations (739, 15%) were excluded from the analysis.

The population PK model was developed using NONMEM via nonlinear mixed-effects modeling. The results show that a two-compartment model incorporating a constant clearance component (CL_{inf}) and a time-dependent clearance component (CLt) best fitted the data. The time-dependent clearance was described by the function: $CLt=CL_{T0}*exp(-kdes*TIME)$, where CL_{T0} represents the initial value of the time-dependent clearance and kdes represents the decay coefficient. A different initial time-dependent clearance CL_{T02} was estimated for part 2 of study 21493 since it was performed after a long interruption resulting in partial recovery of B-cell counts. ***Table 1*** lists the covariate effects evaluated in the modeling process. Covariate modeling started from a full model and was based on point estimates, confidence intervals and diagnostic plots of the covariate effects. The covariates of body weight on CL_{inf}, CL_{T0}, V_1, V_2 and Q; baseline B-cell count on CL_{inf}, and sex on V_1 were retained in the final model. The effects of these covariates on PK parameters are illustrated in ***Table 3.*** The parameter estimates of the final model are shown in ***Table 2***. ***Figure 1*** shows change of typical total clearance (CL_{inf} + CLt) over time, demonstrating that the contribution of time-dependent clearance of the total clearance is relatively small.

Table 1: Covariates Evaluated in the Population PK Modeling

Covariate	Model Component	Rationale
Weight	All clearance, and volume parameters	Body size influences the model parameters for many of known drugs. Its influence was evaluated by inclusion into the model.
Sex	Clearance and central volume	Evaluation of the gender effect is clinically important. Gender may influence clearance and/or volume. Its influence was evaluated by inclusion into the model.
Race and Ethnicity	Clearance and central volume	Evaluation of the effects race and ethnicity is clinically important. Their influence was evaluated by inclusion into the model (or, for groups with low representation, by diagnostic plots).
Baseline B-cell count	Clearance	Target level may influence clearance of drugs with target-mediated disposition. Its influence was evaluated by inclusion into the model.
Calculated creatinine clearance, Normalized creatinine clearance	Clearance, central volume	Markers of renal function were investigated only by the diagnostic plots, as the high molecular weight of ocrelizumab (approximately 148 kD) precludes its elimination through renal excretion.
Aspartate aminotransferase, alanine aminotransferase, total bilirubin	Clearance	Markers of hepatic function were investigated only by the diagnostic plots, as monoclonal antibodies are generally eliminated by catabolism and/or receptor mediated processes and not by hepatic metabolic clearance.

Source: RMS PopPK report Table 1 on page 43

Table 2: Parameter Estimates for the Final Model

Parameter		Estimate	RSE (%)	95%CI		
CL_{inf} (L/day)	θ1	0.17	1.26	0.166 - 0.174		
V_1 (L)	θ2	2.78	1.35	2.71 - 2.85		
V_2 (L)	θ3	2.68	2.76	2.53 - 2.82		
Q (L/day)	θ4	0.294	7.46	0.251 - 0.337		
k_{des} ($year^{-1}$)	θ5	1.11	5.95	0.979 - 1.24		
CL_{T0} (L/day)	θ6	0.0489	2.62	0.0464 - 0.0514		
CL_{T02} (L/day)	θ7	0.0199	8.16	0.0167 - 0.0231		
$CL_{inf,WT}$ [a]	θ8	0.684	5.19	0.615 - 0.754		
$V_{1,WT}$ [a]	θ9	0.397	8.4	0.331 - 0.462		
$V_{2,WT}$ [a]	θ10	0.853	6.46	0.745 - 0.961		
$Q_{,WT}$ [a]	θ11	0.75 Fix	NA	NA		
$CL_{T0,WT}$ [a]	θ12	0.981	7.82	0.831 - 1.13		
$V_{1, Male}$ [b]	θ13	1.12	2.08	1.07 - 1.16		
$CL_{inf,BCD19}$ [c]	θ14	0.0403	13.6	0.0295 - 0.051		
					Variability	**Shrinkage**
ω^2_{CLinf}	Ω(1,1)	0.0535	5.07	0.0482 - 0.0588	CV=23.1%	7.1%
$\omega_{CLinf}\,\omega_{V1}$	Ω(1,2)	0.026	11.3	0.0202 - 0.0318	R=0.528	NA
ω^2_{V1}	Ω(2,2)	0.0453	8.23	0.038 - 0.0526	CV=21.3%	31.30%
ω^2_{Q}	Ω(3,3)	0.239	8.91	0.197 - 0.281	CV=48.9%	53.30%
ω^2_{CLT0}	Ω(4,4)	0.125	12.3	0.095 - 0.156	CV=35.4%	47.20%
$\sigma^2_{TAD\leq1}$	Σ(1,1)	0.0346	9.01	0.0285 - 0.0407	CV=18.6%	28.7%
$\sigma^2_{TAD>1}$	Σ(2,2)	0.0487	1.31	0.0474 - 0.0499	CV=22.1%	17.9 %

a. Power coefficient of the power function with the reference value of 75 kg.

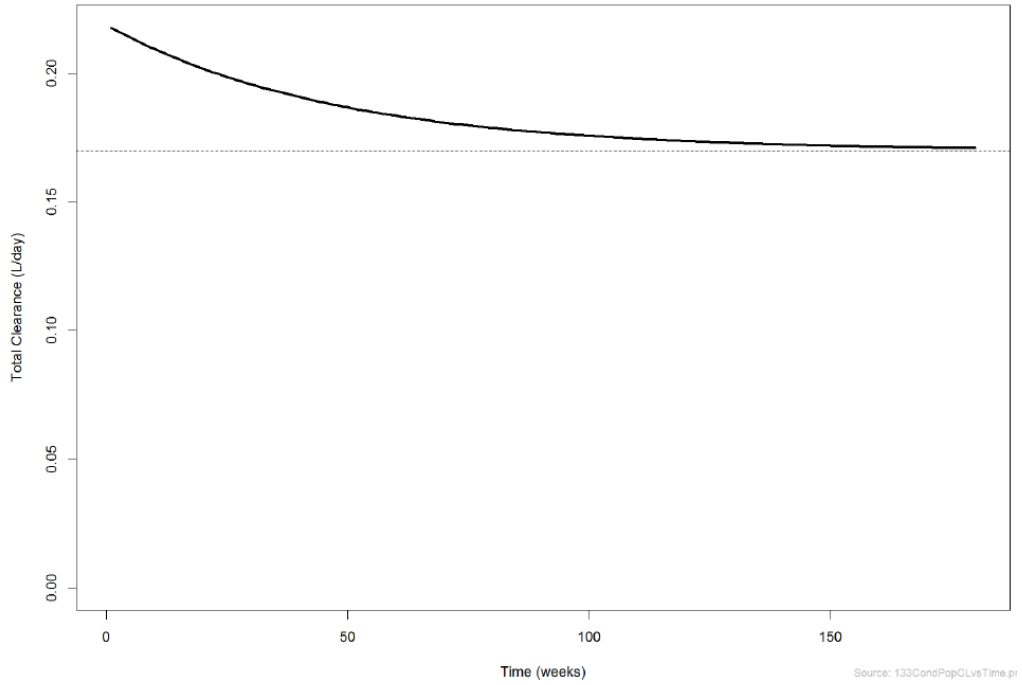
b. Multiplicative factor for the respective subpopulation compared to the rest of patients.

c. Power coefficient of the power function with the reference value of $0.225*10^9$/L.

SE: Standard Error: %RSE: Relative Standard Error, RSE=100·SE/PE, where PE is parameter estimate. 95% CI: 95% confidence interval. CV: coefficient of variation computes as 100% multiplied by the square root of the variance, R: correlation coefficient.

Source: RMS PopPK report Table 11 on page 53

Figure 1: Change of Total Ocrelizumab Clearance over Time; the solid line represents typical total clearance and the dotted line represents typical constant clearance



Source: RMS PopPK report Figure 41 on page 102

Table 3: Covariate Effects in the Final Model

Parameter	Covariate	Reference Value	Covariate Value[a]	Covariate Effect Value [95%CI](%)
CL_{inf}	Body Weight (kg)	75	48.5	-25.8 [-23.5;-28]
			116	34.8 [30.7;38.9]
	B-cell count at baseline (10^9/L)	0.225	0.0715	-2.7 [-2;-3.5]
			0.598	6.7 [4.9;8.5]
V_1	Body Weight (kg)	75	48.5	-15.9 [-13.4;-18.2]
			116	18.9 [15.5;22.3]
	Sex	Female	Male	11.7 [7.2;16.3]
CL_{T0}	Body Weight (kg)	75	48.5	-34.8 [-30.4;-38.9]
			116	53.4 [43.7;63.8]
V_2	Body Weight (kg)	75	48.5	-31.1 [-27.7;-34.2]
			116	45.1 [38.4;52.1]
Q	Body Weight (kg)	75	48.5	-27.9 [-27.9;-27.9]
			116	38.7 [38.7;38.7]

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

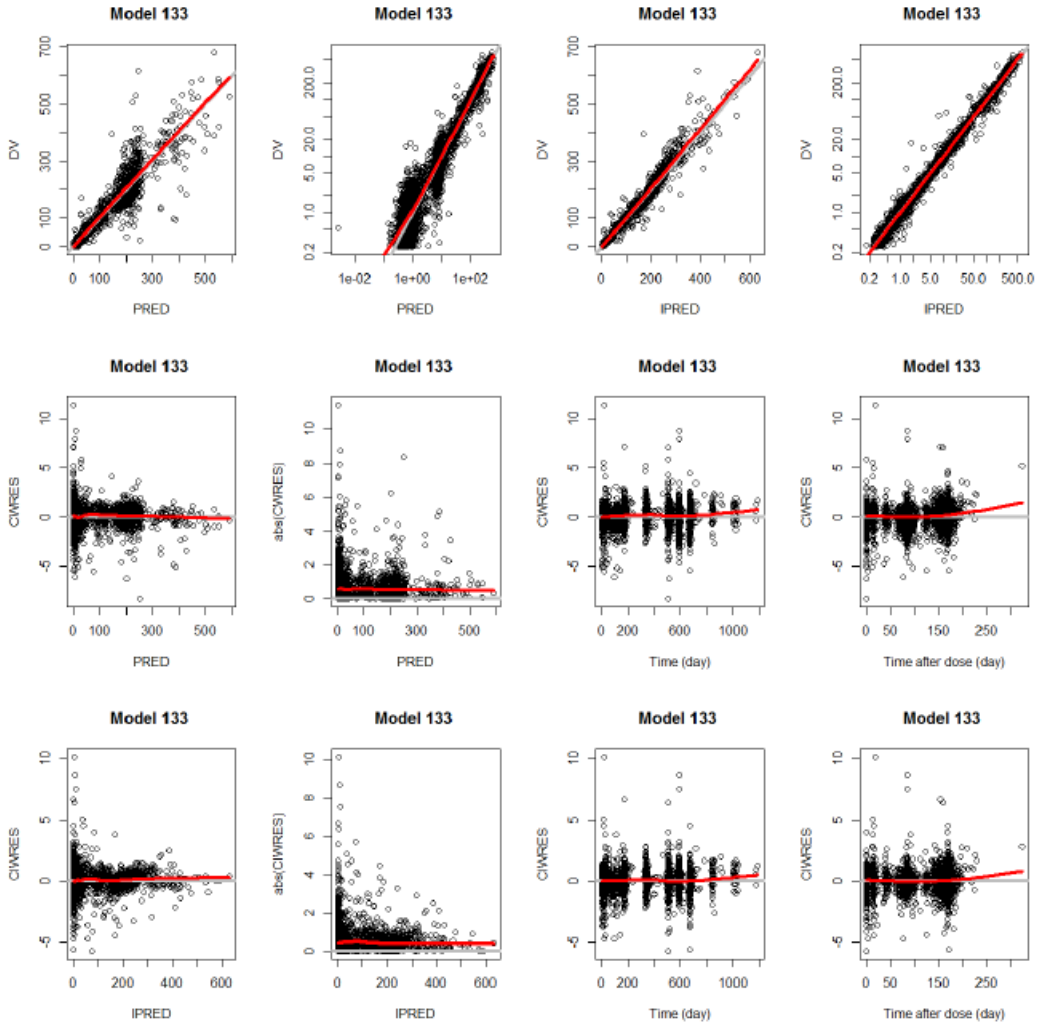
Source: RMS PopPK report Table 12 on page 54

Diagnostic plots were used for final model evaluation and the results are shown in ***Figure 2***. In addition, visual predicative check (VPC) stratified by study and dose was performed to evaluate the predictive performance of the final model and the results are shown in

Figure 3**.** Moreover, the final model was re-run using the dataset including the previously excluded data points and the results shown that the structural and covariate parameters were estimated to be similar (within 15%) to those of the final model.

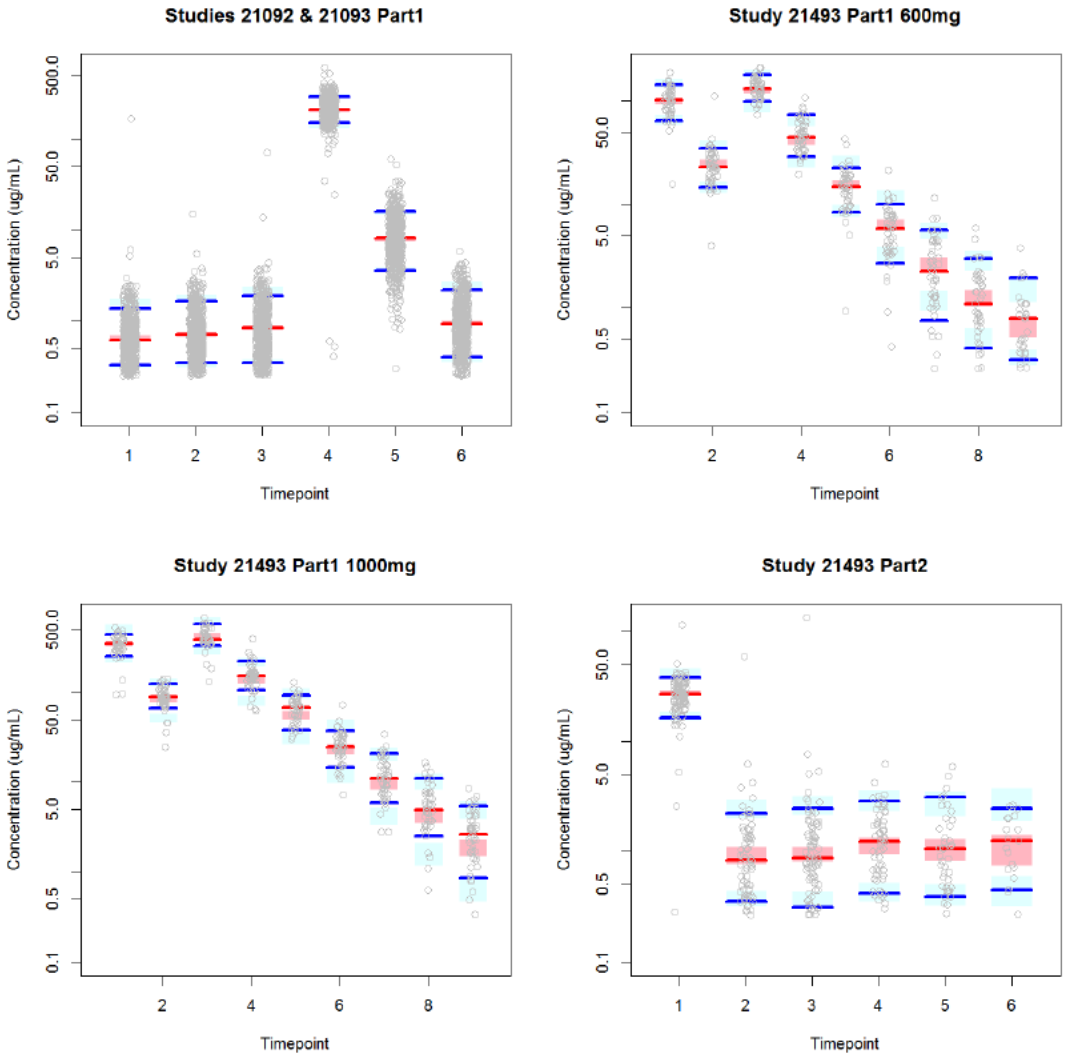
Figure 2: Goodness of Fit Plots for the Final Model

DV: Observed concentrations; **PRED:** population predictions of the model; **IPRED:** individual predictions c the model; **CWRES:** conditional weighted residuals; **CIWRES:** individual weighted residuals; **TIME:** time after the first dose; **TAD:** time after the most recent dose. The gray solid y=x or y=0 lines are included for reference. The bold red lines are the lowess (local regression smoother) trend lines.



Source: RMS PopPK report Figure 49 on page 110

Figure 3: VPC Results (Semi-log Scale)



Note: The lines show median (red), and the 5th and 95th percentiles (blue) of the observed concentrations (circles). The shaded regions show the 90% confidence intervals on these quantities obtained by simulations. The simulated values were computed from 1000 trials with dosing, sampling, and the covariate values of the analysis dataset. Time point: for studies 21092 and 21093: 1= Nominal Day (NDAY) 169, 2= NDAY 337, 3 = NDAY 505 pre-dose, 4 = NDAY 505 post-dose, 5 = NDAY 589, 6 = NDAY 673; for study 21493 Part 1: 1= NDAY 1 post-dose, 2= NDAY 15 pre-dose, 3= NDAY 15 post-dose, 4= NDAY 29, 5= NDAY 57, 6= NDAY 85, 7= NDAY 113, 8= NDAY 141, 9= NDAY 169 pre-dose; for study 21493 Part 2: 1= NDAY 15, 2= NDAY 169, 3= NDAY 337, 4= NDAY 505, 6= NDAY 673, 6= NDAY 841.

Source: RMS PopPK report Figure 72 on page 133

Reviewer's comments:

The applicant's population PK model adequately described ocrelizumab concentration-time data from one Phase 2 RRMS study (WA21493) and two Phase 3 RMS studies (WA21092 and WA21093). The covariate effects on ocrelizumab disposition were reasonably investigated with the established model. The applicant's analysis results show that the PK parameter estimates were typical for a monoclonal antibody with a constant clearance of 0.173 L/day, Vss of 5.6 L, and terminal half-life of 26.8 days. The covariate modeling results show that the effect of body weight on ocrelizumab PK was relatively small, resulting in 19% higher Cmax,ss for patients weighing < 60 kg and 13% lower Cmax,ss for patients weighing >90 kg compared with the 60-90 kg weight group; and 26% higher AUCτ,ss for patients weighing < 60 kg and 21% lower AUCτ,ss for patients weighing > 90 kg compared with the 60-90 kg weight group. The results also show that other covariate effects were also small (<12% for sex on V1 and <7% for baseline B-cell count on CL_{inf}*). Based on the finding, the applicant's proposal of no dose adjustment for these covariates is considered acceptable.*

The time-dependent PK of ocrelizumab was adequately characterized by a time-varying clearance component in addition to a constant clearance component. The results show that the time-dependent clearance component represents about 20% of the total clearance at baseline, resulting in a small exposure increase at later dosing intervals. The applicant stated that the time-dependent PK can be attributed to target mediated drug disposition with B-cell count declining after ocrelizumab treatment, which is considered reasonable.

The influence of anti-drug antibody (ADA) on ocrelizumab disposition was not assessed in the population PK model due to limited number of subjects (n=3) with treatment-emergent ADA detected. This is considered to be reasonable.

4.4.2 Applicant's Population PK analysis for PPMS

The applicant conducted a population PK analysis to evaluate the previously developed RMS population PK model program using data from the Phase 3 PPMS study WA25046 and to update PK parameters using combined data if necessary.

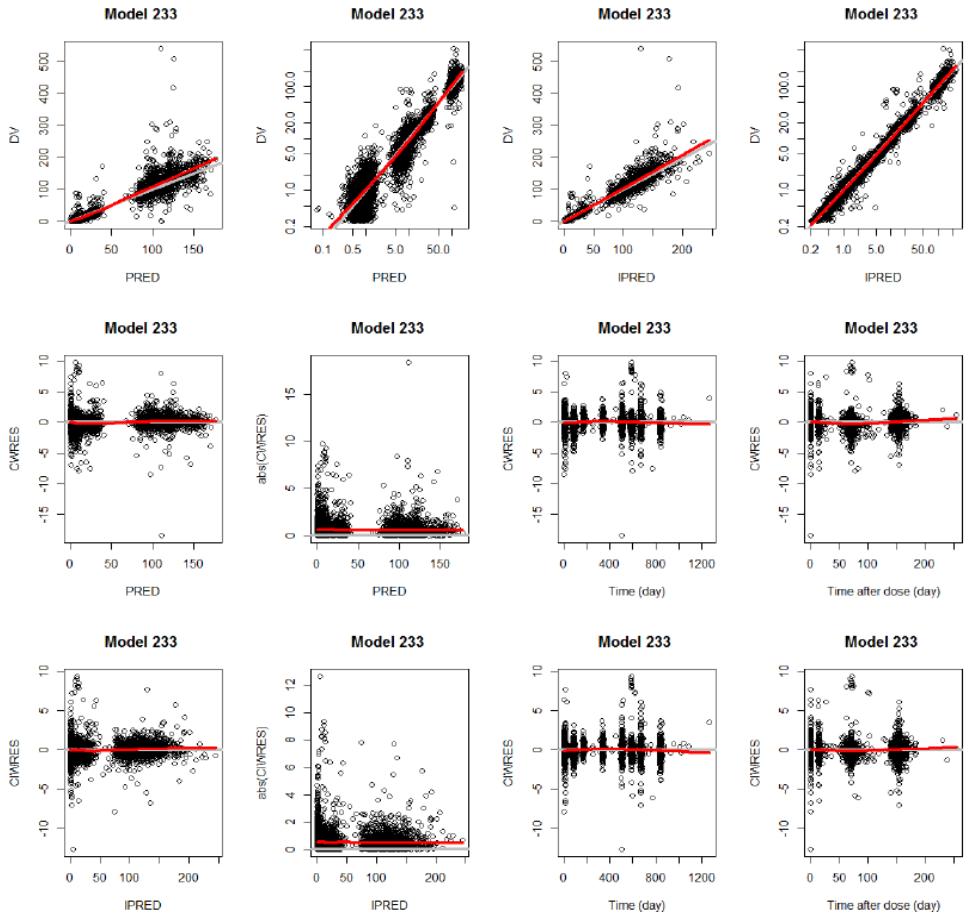
Data from study WA25046 was used in this population PK analysis. Study WA25046 is a Phase 3, multicenter, randomized, parallel-group, double-blind, placebo-controlled study to evaluate the efficacy and safety of ocrelizumab in adults with PPMS. Patients were randomized (2:1) to either ocrelizumab or placebo arms and underwent at least five treatment cycles of 24 weeks in duration each. PK samples were collected pre-dose (before methylprednisolone infusion) on Day 1 (baseline) and 15, and at weeks 24, 48, 72, and 96; 30 minutes after completion of ocrelizumab/placebo infusion on Days 1 and 15, and at Week 72; at weeks 12, 84 and 120, and also on the withdrawal from the study visit in case of early withdrawal. The final dataset contained 4340 PK samples from 482 patients.

The population PK analysis was conducted via nonlinear mixed-effects modeling with the NONMEM software. The population PK model developed using data from studies WA21493, WA21092, and WA21093 was fitted to the data from study WA25046. The model parameters were fixed to the values in the developed model (***Table 2***). Post hoc predictions of population and individual concentrations, individual random effects and residuals were computed. The results show that the previously developed model for the RMS studies can describe the study WA25046 data well, as shown in the diagnostic plots (

Figure 4). VPC plots also show reasonable predictive performance of the model in the PPMS population (***Figure*** 5). In addition, plots of inter-individual random effects versus body weight, sex, and baseline B-cell counts (***Figure 6, Figure 7, and Figure 8***) show that originally identified covariate effects hold true for the PPMS population.

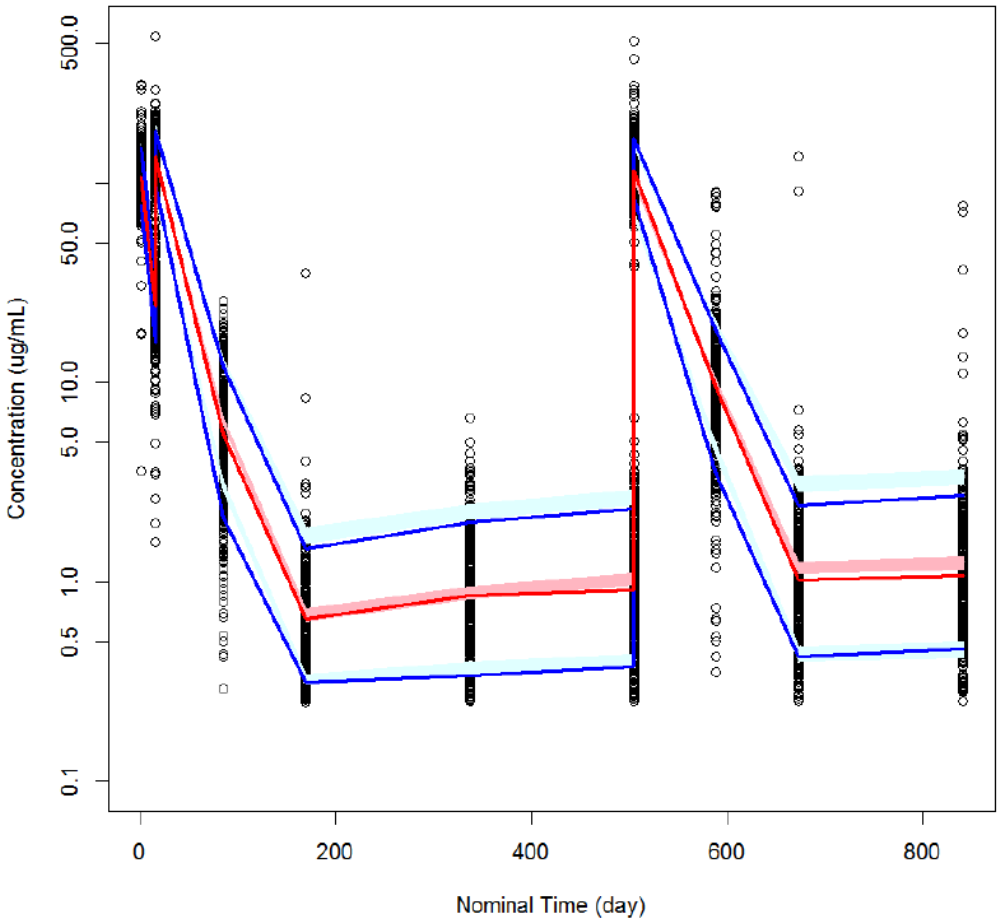
Figure 4: Goodness of Fit Plots (linear and semi-log scales)

DV: Observed concentrations; **PRED**: population predictions of the model; **IPRED**: individual predictions the model; **CWRES**: conditional weighted residuals; **CIWRES**: individual weighted residuals; **TIME**: time after the first dose; **TAD**: time after the most recent dose. The gray solid y=x or y=0 lines are included for reference. The bold red lines are the lowess (local regression smoother) trend lines.



Source: PPMS PopPK report Figure 6 on page 49

Figure 5: VPC Results (Semi-log Scale)

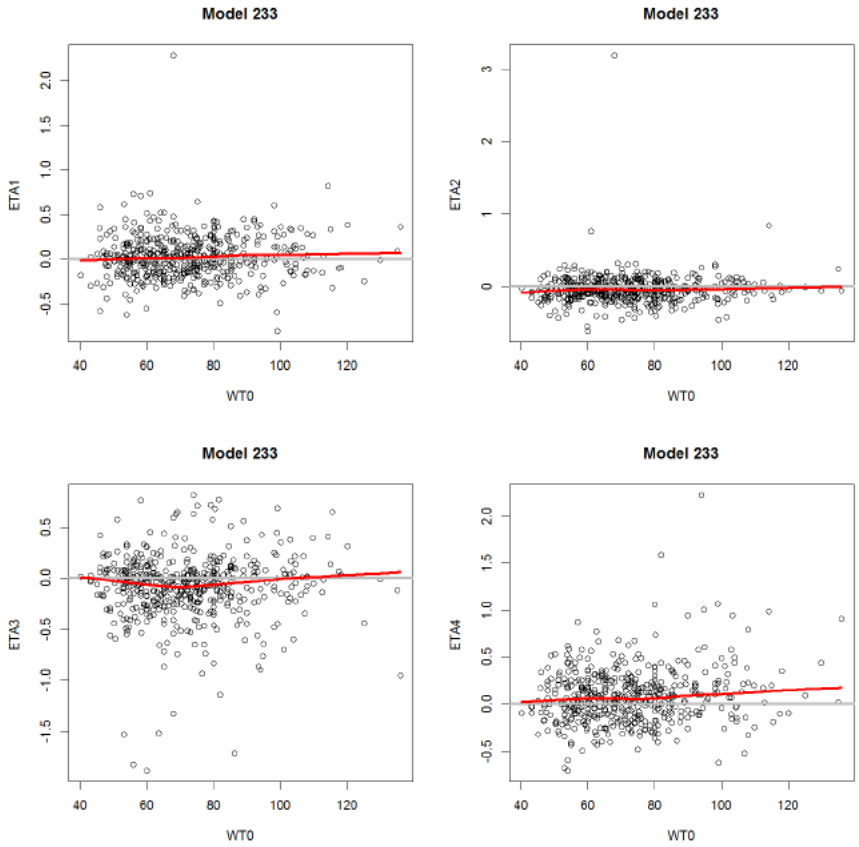


Note: The lines show median (red), and the 5th and 95th percentiles (blue) of the observed concentrations (circles). The shaded regions show the 90% confidence intervals on these quantities obtained by simulations. The simulated values were computed from 1000 trials with dosing, sampling, and the covariate values of the analysis dataset.

Source: PPMS PopPK report Figure 24 on page 67

Figure 6: Relationships of the Inter-Individual Random Effects with Body Weight

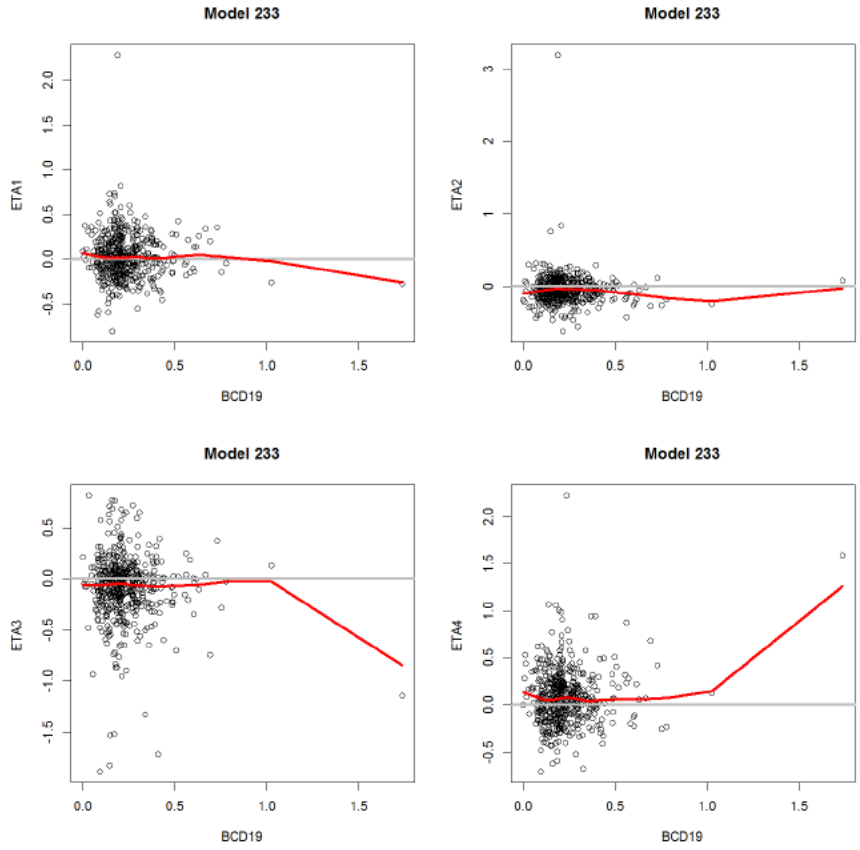
The individual random effects are plotted versus body weight (WT0, kg). Solid lines at y = 0 are included for reference. The red lines show the lowess trend lines. ETA1: the random effect on constant clearance (CL_{inf}); ETA2: the random effect on central volume (V_1); ETA3: the random effect on inter-compartment clearance (Q); ETA4: the random effect on initial time-dependent clearance (CL_{T0}).



Source: PPMS PopPK report Figure 12 on page 55

Figure 7: Relationships of the Inter-Individual Random Effects with Baseline B-cell Count

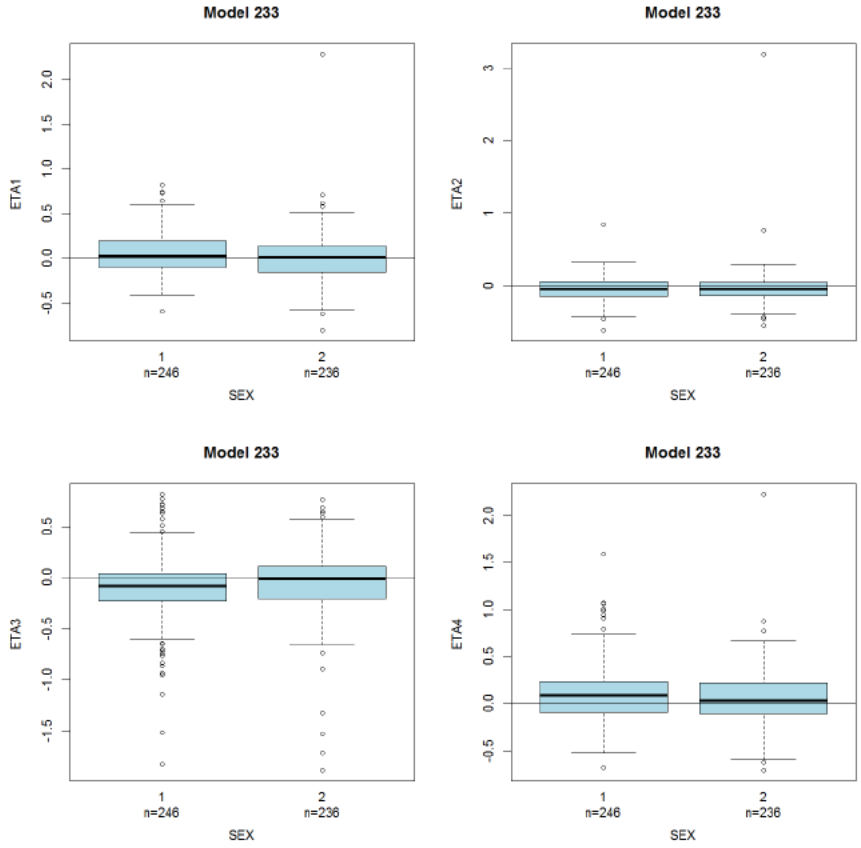
The individual random effects are plotted versus $CD19^+$ B-cell count at baseline (BCD19, 10^9/L). Solid line at y = 0 are included for reference. The red lines show the lowess trend lines. ETA1: the random effect or constant clearance (CL_{inf}); ETA2: the random effect on central volume (V_1); ETA3: the random effect on inter-compartment clearance (Q); ETA4: the random effect on initial time-dependent clearance (CL_{T0}).



Source: PPMS PopPK report Figure 13 on page 56

Figure 8: Relationships of the Inter-Individual Random Effects with Sex

The individual random effects (circles) are plotted versus gender (SEX) using box and whisker plots. Median values of the random effects are designated by black lines in the center of the boxes. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR. Solid lines at y = 0 are included for reference. SEX: 1= Males, 2= Females. ETA1: the random effect on constant clearance (CL_{inf}); ETA2: the random effect on central volume (V_1); ETA3: the random effect on inter-compartment clearance (Q); ETA4: the random effect on initial time-dependent clearance (CL_{T0}).



Source: PPMS PopPK report Figure 14 on page 57

Reviewer's comments:

The population PK model previously developed using data from RMS studies was externally evaluated using data from PPMS study WA25046. The results show that the model is able to describe the study WA25046 data reasonably well. Therefore, no parameter re-estimation was conducted. Based on the results, it is reasonable to assume that different disease stages of MS do not affect disposition of ocrelizumab.

4.5 Pharmacometrics Assessment: Exposure-Response Analyses

4.5.1 Exposure-Response Analyses for RMS

4.5.1.1 Exposure-Efficacy Analyses for RMS

4.5.1.1.1 Applicant's Exposure-Efficacy Analyses for RMS

Relationships between ocrelizumab exposure and efficacy endpoints were evaluated in patients with RMS using pooled data from studies WA21092 and WA21093. Average ocrelizumab concentration over the entire treatment period (Cmean) was used as the main exposure metric, calculated as the ratio of cumulative AUC up to the end of the last dosing interval and duration of time from zero till the end of the last dosing interval. Patients were divided into four exposure subgroups base on Cmean quantiles. Association of the primary efficacy endpoint of ARR with ocrelizumab exposure was assessed by comparing the percentage of patients with relapses between the exposure subgroups. The results show similar relapse rates in patients across the four exposure quartiles (***Table 1***), suggesting no relationship between individual ocrelizumab exposure (Cmean) and relapse rate in patients on the 600 mg ocrelizumab dose.

The applicant also conducted exploratory analyses evaluating the association of the secondary endpoints of time to 12-week CDP and time to 24-week CDP with ocrelizumab exposure. The proportion of patients with onset of CDP by exposure quantiles was estimated using a Kaplan-Meier approach and the results are shown in ***Figure 1*** and ***Figure 2***. Hazard ratios comparing each exposure quantile with the interferon beta-1a reference group regarding time to 12-week CDP were estimated via a Cox regression model with treatment group as the predictor and study, geographical region (US versus ROW) and baseline EDSS (<4.0 versus >=4.0) as covariates and the results are shown in ***Table 2***. The results appear to suggest that patients with higher ocrelizumab exposure had greater risk reduction for CDP.

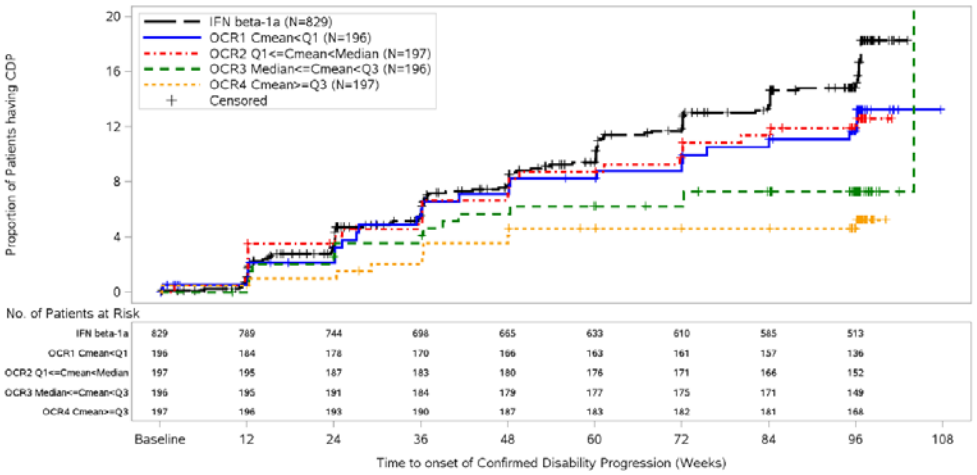
Table 1: RMS (WA21092 and WA21093): ARR by Exposure Quantiles

Exposure Category	Cmean (µg/mL)	N of patients in category	N of patients with relapses	ARR (95% CI)
1	<15.4	196	41	0.14 (0.10, 0.20)
2	15.4 – 18.7	197	56	0.18 (0.13, 0.25)
3	18.7 – 22.2	196	41	0.13 (0.09, 0.19)
4	>22.2	197	52	0.17 (0.12, 0.23)

Interferon beta-1a	NA	829	334	0.29 (0.25, 0.34)

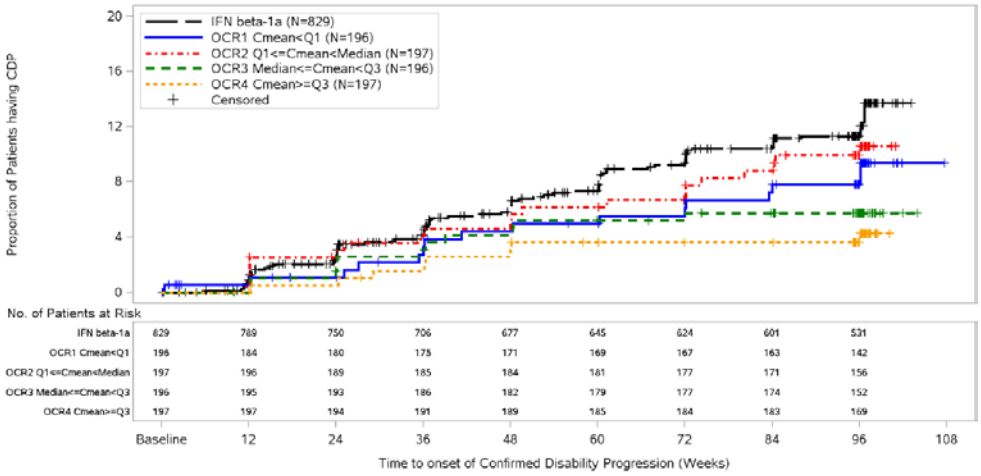
Source: Summary of Clinical Pharmacology Studies Table 14 on page 55

Figure 1: Kaplan-Meier Plot for Time to 12-Week CDP by Exposure Quantiles



Source: Summary of Clinical Pharmacology Studies Figure 16 on page 56

Figure 2: Kaplan-Meier Plot for Time to 24-Week CDP by Exposure Quantiles



Source: Summary of Clinical Pharmacology Studies Figure 17 on page 56

Table 2: Hazard Ratio Estimates for Time to 12-Week CDP by Exposure Quantiles

Exposure group	Hazard Ratio	95% CI	p-value
Reference = IFN			

OCR Cmean < Q1	0.77	(0.49, 1.21)	0.2543
OCR Cmean >= Q1 and < Median	0.80	(0.51, 1.24)	0.3084
OCR Cmean >= Median and < Q3	0.45	(0.26, 0.79)	0.0054
OCR Cmean >= Q3	0.33	(0.17, 0.64)	0.0009

Note: Adjusted for Study, Baseline EDSS (<4.0 vs. >=4.0) and Region (US vs. ROW)

Source: Summary of Clinical Pharmacology Studies Table 15 on page 57

Reviewer's comment:

No correlation between ocrelizumab exposure and the primary RMS efficacy endpoint of annualized relapse rate (ARR) in patients on the 600 mg ocrelizumab dose was observed. In contrast, analyses with secondary endpoints of time to 12-week and 24-week CDP appeared to show that patients with higher ocrelizumab exposure had greater risk reduction for CDP. However, the exposure-response analyses with CDP have a major limitation in that only a single dose of 600 mg was evaluated in the phase III studies and risk factors for CDP might be unbalanced among different exposure quantiles resulting in confounded comparison of CDP results among the four subgroups. Therefore, the positive exposure-response finding for CDP needs to be interpreted with caution and could not be used to support alternative dose or dosing regimen. Moreover, the result from the Phase 2 study WA21493 show that no clear sepration in the efficacy endpoints including the total number of gd-enhancing T1 leisons observed in MRI scans of the brain by week 24, ARR by week 24, and proportion of pateints who remained relapse-free by week 24 were observed between the 2 × 300 mg and 2 × 1000 mg ocrelizumab doses.

4.5.1.1.2 Reviewer's Exposure-Efficacy Analyses for RMS

Introduction

Limitations exist in the applicant's exposure-response analyses for the CDP endpoints. One major limitation is the potentially unbalanced risk factors for CDP among different exposure quantiles. Another potential limitation is that the time-dependent PK may confound the exposure-exposure relationship since the decreasing clearance over time, thus increased exposure, is believed to be a result of ocrelizumab treatment through reducing B-cell counts, which is the mechanism of action for ocrelizumab. The reviewer conducted independent exposure-efficacy analyses for time to 12-week CDP trying to address the limitations of the applicant's analyses.

Objective

The objectives of the analysis are

- To evaluate the exposure-response relationship for time to 12-week CDP by employing different PK metrics that may eliminate the confounding effect of time-dependent PK on efficacy.
- To explore the exposure-response relationship for time to 12-week CDP after adjusting for multiple potential confounding factors for efficacy.

Data Sets

Data sets used are summarized in the table below.

Table 3: Analysis Data sets

Study Number	Name	Link to EDR
WA21092, WA21093 (pooled)	ADSLCMN.xpt	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ocrelizumab_BLA761053_XW\ER Analyses\RMS_ER
WA21092, WA21093 (pooled)	ATE.xpt	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ocrelizumab_BLA761053_XW\ER Analyses\RMS_ER
WA21092, WA21093 (pooled)	PKPARAM.xpt	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ocrelizumab_BLA761053_XW\ER Analyses\RMS_ER

Software

The statistical software NONMEM (version 7) and R (version 2.15.3) were utilized for dataset construction, analyses, and graphics generation.

Methods

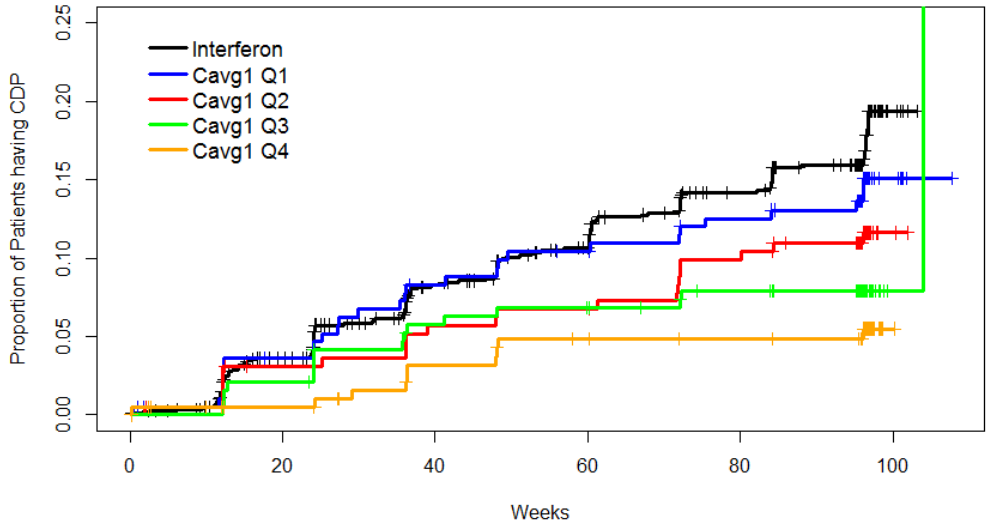
Ocrelizumab exposure after the first dose, i.e. average concentration over the first dosing interval (Cavg1), derived from the applicant's final PK model was employed to evaluate the exposure-response relationship for CDP. The rationale is that utilizing of exposure after the first dose when the time-dependent PK change has not occurred may address the confounding effect of time-dependent PK on efficacy.

Multivariate cox regression model including additional risk factors for efficacy was employed by the reviewer trying to adjust for potentially confounding factors in the exposure-efficacy analysis

Results

The proportion of patients with onset of CDP by exposure quantiles based on ocrelizumab exposure after the first dose was estimated using a Kaplan-Meier approach and the results are similar to the applicant's analysis results with average ocrelizumab concentration over the entire treatment period, as shown in ***Figure 3***. It appears that time-dependent PK of ocrelizumab did not substantially affect the exposure-response relationship for CDP.A possible explanation is that the proportion of time-dependent clearance component is relatively small for ocrelizumab, only accounting for about 20% of the total clearance at baseline.

Figure 3: Kaplan-Meier Plot for Time to 12-Week CDP by Exposure Quantiles based on Exposure after the First Dose



Hazard ratios comparing each exposure quantile with the interferon beta-1a reference group regarding time to 12-week CDP were estimated via a Cox regression model with treatment group as the predictor and study, geographical region (US versus ROW), baseline EDSS (<=5.5 versus >5.5), age (<=45 versus >45 years), sex, presence of Gd+ T1 lesion at baseline (yes versus no), duration since MS symptom onset (<=3, >3 to <=5, >5 to <=10, or >10 years), prior MS treatment (yes versus no), baseline body weight (<=75 versus >75 kg) as potential risk factors. The results are shown in ***Table 4*** and are similar to the applicant's cox regression results. It appears that including additional potential risk factors did not alter the observed exposure-response relationship. However, there is also limitation with the reviewer's analysis because even though additional risk factors were included in the cox regression model, there still might be unknown risk factors that are unbalanced among exposure groups and cannot be adjusted in the model, therefore confounding the exposure-response relationship. Therefore, the observed

exposure-response relationship needs to be interpreted with caution and may not be used to support alternative doses or dosing regimens.

Table 4: Reviewer's Hazard Ratio Estimates for Time to 12-Week CDP by Exposure Quantiles

Exposure group	Hazard Ratio	95% CI	p-value
Reference = IFN			
OCR Cmean < Q1	0.68	(0.43, 1.09)	0.11
OCR Cmean >= Q1 and < Median	0.81	(0.53, 1.24)	0.33
OCR Cmean >= Median and < Q3	0.41	(0.24, 0.72)	0.0018
OCR Cmean >= Q3	0.29	(0.15, 0.58)	0.0004

Note: Adjusted for Study, Baseline EDSS (<=5.5 versus >5.5), Region (US vs. ROW), age (<=45 versus >45 years), sex, presence of Gd+ T1 lesion at baseline (yes versus no), duration since MS symptom onset (<=3, >3 to <=5, >5 to <=10, or >10 years), prior MS treatment (yes versus no), baseline body weight (<=75 versus >75 kg)

Listing of Analysis Codes and Output Files

File Name	Description	Link to EDR
ER_RMS.r	Exposure-response analyses for RMS with data from studies WA21092 and WA21093	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ocrelizumab_BLA761053_XW\ER Analyses\RMS_ER

4.5.1.2 Applicant's Exposure-Safety Analyses for RMS

Analyses were conducted by the applicant to evaluate the relationship between ocrelizumab exposure and several safety endpoints including serious adverse event (SAE), serious infection (SI), and infusion related reaction (IRR) using data from studies WA21493, WA21092, and WA21093. The relationships between rates of SAE, SI, and IRR and ocrelizumab exposure were evaluated by comparing rates between the following 6 subgroups: subgroups of patients in 4 exposure quantiles at 600 mg ocrelizumab dose level, subgroup of patients in the 1000 mg ocrelizumab regimen, and patients on interferon beta-1a (IFN). The results show that the rates of SAE and SI were not higher in the higher exposure quantiles for patients who received 600 mg ocrelizumab dose. The rates of events were higher for patients in the 1000 mg group and for patients that received IFN, but 95% confidence intervals overlapped with 600 mg regimen

groups (***Table 5***). ***Table 5*** also shows that the rate of IRR was not higher in the higher exposure quartiles for patients that received 600 mg regimen, but was higher for patients in the 1000 mg group. The rate of IRR was lower in patients on IFN.

In addition, the association of the grades of SAE, SI, and IRR events with ocrelizumab exposure was also explored by comparing the distributions of ocrelizumab exposures between different grades of these events and the results show that there were no relationships between ocrelizumab exposure and the grades of SAE, SI, and IRR in patients treated with ocrelizumab, as shown in ***Figure 4***, ***Figure 5***, and ***Figure 6*** for SAE, SI, and IRR respectively.

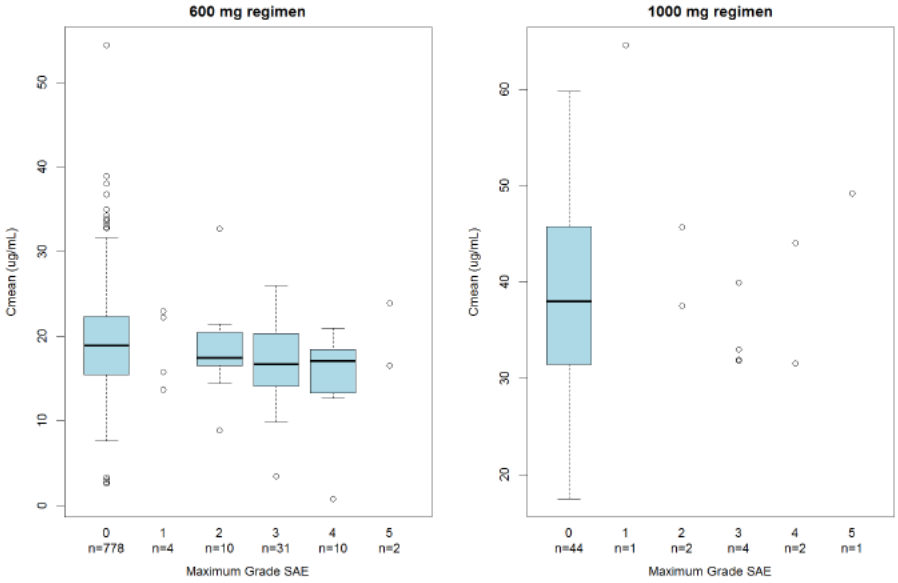
Table 5: Rate of SAE, SI, and IRR by Ocrelizumab Exposure Groups in RMS (WA21493, WA21092 and WA21093)

Event Type	Cmean Exposure Category	N patients	N patients with events	% patients with events (95% CI)
SAE	Q1	210	18	8.57 (5.30 - 13.42)
	Q2	210	20	9.52 (6.06 - 14.53)
	Q3	207	10	4.83 (2.47 - 8.96)
	Q4	208	9	4.33 (2.13 - 8.32)
	1000 mg	54	10	18.52 (9.7 - 31.87)
	IFN	825	75	9.09 (7.26 - 11.31)
SI	Q1	210	5	2.38 (0.88 - 5.77)
	Q2	210	5	2.38 (0.88 - 5.77)
	Q3	207	2	0.97 (0.17 - 3.82)
	Q4	208	3	1.44 (0.37 - 4.50)
	1000 mg	54	2	3.7 (0.64 - 13.84)
	IFN	825	34	4.12 (2.91 - 5.77)
	Q1	210	89	42.38 (35.66 - 49.38)
	Q2	210	67	31.9 (25.75 - 38.73)

IRR	Q3	207	58	28.02 (22.12 - 34.75)
	Q4	208	70	33.65 (27.36 - 40.57)
	1000 mg	54	27	50 (37.11 - 62.89)
	IFN	825	81	9.82 (7.92 - 12.1)

Source: RMS popPK report Table 16, Table 17 on page 58, 59

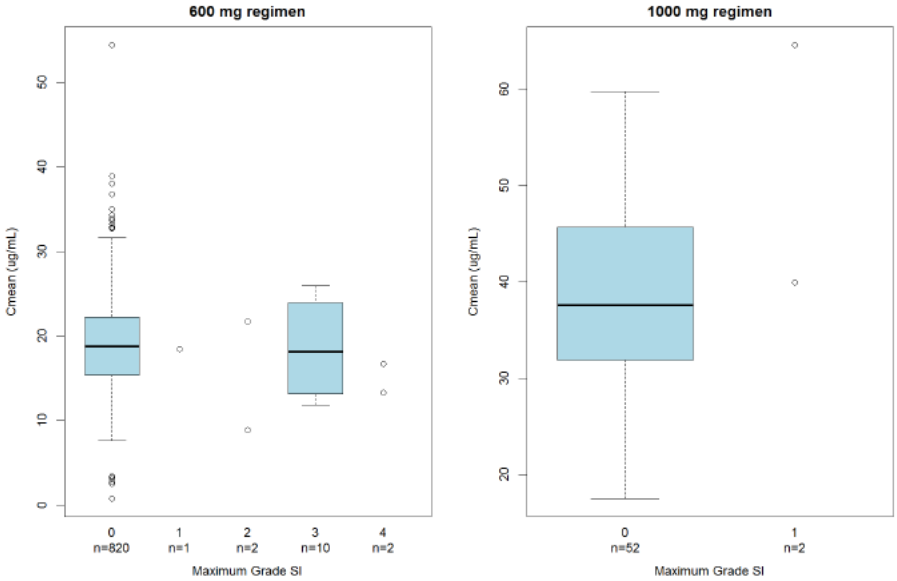
Figure 4: Relationship between Ocrelizumab Exposure and Grade of SAE



Note: Distributions of Cmean by maximum SAE grade for patients receiving ocrelizumab. Grade=0 corresponds to no SAE for a patient during the trial.

Source: RMS popPK report Figure 79 on page 140

Figure 5: Relationship between Ocrelizumab Exposure and Grade of Serious Infection



Note: Distributions of Cmean by maximum SI grade for patients receiving ocrelizumab. Grade=0 corresponds to no SI for a patient during the trial.

Source: RMS popPK report Figure 80 on page 141

Figure 6: Relationship between Ocrelizumab Exposure (Predicted Cmax Preceding IRR) and Grade of IRR

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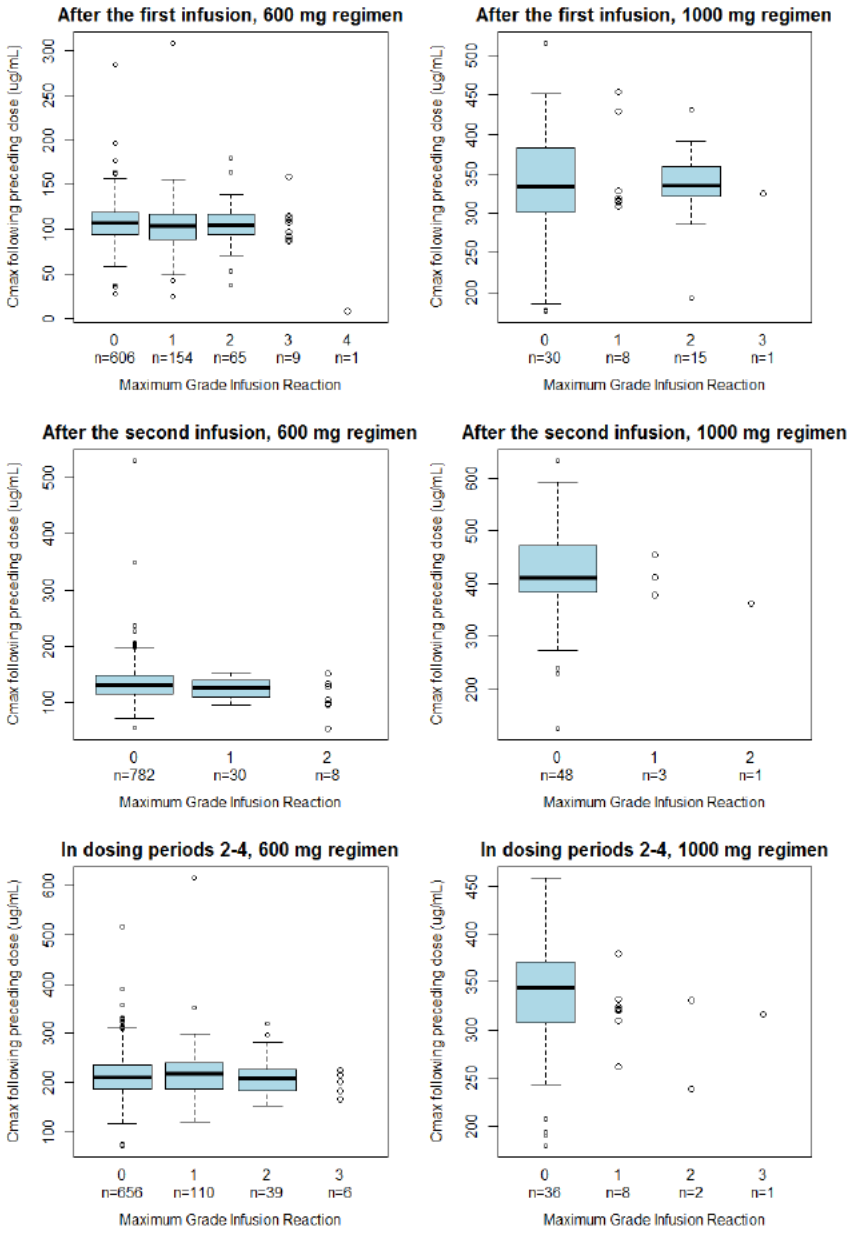

Source: RMS popPK report Figure 85 on page 146

Reviewer's comments: The relationships between ocrelizumab exposure and the selected relevant AEs associated with ocrelizumab treatment, i.e. SAE, serious infection, and IRR were evaluated by the applicant. Although numerically higher event rates were observed in patients that received 1000 mg ocrelizumab regimen in study WA21493, the sample size was relatively small and the 95% CI overlapped with the four exposure quantiles at 600 mg dose level. Thus, no exposure-response relationship for these safety endpoints could be established based on the data. The applicant's exposure-safety analyses are acceptable.

4.35.2 Exposure-Response Analyses for PPMS

4.5.2.1 Exposure-Efficacy Analyses for PPMS

4.3.2.1.1 Applicant's Exposure-Efficacy Analyses for PPMS

Association of the selected efficacy endpoints for PPMS, including the primary endpoint of time to 12-week CDP with ocrelizumab exposure and secondary endpoints such as time to 24-week CDP, change from baseline in T25-Foot Walk (FW) test, and change in brain volume, was explored by the applicant. Data from the PPMS pivotal study WA25046 was used for the analysis. Average ocrelizumab concentration over the entire treatment period (Cmean) was used as the main exposure metric, calculated as the ratio of cumulative AUC up to the end of the last dosing interval and duration of time from zero till the end of the last dosing interval. Patients were divided into four exposure subgroups base on Cmean quantiles. The proportion of patients with CDP by exposure quantiles was estimated using a Kaplan-Meier approach and the results are shown in ***Figure 7***. Hazard ratios comparing each exposure quantile with the placebo group regarding time to 12-week CDP were estimated via a Cox regression model with treatment group as the predictor and geographical region (US versus ROW) and age (<=45 versus >45 years) as covariates and the results are shown in ***Table 6***. The results appear to show a lower risk of CDP for patients in the highest exposure quantile compared with patients in the placebo group. No significant difference between the other three lower exposure quantiles was observed. Similar results were observed for 24-week CDP, as shown in ***Figure 8.*** The applicant also explored the association of change from baseline in T25-FW test and change from baseline in brain volume with ocrelizumab exposure and no relationships were observed, as shown in ***Figure 9*** and ***Figure 10.***

Figure 7: Kaplan-Meier Plot for Time to 12-Week CDP by Exposure Quantiles

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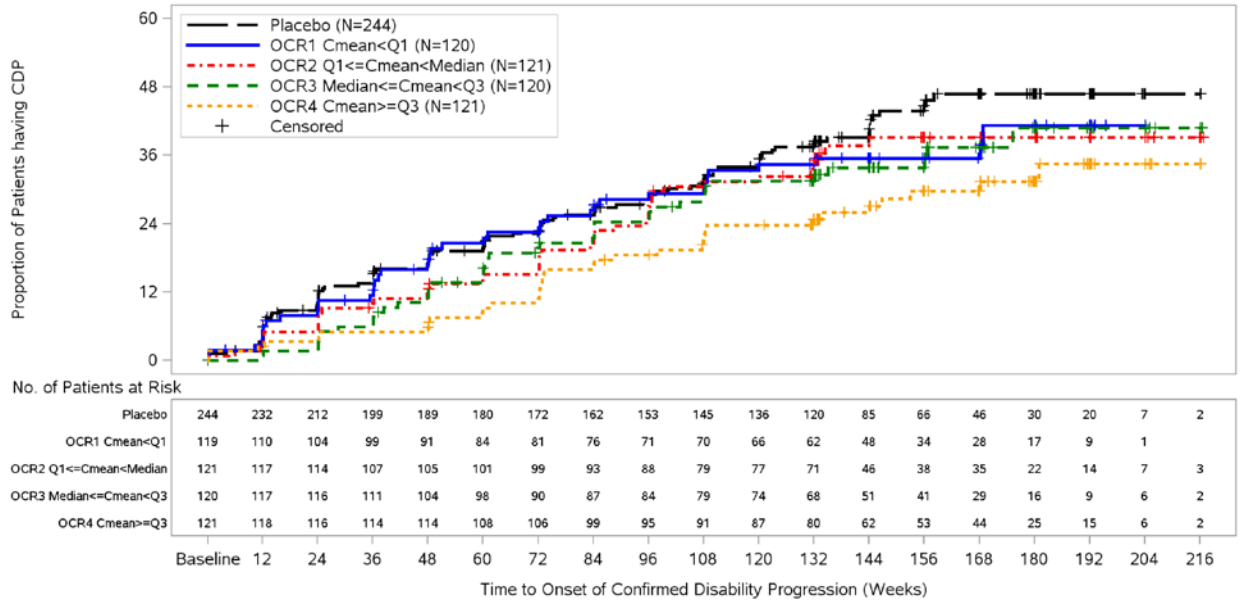
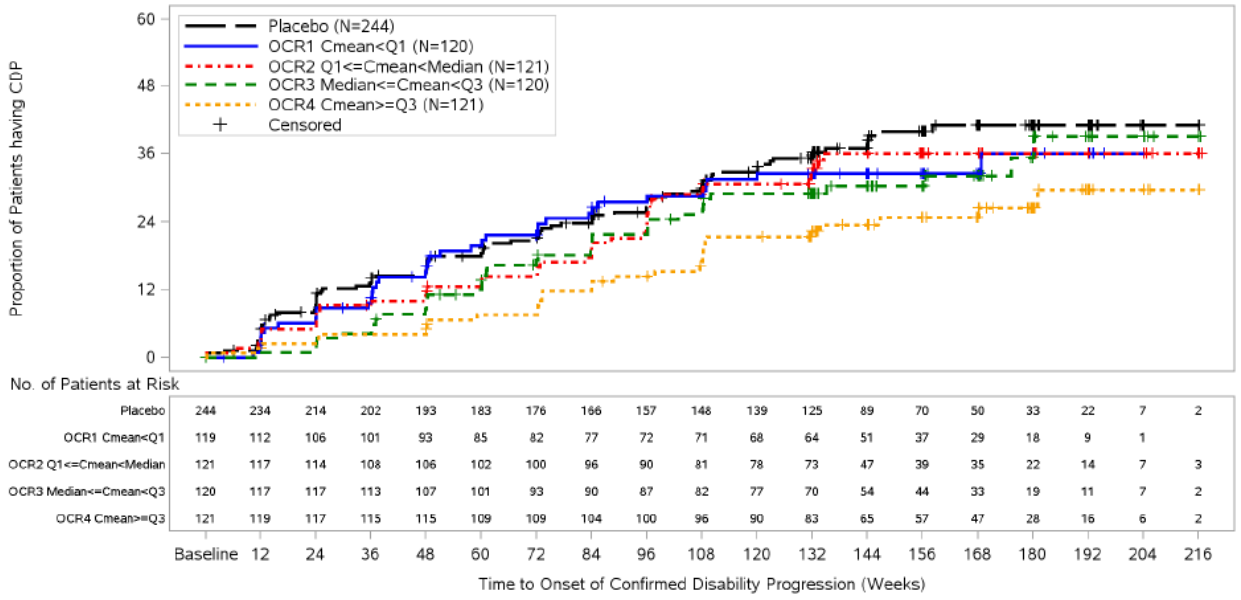


Source: Summary of Clinical Pharmacology Figure 25 on page 70

Figure 8: Kaplan-Meier Plot for Time to 24-Week CDP by Exposure Quantiles



Source: Summary of Clinical Pharmacology Figure 26 on page 71

Table 6: Hazard Ratio Estimates for Time to 12-Week CDP by Exposure Quantiles

Exposure group	Hazard Ratio	95% CI	p-value
Reference = Placebo			

OCR Cmean < Q1	0.87	(0.60, 1.27)	0.4784
OCR Cmean >= Q1 and < Median	0.83	(0.58, 1.19)	0.3084
OCR Cmean >= Median and < Q3	0.78	(0.54, 1.13)	0.1889
OCR Cmean >= Q3	0.59	(0.40, 0.86)	0.0071

Note: Adjusted for Region (US vs. ROW) and Age (<=45 vs. >45 years)

Source: Summary of Clinical Pharmacology Table19 on page 71

Figure 9: Distribution of Change from Baseline for Time to Complete 25-foot Walk Test versus Treatment Time by Exposure Group

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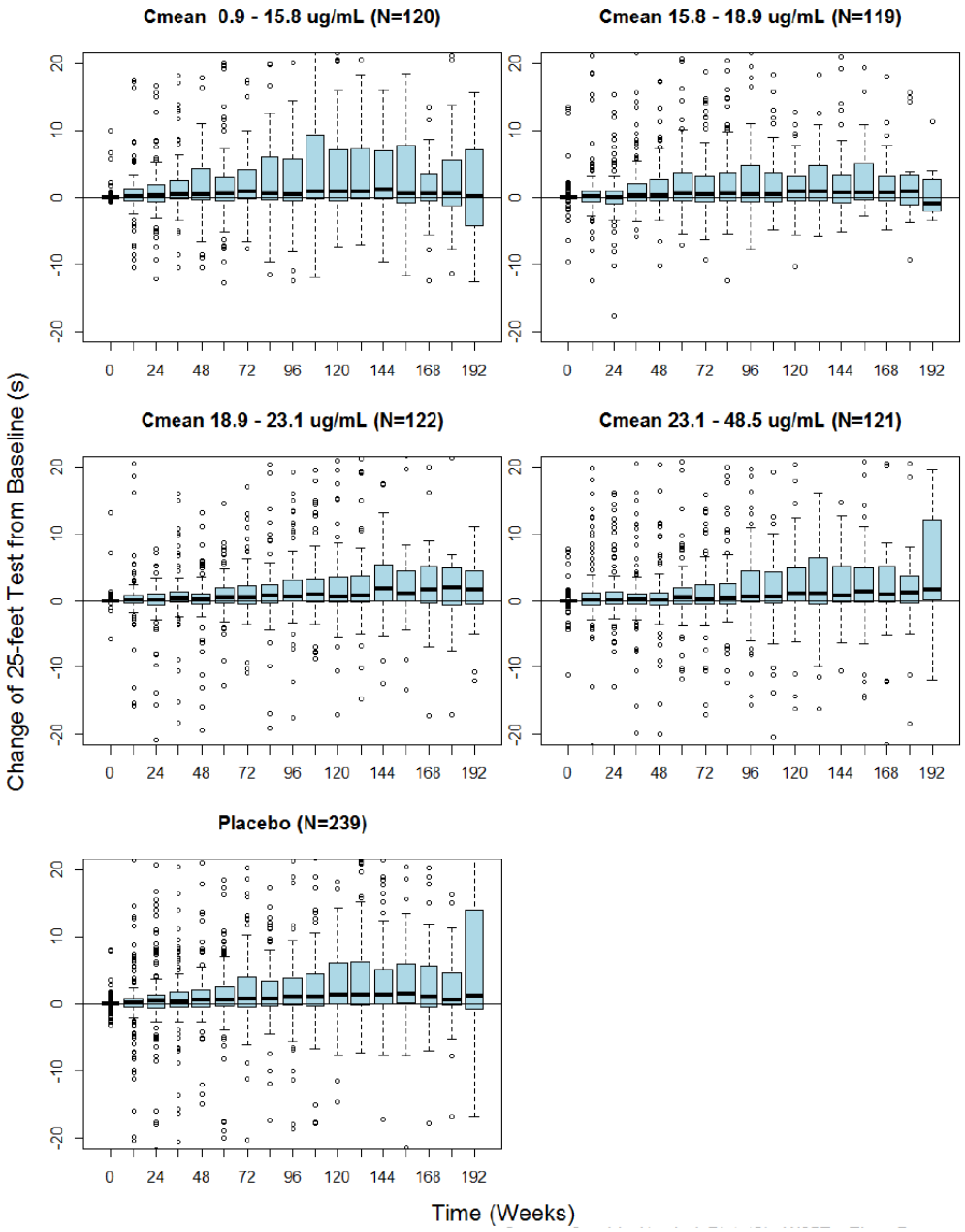
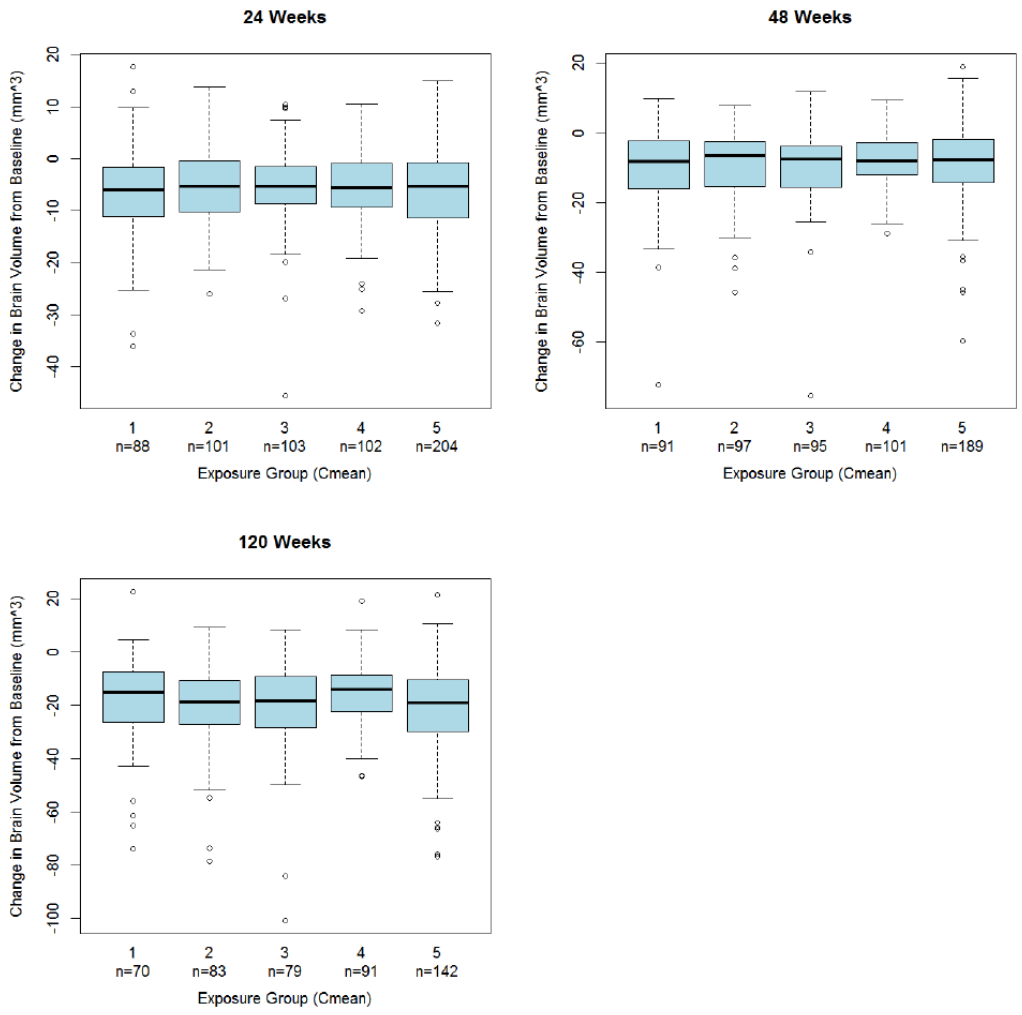


Source: PPMS popPK report Figure 47 on page 90

Figure 10: Distribution of Change in Brain Volume from Baseline versus Ocrelizumab Exposure at Week 24, 48, and 120



Note: Exposure groups 1-4 correspond to quartiles of Cmean for patients on ocrelizumab. Exposure group 5 corresponds to patients on placebo.

Source: PPMS popPK report Figure 52 on page 95

Reviewer's comments: The exposure-response analysis results with different efficacy endpoints are not consistent. While no association of change from baseline in T25-Foot Walk (FW) test and brain volume with ocrelizumab exposure *was identified, positive results were observed for CDP endpoints. Although the exposure-response analyses with CDP endpoints appeared to show that patients in the highest ocrelizumab exposure quantile had greater risk reduction for CDP, such finding needs to be interpreted with caution. Because the exposure-response analyses with CDP have a major limitation in that only a single dose of 600 mg was evaluated in the phase III study and risk factors for CDP might be unbalanced among different exposure quantiles resulting in confounded comparison of CDP results among the four subgroups. Therefore, the exposure-*

response finding for CDP can't be concluded and should not be used to support alternative dose or dosing regimen.

4.3.2.1.2 Reviewer's Exposure-Efficacy Analyses for PPMS

Introduction

Limitations exist in the applicant's exposure-response analyses for the CDP endpoints. One major limitation is the potentially unbalanced risk factors for CDP among different exposure quantiles. Another potential limitation is that the time-dependent PK may confound the exposure-exposure relationship since the decreasing clearance over time, thus increased exposure, is believed to be a result of ocrelizumab treatment through reducing B-cell counts, which is the mechanism of action for ocrelizumab. The reviewer conducted independent exposure-efficacy analyses for time to 12-week CDP trying to address the limitations of the applicant's analyses.

Objective

The objectives of the analysis are

- To evaluate the exposure-response relationship for time to 12-week CDP by employing different PK metrics that may eliminate the confounding effect of time-dependent PK on efficacy.
- To explore the exposure-response relationship for time to 12-week CDP after adjusting for multiple potential confounding factors for efficacy.

Data Sets

Data sets used are summarized in the table below.

Table 7: Analysis Data sets

Study Number	Name	Link to EDR
WA25046	ADSLCMN.xpt	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ocrelizumab_BLA761053_XW\ER Analyses\WA25046
WA25046	ATE.xpt	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ocrelizumab_BLA761053_XW\ER Analyses\WA25046
WA25046	PKPARAM.xpt	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ocrelizumab_BLA761053_XW\ER Analyses\WA25046

Software

The statistical sofeware NONMEM (version 7) and R (version 2.15.3) was utilized for dataset construction, analyses, and graphics generation.

Methods

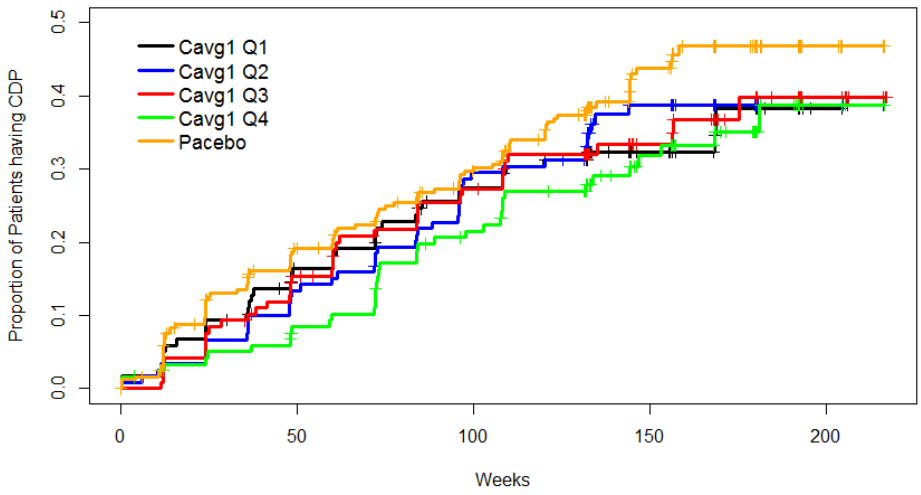
Ocrelizumab exposure after the first dose, i.e. average concentration over the first dosing interval (Cavg1), derived from the applicant's final PK model was employed to evaluate the exposure-response relationship for CDP. The rationale is that utilizing of exposure after the first dose when the time-dependent PK change has not occurred may address the confounding effect of time-dependent PK on efficacy.

Multivariate cox regression model including additional risk factors for efficacy was employed by the reviewer trying to adjust for potentially confounding factors in the exposure-efficacy analysis

Results

The proportion of patients with onset of CDP by exposure quantiles based on ocrelizumab exposure after the first dose was estimated using a Kaplan-Meier approach and the overall results are similar to the applicant's analysis results with average ocrelizumab concentration over the entire treatment period except that survival curve for the highest exposure quantile tends to overlap with those for the lower exposure quantiles at later time, as shown in ***Figure 11***. It appears that time-dependent PK of ocrelizumab did not substantially affect the exposure-response relationship for CDP and possible explanation is that the proportion of time-dependent clearance component is relatively small for ocrelizumab, only accounting for about 20% of the total clearance at baseline.

Figure 11: Kaplan-Meier Plot for Time to 12-Week CDP by Exposure Quantiles based on Exposure after the First Dose



Hazard ratios comparing each exposure quantile with the interferon beta-1a reference group regarding time to 12-week CDP were estimated via a Cox regression model with treatment group as the predictor and geographical region (US versus ROW), baseline EDSS (<=5.5 versus >5.5), age (<=45 versus >45 years), sex, presence of Gd+ T1 lesion at baseline (yes versus no), duration since MS symptom onset (<=3, >3 to <=5, >5 to <=10, or >10 years), prior MS treatment (yes versus no), baseline body weight (<=75 versus >75 kg) as potential risk factors. The results are shown in ***Table 8*** and are similar to the applicant's cox regression results. It appears that including additional potential risk factors did not alter the observed exposure-response relationship. However, there are also limitations with the reviewer's analysis because even though additional risk factors were included in the cox regression model, there still might be unknown risk factors that are unbalanced among exposure groups and cannot be adjusted in the model, therefore confounding the exposure-response relationship. Therefore, the observed exposure-response relationship needs to be interpreted with caution and may not be used to support alternative doses or dosing regimens.

Table 8: Reviewer's Hazard Ratio Estimates for Time to 12-Week CDP by Exposure Quantiles

Exposure group	Hazard Ratio	95% CI	p-value
Reference = IFN			
OCR Cmean < Q1	0.90	(0.57, 1.41)	0.64
OCR Cmean >= Q1 and < Median	0.82	(0.54, 1.26)	0.37
OCR Cmean >= Median and < Q3	0.75	(0.49, 1.16)	0.20
OCR Cmean >= Q3	0.51	(0.31, 0.82)	0.006

Note: Adjusted for Baseline EDSS (<=5.5 versus >5.5), Region (US vs. ROW), age (<=45 versus >45 years), sex, presence of Gd+ T1 lesion at baseline (yes versus no), duration since MS symptom onset (<=3, >3 to <=5, >5 to <=10, or >10 years), prior MS treatment (yes versus no), baseline body weight (<=75 versus >75 kg)

Listing of Analysis Codes and Output Files

File Name	Description	Link to EDR
ER_PPMS.r	Exposure-response analyses for PPMS with data from study WA25046	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ocrelizumab_BLA761053_XW\ER Analyses\WA25046

4.5.2.2 Applicant's Exposure-Safety Analyses for PPMS

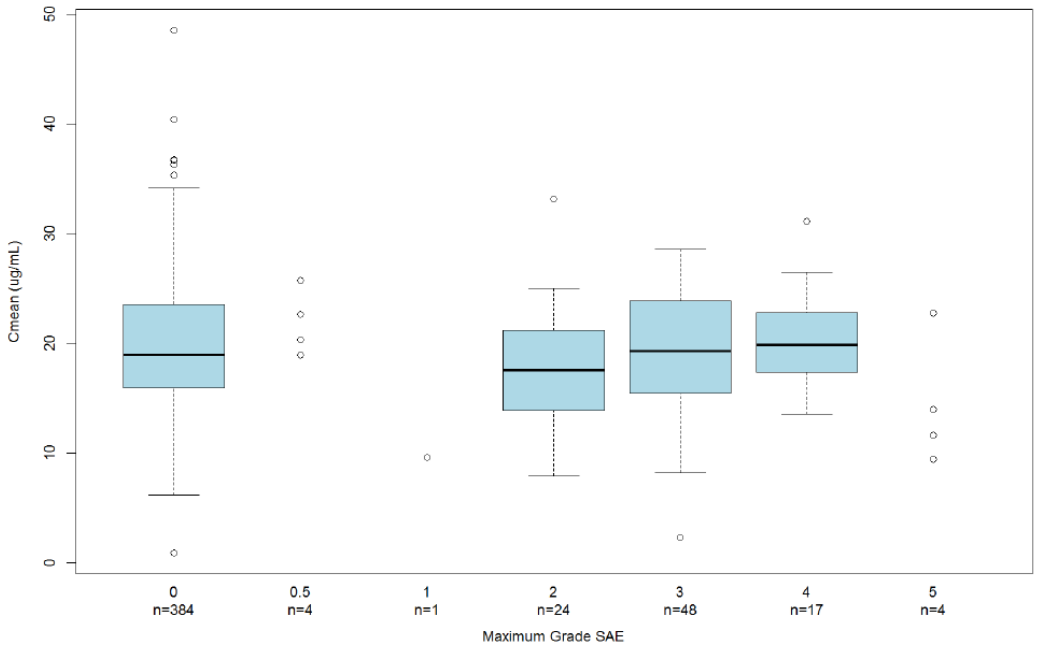
Analyses were conducted by the applicant to evaluate the relationship between ocrelizumab exposure and several safety endpoints including serious adverse event (SAE), serious infection (SI), and infusion related reaction (IRR) using data from study WA25046. The relationships between rates of SAE, SI, and IRR and ocrelizumab exposure were evaluated by comparing rates between the following 5 subgroups: 4 exposure quantiles and the placebo group. The results show that the rates of SAE and SI did not differ between patients in different exposure groups, and are also similar between patients on ocrelizumab and placebo, as shown in ***Table 9***. For IRR, the rate of IRR in patients on placebo appeared to be lower. However, in patients on ocrelizumab treatment, no trend was observed among the four exposure groups (***Table 9***). In addition, the association of the grades of SAE, SI, and IRR events with ocrelizumab exposure was also explored by comparing the distributions of ocrelizumab exposures between different grades of these events and the results show that there were no relationships between ocrelizumab exposure and the grades of SAE, SI, and IRR in patients treated with ocrelizumab, as shown in ***Figure 12***, ***Figure 13***, and ***Figure 14*** for SAE, SI, and IRR respectively.

Table 9: Rates of SAEs, SIs, and IRRs in Patients on Ocrelizumab by Exposure Quantiles and in Patients on Placebo

Event Type	C_{mean} Exposure Category	C_{mean} (µg/mL)	N patients	N patients with events	% (95%CI) patients with events
SAE	1	0.9 - 15.8	120	29	24.17 (17.03 - 33.00)
	2	15.8 - 18.9	119	19	15.97 (10.13 - 24.07)
	3	18.9 - 23.1	122	28	22.95 (16.03 - 31.61)
	4	23.1 - 48.5	121	22	18.18 (11.98 - 26.45)
	5	Placebo	239	53	22.18 (17.18 - 28.08)
SI	1	0.9 - 15.8	120	8	6.67 (3.13 - 13.12)
	2	15.8 - 18.9	119	5	4.2 (1.56 - 10.02)
	3	18.9 - 23.1	122	13	10.66 (6.02 - 17.86)
	4	23.1 - 48.5	121	6	4.96 (2.03 - 10.93)
	5	Placebo	239	15	6.28 (3.68 - 10.35)
IRR	1	0.9 - 15.8	120	47	39.17 (30.51 - 48.53)
	2	15.8 - 18.9	119	44	36.97 (28.45 - 46.35)
	3	18.9 - 23.1	122	55	45.08 (36.15 - 54.33)
	4	23.1 - 48.5	121	47	38.84 (30.25 - 48.16)
	5	Placebo	239	61	25.52 (20.22 - 31.63)

Source: PPMS popPK report Table 10 on page 42

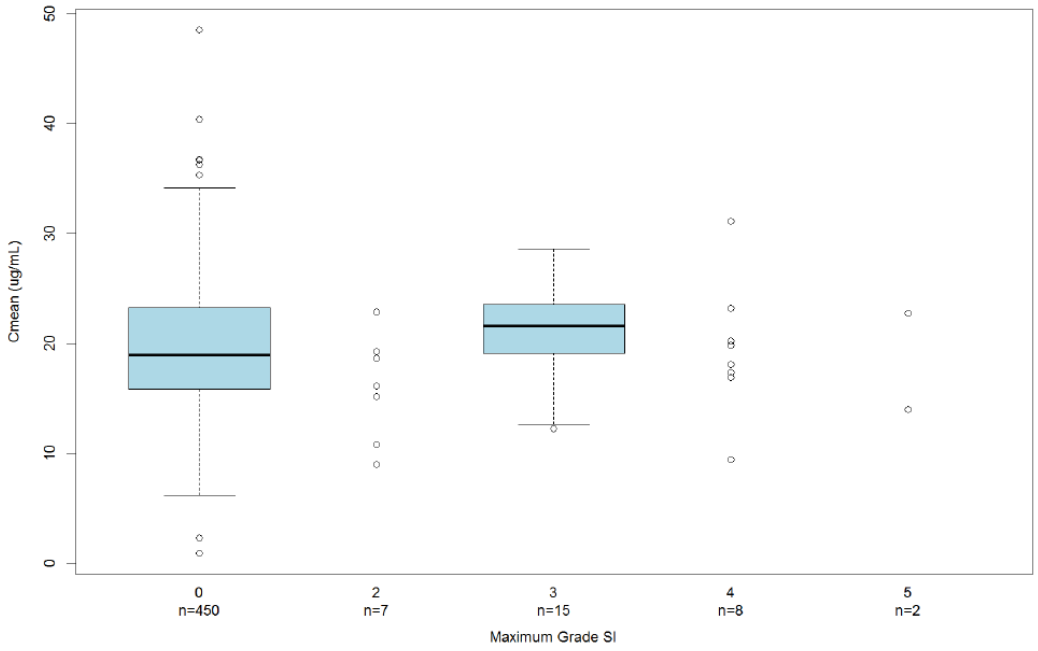
Figure 12: Relationship between Ocrelizumab Exposure and Grade of SAEs



Note: Distributions of Cmean by maximum SAE grade for patients receiving ocrelizumab. Grade=0 corresponds to no SAE for a patient during the trial. Grade 0.5 corresponds to SAEs with unknown grade.

Source: PPMS popPK report Figure 28 on page 71

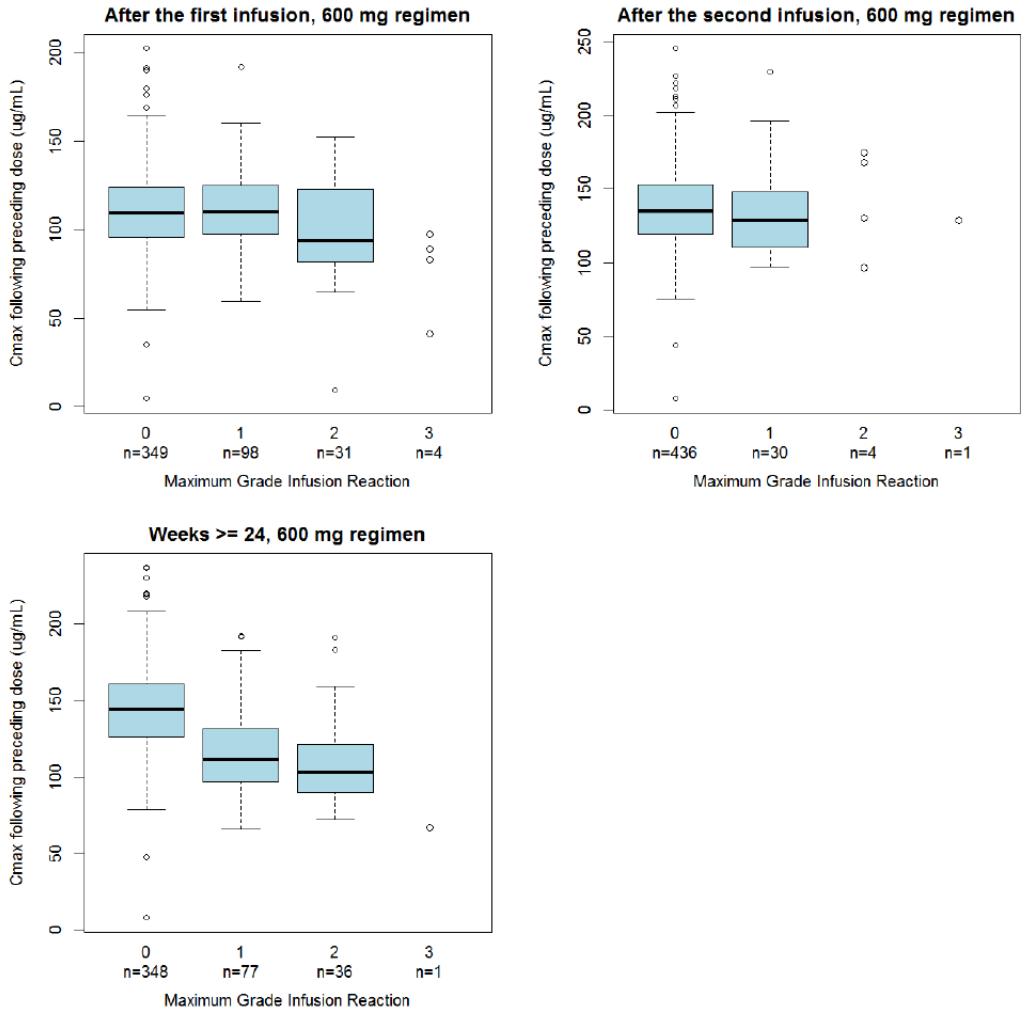
Figure 13: Relationship between Ocrelizumab Exposure and Grade of Serious Infections



Note: Distributions of Cmean by maximum SI grade for patients receiving ocrelizumab. Grade=0 corresponds to no SI for a patient during the trial.

Source: PPMS popPK report Figure 29 on page 72

Figure 14: Relationship between Ocrelizumab Exposure (Predicted Cmax Preceding IRR) and Grade of IRR



Source: PPMS popPK report Figure 35 on page 78

Reviewer's comments: The relationships between ocrelizumab exposure and the most relevant AEs associated with ocrelizumab treatment, i.e. infections and IRR, as well as SAE were evaluated by the applicant and no exposure-response relationship for these safety endpoints was established based on the data. The applicant's exposure-safety analyses are acceptable.

4.6 Pharmacometrics Assessment: Dosing Harmonization Analyses

In all MS Phase III trials (WA21092, WA21093, and WA25046), the initial dose of 600 mg ocrelizumab was divided into two separate IV infusions of 300 mg 14 days apart. In the two RMS Studies WA21092 and WA21093, subsequent doses of ocrelizumab were administered as a single infusion of 600 mg every 24 weeks whereas in the PPMS Study WA25046, subsequent doses of 600 mg were administered every 24 weeks as dual 300 mg infusions 14 days apart.

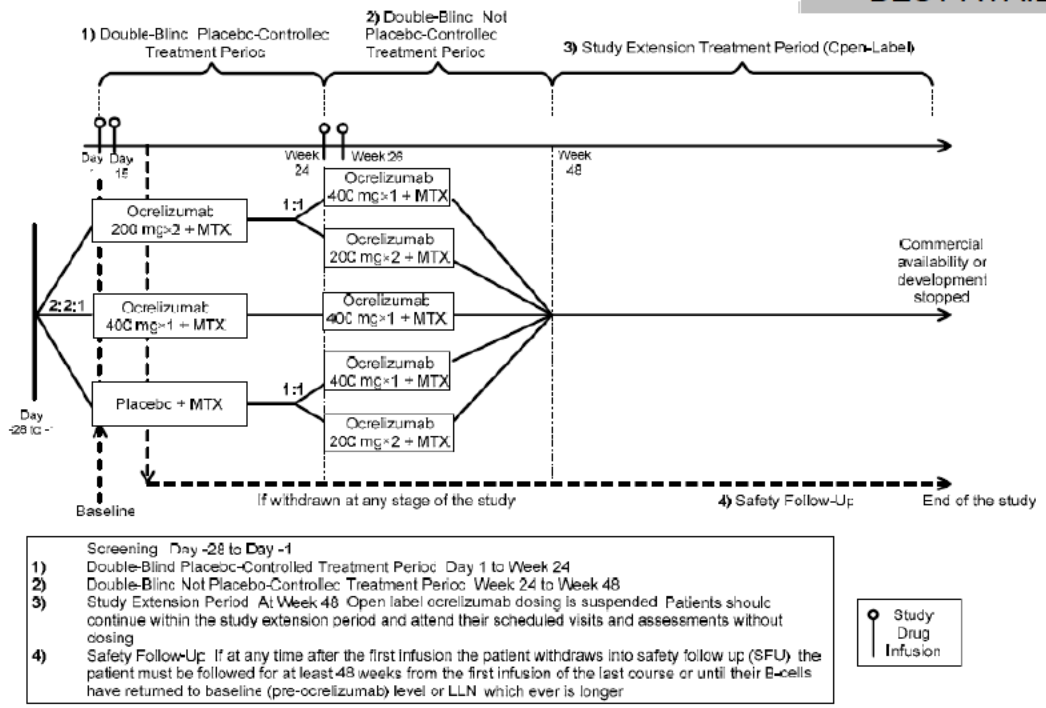
4.6.1 Rationale for Different Regimen Selection for RMS and PPMS Studies

The rationale for selecting the dual-infusion regimen in the PPMS study WA25046 was based on early data from a Phase 3 study in rheumatoid arthritis (RA), study WA20496. Study WA20496 was a randomized, double-blind, parallel-group, placebo-controlled study to evaluate the safety and efficacy of 400 mg ocrelizumab given as a single Infusion (400 mg x 1) or dual infusion (200 mg x 2) in patients with active rheumatoid arthritis (RA) who have an inadequate response to methotrexate therapy. The study consisted a 24-week double-blind, randomized, placebo-controlled treatment period, followed by a 24-week double-blind, randomized, not placebo-controlled treatment period, an open-label extension period, and a safety follow-up period, as shown in ***Figure 1***. Early data from the first 24-week treatment period showed that administration of ocrelizumab via dual infusion (200 mg x 2) appeared to be associated with a numerically better clinical response as measured as ACR20 response compared to ocrelizumab single infusion (400 mg x 1), as shown in ***Table 1***. However, analyses of data from the second 24-week treatment period suggested that the efficacy achieved after an initial dosing with dual infusion of ocrelizumab (200 mg x 2) during the first period could be maintained at similar levels by either an 400 mg single infusion or by an 200 mg x2 dual infusion as a second treatment, as shown in ***Table 2***. At the time that WA25046 study design was being finalized, only the 24-week data from study WA20496 was available, and therefore, the dual infusion regimen (300 mg x 2) was selected for the PPMS study WA25046. However, when the two RMS studies WA21092 and WA21093 were initiated, the final data and conclusion of the RA study WA20496 became available, thus the single infusion regimen was selected for the RMS studies.

Reviewer's comment: Early data from the first 24-week treatment period of study WA20496 showed that the dual infusion (200 mg x 2) resulted in better efficacy compared with the single infusion regimen (400 mg x 1). Even if such finding proved to be robust, data from the second 24-week treatment period suggested that the efficacy achieved after an initial dosing with dual infusion of ocrelizumab (200 mg x 2) during the first period could be maintained at similar levels by either a 400 mg single infusion or by an 200 mg x 2 dual infusion as a second treatment. If one were to accept these findings, it would suggest that splitting the first dose into two separate infusions is the key to achieve desirable clinical response and whether or not subsequent doses are split into two infusions would have little influence on clinical response.

Such a hypothesis seems to be supported by the pivotal study results where pre-specified clinical endpoints were met in both the RMS trials with single infusion regimen from 2nd dose onward and the PPMS trial using dual infusion regimen from 2nd dose onward. It is worth noting that for both indications, the initial dose will be administered as two separate infusions. In addition, safety analysis showed that there was no clear difference in the pattern of infusion related reactions between RMS and PPMS regimens. The incidence, severity, as well as symptoms of IRR were comparable between the two regimens. Thus, there seems to be no additional benefit in terms of safety for MS patients to receive dual infusions after the first dose.

Figure 1: WA20496 Study Design



Source: CSR WA20496 Figure 1 on page 83

Table 1: Summary of Percentage of Patients with an ACR20 Response at Week 24

	Placebo (N=64)	OCR 400 mg x 1 (N=117)	OCR 200 mg x 2 (N=131)
n	64	117	131
Responders	18 (28.1%)	44 (37.6%)	69 (52.7%)
95% C.I.	[17.1, 39.1]	[28.8, 46.4]	[44.1, 61.2]
Weighted difference vs. Placebo		8.6	24.5
95% C.I. of weighted difference		[-5.3, 22.4]	[10.6, 38.5]

Source: CSR WA20496 Table 18 on page 161

Table 2: Proportion of Patients with an ACR20 Response at Week 48 by ACR20 Response at Week 24

	Period 1: 200 mg x 2/ Period 2: 200 mg x 2 (N=61)	Period 1: 200 mg x 2/ Period 2: 400 mg x 1 (N=61)
Responders at Week 24		
n	36	32
Responders at Week 48	28 (77.8%)	25 (78.1%)
95% C.I.	[64.2, 91.4]	[63.8, 92.4]
Non-Responders at Week 24		
n	25	29
Responders at Week 48	8 (32.0%)	8 (27.6%)
95% C.I.	[13.7, 50.3]	[11.3, 43.9]

Source: CSR WA20496 Table 21 on page 165

4.6.2 Reviewer's Analysis to Support Dosing Regimen Harmonization

The reviewer's analysis to support the dosing regimen harmonization between RMS and PPMS focused on the PK and PD aspects. From the PK perspective, typical PK profiles following administration of the two different regimens were simulated using the applicant's final population PK model. The results show that the two regimens would result in similar AUC and Ctrough while single 600 mg infusion resulted in ~50% increase in Cmax comparing to double 300 mg infusions (***Figure 9 in section 3.3***). Such increase in Cmax was not considered clinically significant since the exposure-safety relationship shows no obvious increase in safety findings with increased exposure within the exposure range at 600 mg dose level.

To evaluate the PD profiles following administration of the two different regimens, the reviewer compared the absolute CD19+ B-cell counts in the RMS studies with those in the PPMS study. Results show that the two regimens resulted in comparable absolute B-cell count profiles, as shown in ***Figure 10 in section 3.3***. In addition to the absolute B-cell counts, the distributions of B-cell counts at various study visits were also compared using cumulative density of B-cell counts. The results are illustrated in ***Figure 11 in section 3.3, Figure 2, Figure 3, and Figure 4***, suggesting comparable B-cell count distribution between the two regimens at week 24, 48, 72, and 96. Moreover, the reviewer also assessed the absolute CD3+, CD4+, and CD8+ T-cell counts as well as NK cell counts in the RMS studies with those in the PPMS study. Results show that the distributions of CD3+, CD4+, CD8+ T-cell counts and NK cell counts at different study visits are comparable between the two regimens, as shown in ***Figure 5***, ***Figure 6***, ***Figure 7***, and ***Figure 8*** for CD3+, CD4+, CD8+ T-cells and NK cells respectively. The T cell and NK cell data provide additional support to the conclusion of comparable PD profiles between the two regimens.

Figure 2: Comparison of B-Cell Count Distribution between the Two Regimens at Week 48

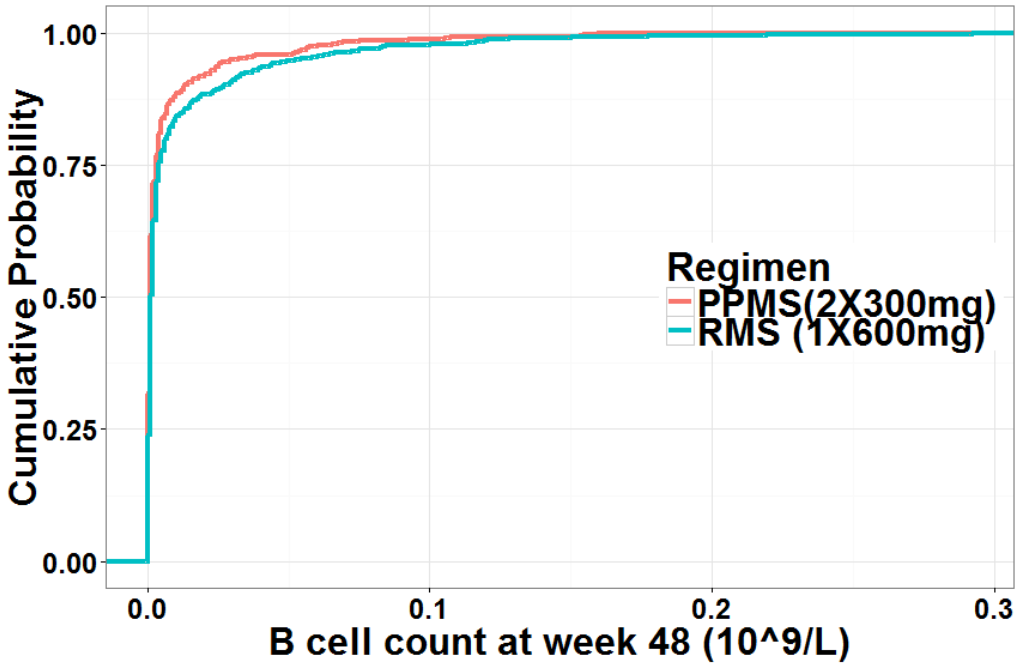


Figure 3: Comparison of B-Cell Count Distribution between the Two Regimens at Week 72

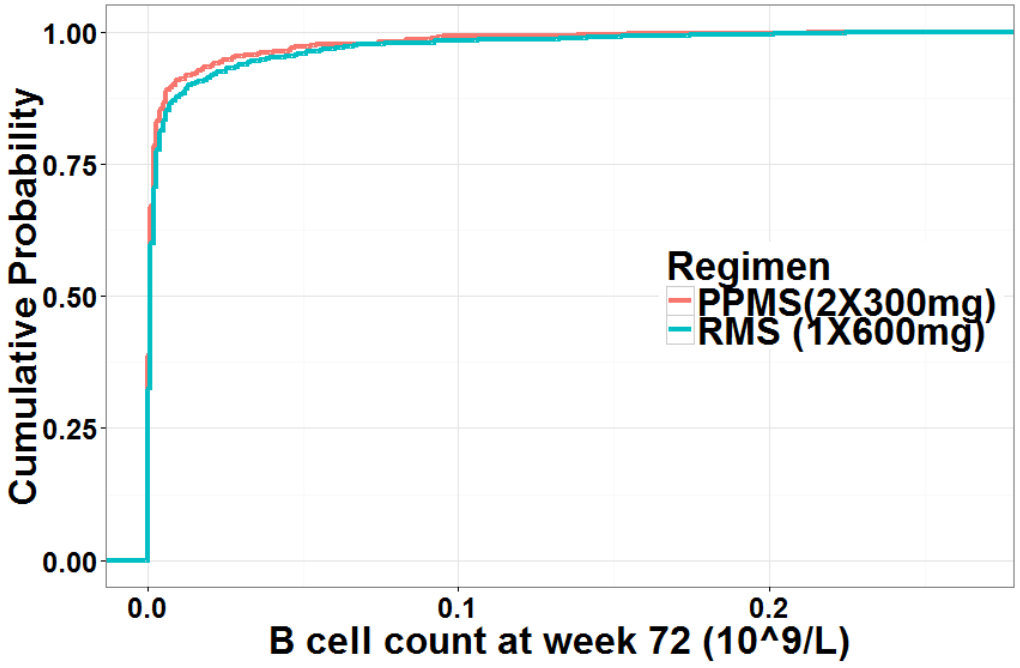


Figure 4: Comparison of B-Cell Count Distribution between the Two Regimens at Week 96

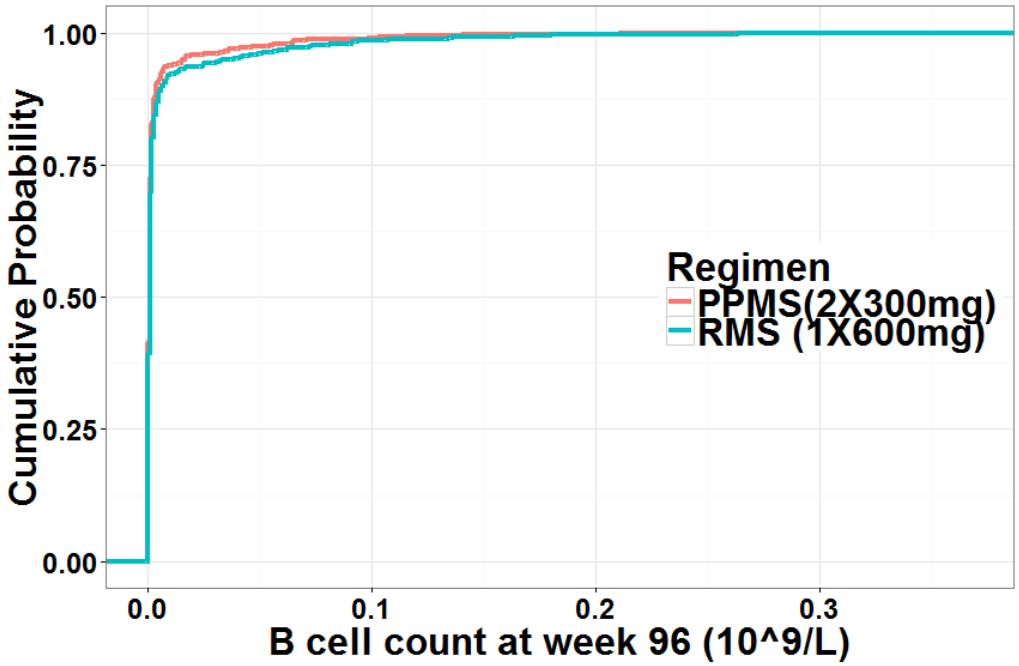


Figure 5: Comparison of CD3+ T Cell Counts between the Two Regimens

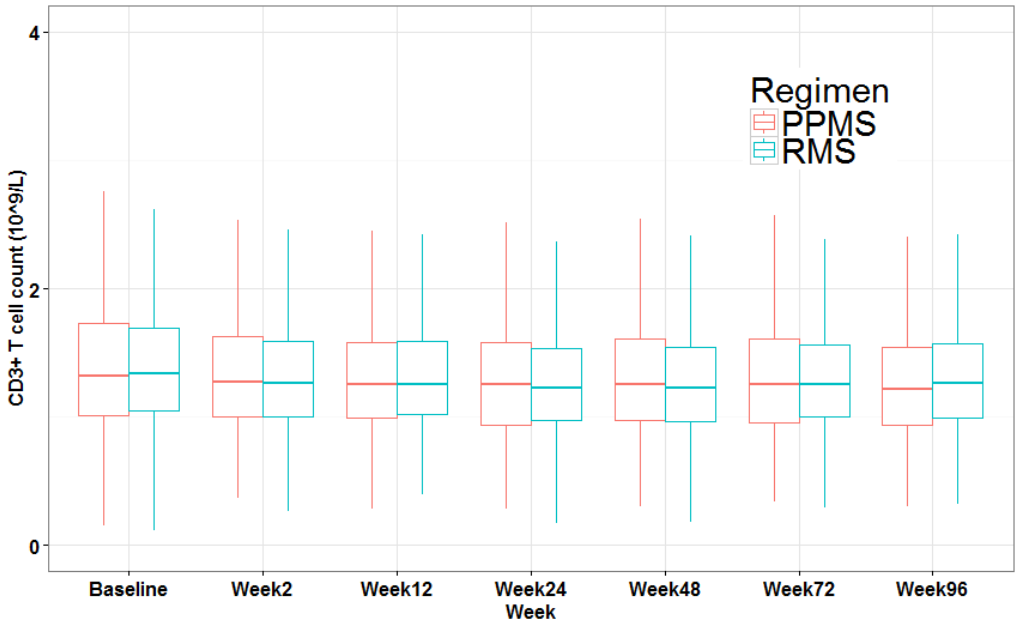


Figure 6: Comparison of CD4+ T Cell Counts between the Two Regimens

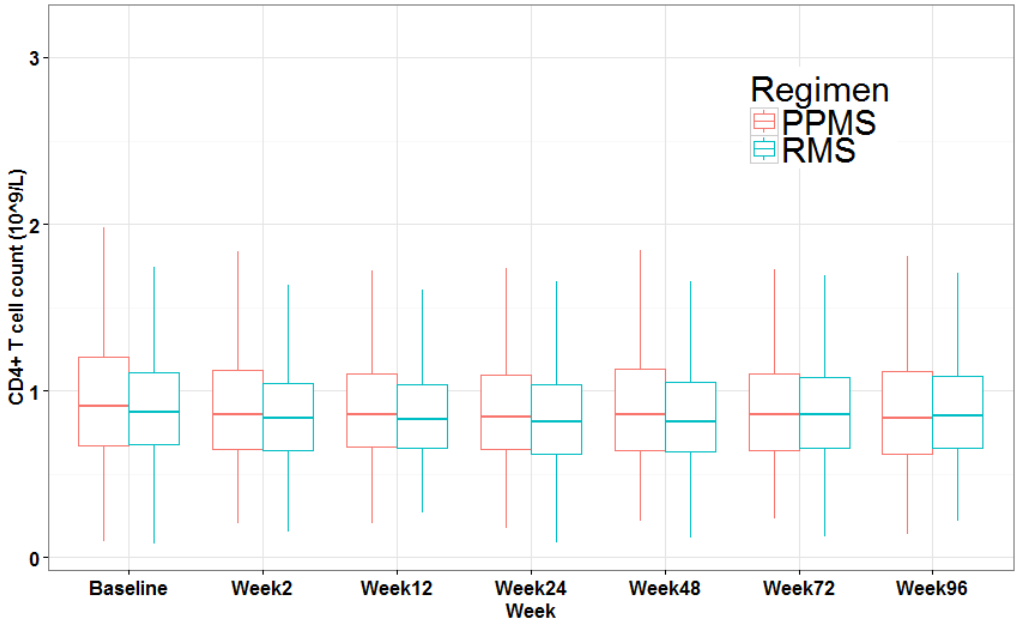


Figure 7: Comparison of CD8+ T Cell Counts between the Two Regimens

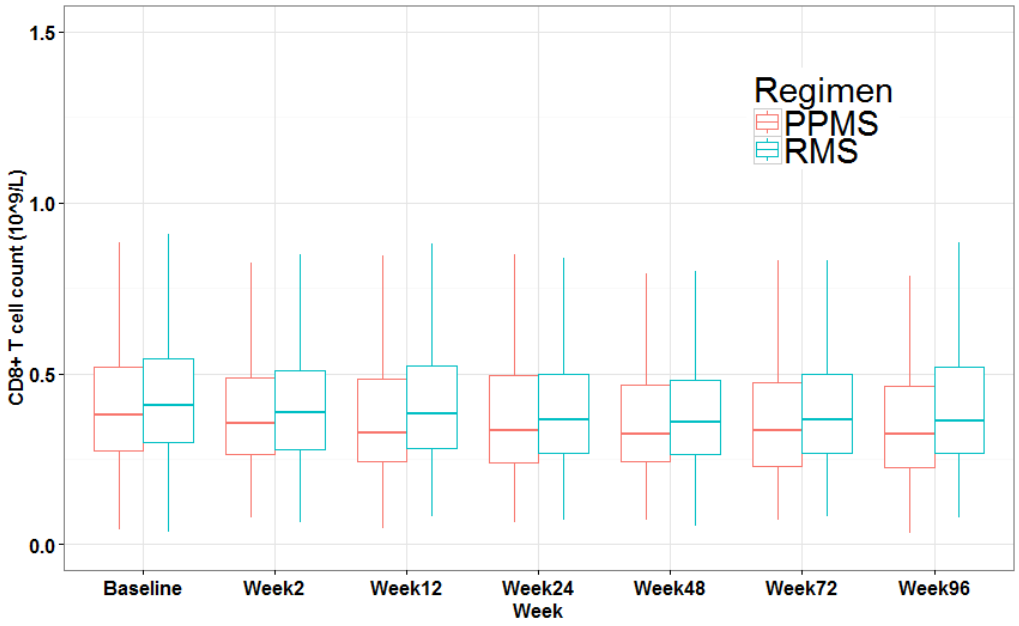
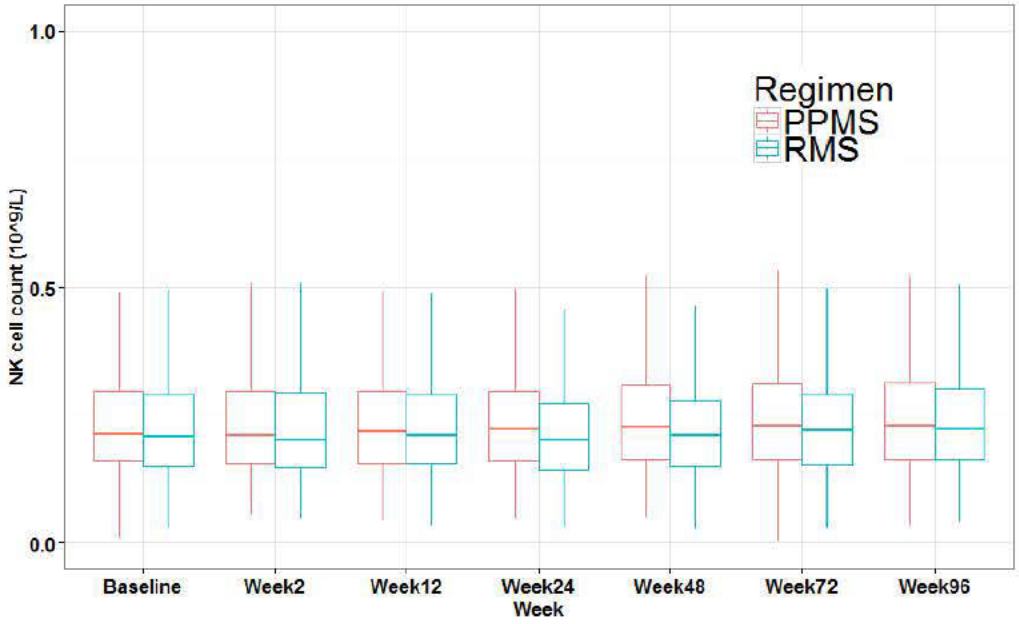


Figure 8: Comparison of NK Cell Counts between the Two Regimens



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