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ORIGINAL ARTICLE

Ocrelizumab in relapsing and primary progressive multiple sclerosis: Pharmacokinetic and pharmacodynamic analyses of OPERA I, OPERA II and ORATORIO

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Aims: Ocrelizumab is a humanized monoclonal antibody that selectively targets CD20-positive B cells and is indicated for treatment of patients with relapsing forms of multiple sclerosis (RMS) or primary progressive multiple sclerosis (PPMS). The pharmacokinetics and pharmacodynamics of ocrelizumab in patients with RMS or PPMS were assessed.

Methods: A population pharmacokinetic model was developed based on data from the Phase II study and the Phase III studies OPERA I and OPERA II in patients with RMS. Data from the ORATORIO Phase III study in patients with PPMS became available after model finalization and was used for external model evaluation.

Results: The ocrelizumab serum concentration *vs* time course was accurately described by a 2-compartment model with time-dependent clearance. Body weight was found to be the main covariate. The area under the concentration–time curve over the dosing interval was estimated to be 26% higher for patients with RMS weighing <60 kg and 21% lower for patients weighing >90 kg when compared with the 60–90 kg group. The terminal half-life of ocrelizumab was estimated as 26 days. The extent of B-cell depletion in blood, as the pharmacodynamic marker, was greater with increasing ocrelizumab exposure.

Conclusion: The pharmacokinetics of ocrelizumab was described with pharmacokinetic parameters typical for an immunoglobulin G1 monoclonal antibody, with body weight as the main covariate. The pharmacokinetics and B-cell depletion in blood were comparable across the RMS and PPMS trials, and the extent of blood B-cell depletion was greater with higher exposure.

KEYWORDS

pharmacokinetic–pharmacodynamic, pharmacodynamics, population analysis, multiple sclerosis, neurology

The authors confirm that the Principal Investigator for this paper is Professor Ludwig Kappos and that he had direct clinical responsibility for patients.

1 | INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating and neurodegenerative disease of the central nervous system and a common cause of disability in young adults. MS is characterized by symptoms such as: visual loss; paresis and spasticity; sensory disturbances and numbness; incoordination; bowel, bladder and sexual dysfunction; fatigue; pain; and cognitive defects.[1,2] MS can be categorized as relapsing or progressive but is largely considered a progressive disease in most patients, regardless of the phenotype.[3] Relapsing MS (RMS) begins as an episodic disorder, but can evolve into a condition characterized by progressive neurological disability termed secondary progressive MS.[1,2,4] Primary progressive MS (PPMS), which accounts for 10–15% of the MS patient population,[5] presents with a disease course that consists mainly of gradual worsening of neurological disability from symptom onset, although relapses may occur.[6]

MS was long thought to be a T-cell-mediated autoimmune disorder, causing inflammatory demyelination and neuronal damage, which slows or prevents nerve signalling.[7] More recently, B cells have been shown to play an important role in the pathogenesis of MS, probably via a number of mechanisms, such as the presentation of autoantigens and costimulatory signals to activate T cells and the secretion of proinflammatory cytokines.[8–12]

Ocrelizumab is a recombinant humanized monoclonal antibody (mAb) that targets **CD20**-positive B cells.[13] CD20 is a cell surface antigen found on pre-B cells, mature B cells and memory B cells, but is not expressed on lymphoid stem cells and mature plasma cells. The precise mechanisms by which ocrelizumab exerts its therapeutic clinical effects in MS are not fully elucidated but involve binding to CD20, which results in antibody-dependent cellular cytolysis, antibody-dependent cellular phagocytosis, apoptosis and/or complement-mediated lysis of B cells.[14]

Ocrelizumab is the first CD20 + B-cell-selective monoclonal antibody approved for treatment of RMS and PPMS, at a dose of 600 mg intravenous (IV) twice-yearly, with significant benefit on disability progression, and with sustained efficacy with continuous therapy up to 6.5 years in the open-label extensions of the Phase III studies.[15,16]

A randomized, parallel, placebo-controlled Phase II study (NCT00676715; WA21493) in patients with relapsing–remitting MS (RRMS) demonstrated that ocrelizumab is highly efficacious and well tolerated, with pronounced effects on magnetic resonance imaging and relapse-related outcomes.[17] Two identical, pivotal Phase III studies in patients with RMS, OPERA I (NCT01247324; WA21092) and OPERA II (NCT01412333; WA21093), demonstrated the superiority of ocrelizumab 600 mg IV every 6 months over interferon β-1a on relapse rate, confirmed disability progression, and brain lesion activity over the 2-year controlled treatment period.[18] In a Phase III study in patients with PPMS, ORATORIO (NCT01194570; WA25046), ocrelizumab 600 mg IV every 6 months reduced the risk of confirmed disability progression compared with placebo and was superior on other measures of disease progression including the time required to walk 25 feet, the volume of chronic brain lesions and brain volume loss.[6] Based on the outcomes of these pivotal studies, ocrelizumab 600 mg IV every 6 months is indicated for the treatment of RMS and PPMS.

What is already known about this subject

- B cells are thought to play an important role in the pathogenesis of multiple sclerosis.
- Ocrelizumab is a recombinant humanized monoclonal antibody that selectively targets CD20-positive B cells, resulting in antibody-dependent cellular cytolysis, antibody-dependent cellular phagocytosis, apoptosis and/or complement-mediated lysis of the B cells.

What this study adds

- We demonstrate that the population pharmacokinetics of ocrelizumab are typical of an immunoglobulin G1 monoclonal antibody, with body weight as the main covariate
- The extent of B-cell depletion in blood correlates with higher ocrelizumab exposure

Here we describe a population pharmacokinetic (PK) model developed using all available patient PK data from Phase II and Phase III OPERA I and OPERA II studies in RMS. The aim of this analysis was to characterize the PK of ocrelizumab, to identify covariates influencing drug exposure, and to compute individual patient exposure metrics to allow for the exploration of exposure relationships.

2 | METHODS

2.1 | Acquisition of data

The population PK model was developed based on data from the Phase II trial in patients with RRMS and the Phase III studies OPERA I and OPERA II in patients with RMS (Table 1). Data from the Phase III ORATORIO study in PPMS (Table 1) became available after model finalization and was used for external model evaluation.

In the Phase II study in patients with RRMS, ocrelizumab was administered by IV infusion against placebo and an active control (intramuscular interferon β-1a). Patients in the 600-mg ocrelizumab arm received 300 mg ocrelizumab IV on days 1 and 15 (total dose 600 mg) followed by single 600-mg infusions every 24 weeks. Patients in the 1000-mg ocrelizumab arm received 1000 mg ocrelizumab IV on days 1 and 15 (total dose 2000 mg) followed by 1000 mg ocrelizumab after 24 and 48 weeks, and then 600 mg every 24 weeks. Methylprednisolone (100 mg IV infusion) was given in all studies prior to each ocrelizumab infusion to reduce the risk of infusion-related reactions. Blood samples for ocrelizumab PK assessment in serum were collected 5–30 minutes prior to the

TABLE 1 Ocrelizumab studies included in the pharmacokinetic–pharmacodynamic analyses

Study no.	Study design	Population	No. of patients	Dose, route, regimen
Pivotal Phase III studies in RMS				
WA21092 & WA21093	R, DB, DD, PG for 96 wk (dosed every 24 wk) followed by safety follow-up or OLE Randomized 1:1	MS according to McDonald criteria 2010 (RRMS or SPMS with relapses) Prior to screening: ≥2 relapses in 2 y or 1 relapse in the year before screening	**WA21092:** 821 A: 410 B: 411 **WA21093:** 835 A: 417 B: 418	**2 arms:** **A (IV):** OCR 600 mg[a] every 24 wk **B (SC):** IFN 44 μg 3 times/wk
WA21092 & WA21093	OLE period of WA21092 and WA21093 (dosed every 24 wk)	From WA21092 and WA21093 (see row above)	**WA21092:** 678 A: 352 B: 326 **WA21093:** 647 A: 350 B: 297	**All patients:** OCR 600 mg every 24 wk
Pivotal Phase III study in PPMS				
WA25046	R, DB, PG for a minimum of 120 wk (dosed every 24 wk) followed by safety follow-up or OLE randomized 2:1 (OCR:Placebo)	MS according to McDonald criteria 2005 (PPMS) EDSS at screening 3.0 to 6.5 points	A: 488 B: 244	**2 arms:** **A (IV):** OCR 2 × 300 mg (separated by 2 wk) every 24 wk **B (IV):** Matching placebo
Supporting/dose finding Phase II study				
WA21493	R, PB, PC, PG, IFN, DF for 24 wk followed by 72 wk OCR (dosed every 24 wk); variable treatment-free period Randomized 1:1:1:1	RRMS according to McDonald criteria 2005 Prior to screening: ≥2 relapses in 3 y, with 1 relapse in the year before screening	220 A: 55 B: 55 C: 54 D: 54	**4 arms:** **A (IV):** OCR 2,000 mg (1 dose); OCR 1,000 mg (3 doses)[b] **B (IV):** OCR 600 mg (4 doses)[c] **C (IV):** Placebo (1 dose); OCR 600 mg (3 doses)[d] **D (IM):** IFN 30 μg; OCR 600 mg (3 doses)[e]
WA21493	OLE period of WA21493 (dosed every 24 wk)	From WA21493 (see row above)	103 A: 19 B: 31 C: 29 D: 24	**All patients:** OCR 600 mg

[a]Dose 1: 2 × ocrelizumab 300-mg IV infusions separated by 2 weeks, subsequently 1 × ocrelizumab 600-mg IV infusion every 24 weeks.
[b]Dose 1: 2 × ocrelizumab 1,000-mg IV infusions separated by 2 weeks; Dose 2: 1 × ocrelizumab 1,000-mg IV infusion and 1 × placebo IV infusion separated by 2 weeks; Doses 3 and 4: 1 × ocrelizumab 1,000-mg IV infusion until preferred dose of 600 mg chosen following primary analysis after which point all patients were dosed with 1 × ocrelizumab 600-mg IV infusion.
[c]Dose 1: 2 × ocrelizumab 300-mg IV infusions separated by 2 weeks; Dose 2: 1 × ocrelizumab 600-mg IV infusion and 1 × placebo IV infusion separated by 2 weeks; Doses 3 and 4: 1 × ocrelizumab 600-mg IV infusion.
[d]Dose 1: 2 × placebo IV infusions separated by 2 weeks; Dose 2: 2 × ocrelizumab 300-mg IV infusions separated by 2 weeks; Doses 3 and 4: 1 × ocrelizumab 600-mg IV infusion.
[e]Dose period 1: 30 μg IFN every week; Dose 2: 2 × ocrelizumab 300-mg IV infusions separated by 2 weeks; Doses 3 and 4: 1 × ocrelizumab 600-mg IV infusion.
DB, double-blind; DD, double-dummy; DF, dose-finding; EDSS, Expanded Disability Status Scale; IFN, interferon; IM, intramuscular; IV, intravenous; MS, multiple sclerosis; OCR, ocrelizumab; OLE, open-label extension; PB, partially blind; PC, placebo-controlled; PG, parallel-group; PPMS, primary progressive multiple sclerosis; R, randomized; RMS, relapsing multiple sclerosis; RRMS, relapsing–remitting multiple sclerosis; SC, subcutaneous; SPMS, secondary progressive multiple sclerosis; WA21092, OPERA I; WA21093, OPERA II; WA25046, ORATORIO

methylprednisolone infusion on days 1, 15 and 169; 30 (±10) minutes after completion of the ocrelizumab infusion on days 1 and 15; on days 29, 57, 85, 113 and 141; and also at the withdrawal visit in case of early withdrawal. During the open-label extension (OLE) period, PK samples were collected prior to each infusion.

In the OPERA I and II studies, patients with RMS were randomized to receive either 44 μg interferon β-1a by subcutaneous injection or 600 mg ocrelizumab IV (2 × 300 mg on days 1 and 15; 600 mg infusions thereafter at weeks 24, 48 and 72) followed by the OLE period with 600 mg ocrelizumab IV every 24 weeks. Blood samples for

ocrelizumab PK assessment were taken predose prior to the methylprednisolone infusion at weeks 1, 24, 48, and 72; 30 (±10) minutes after completion of the infusion at week 72; on days 84 and 96; and also at the withdrawal visit in case of early withdrawal. Blood samples for measurement of B cells were collected predose, at week 2, week 12, and every 6 months just before the start of the next ocrelizumab infusion.

In ORATORIO, patients with PPMS were randomized 2:1 to receive ocrelizumab 600 mg IV (300 mg on days 1 and 15) or placebo every 24 weeks. Patients continued to receive 600 mg doses of ocrelizumab (as 2 × 300 mg infusions 14 days apart) every 24 weeks until the last enrolled patient completed at least 120 weeks of study treatment and the planned total number of 253 confirmed disability progression events had been reached. Patients received a median of 7 doses of ocrelizumab during the double-blind study period.[6] Blood samples for PK assessment were drawn predose before methylprednisolone on days 1 and 15; every 6 months at weeks 24, 48, 72 and 96 just before the ocrelizumab infusion; 30 minutes after completion of the ocrelizumab infusion on days 1 and 15 and week 72; at weeks 12, 84 and 120; and on the withdrawal visit in case of early withdrawal. After week 120, samples were drawn preinfusion before the next ocrelizumab dose. Blood samples for measurement of B cells were collected predose, at week 2, week 12, and every 6 months prior to the next ocrelizumab infusion.

2.2 | Measurement of ocrelizumab serum concentration

Ocrelizumab concentration in serum samples was measured with a validated enzyme-linked immunosorbent assay with a lower limit of quantitation of 250 ng/mL.

2.3 | Measurement of B cells in blood

B-cell count in blood was used as the pharmacodynamic (PD) marker. Because ocrelizumab binds to CD20, its presence in blood interferes with a CD20 B-cell count through interaction with the CD20 surface antigen. Therefore, **CD19** was used as another B-cell surface marker that largely mirrors CD20 expression during B-cell development. The percentages and absolute counts of B, T and natural killer cells were determined using the BD Multitest 6-colour TBNK reagents and BD Trucount tubes (Becton Dickinson, CA, USA). These allow cell staining with fluorochrome-labelled antibodies which identify T cells (CD3, CD4 and CD8), B cells (CD19), and natural killer cells (CD16 and CD56). Cells were then assessed by flow cytometry using a FACS Canto II cytometer (Becton Dickinson, CA, USA). Although no formal lower limit of quantitation is defined for this assay, Roche internal data and literature[19] suggested accuracy for B-cell counts at ≥5 cells/μL and therefore this cut-off was used for the presented analysis.

2.4 | Population PK model

The population PK analysis was conducted via nonlinear, mixed-effects modelling using NONMEM software version 7.3.0 (ICON Development Solutions, MD, USA). The first-order conditional estimation method was used with the INTERACTION option (FOCEI). Computer resources included personal computers with Intel processors, Windows 7 Professional operating system and Intel Visual Fortran Professional Compiler (Version 11.0). All pre- and post-processing was performed using R version 3.1.3 for Windows (R project, http://www.r-project.org/).

Data from the Phase II study, OPERA I and OPERA II were used for model development.

Previous studies have shown that mAbs targeting B cells, such as **rituximab** and **obinutuzumab**, exhibit time-dependent clearance, possibly reflecting the decreasing number of target B cells over time with treatment.[20,21] Similarly, a 2-compartment model with time-dependent clearance accurately described the ocrelizumab PK. In addition, 3-compartment models (a mammillary model as well as a catenary model, where the third compartment was exchanging drug with the peripheral compartment) were also tested in the current analysis in an attempt to avoid the use of time-dependent clearance. During model development, all interindividual error terms were described by log-normal distributions, while the combined additive and proportional terms, as well as the exponential model (implemented as an additive error model in the log-transformed concentration scale), were tested for the residual error model.

Model refinement was driven by data and was based on goodness-of-fit indicators, including various diagnostic and simulation-based predictive checks (visual predictive check and normalized prediction distribution errors) plots. All parameter estimates were reported with a measure of estimation uncertainty (asymptotic standard error and 95% confidence interval [CI]). Potential covariate–parameter relationships were identified based on scientific interest, biological plausibility, exploratory analysis and exploratory graphics. The covariates investigated included body weight, age, sex, race and ethnicity, and baseline B-cell count. They were simultaneously included in the *full* model using a multiplicative expression for covariates (using normalized power models for continuous covariates). Inferences regarding covariate effects and their clinical relevance were based on the resulting parameter estimates and measures of estimation precision. Small effects (<10%) that were precisely estimated (CI within 15%) were excluded to arrive at a parsimonious model. For the data derived from the study in patients with PPMS, model diagnostics (using the same goodness-of-fit and simulation-based predictive check plots) and post-hoc estimation of the individual parameters were performed without a change in the model.

Individual concentration–time courses were simulated for all patients using individual PK parameters estimated from the model and nominal dosing. Predicted individual exposure measures (peak concentration, trough concentration, cumulative area under the concentration–time curve [AUC] and AUC over the dosing interval

[AUC_τ]) were computed and summarized for each 24-week period, overall and stratified by covariates. C_{mean} was calculated as the ratio of cumulative AUC up to the time of the last dose plus 24 weeks and duration of time from baseline until the last dose plus 24 weeks. For patients who received all planned doses, this corresponded to the C_{mean} over the entire treatment period of 96 weeks in the RMS study. In the PPMS study, the total treatment duration varied due to the event-driven design of the study.

2.5 | Analysis of the exposure–PD response relationship

Graphical analysis was performed to assess the relationship between measured blood B-cell counts, used as the PD marker of drug action, and C_{mean} ocrelizumab as the exposure metric for all patients with RMS and PPMS. Patients were divided into 4 categories according to the C_{mean} quartiles. The proportion of patients with a B-cell count of ≤5 cells/μL in each category was plotted over time and compared.

2.6 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[22]

3 | RESULTS

3.1 | Population PK analysis

The PK data set consisted of 4901 quantifiable serum samples from 941 patients who received ocrelizumab (Phase II study: 1182 samples from 159 patients; OPERA I: 1866 samples from 393 patients; OPERA II: 1853 samples from 389 patients). The PPMS data consisted of 4340 serum samples from 482 patients enrolled in the Phase III ORATORIO study. In addition, 739 (13%) and 424 (9%) samples in RMS and PPMS data, respectively, were below lower limit of quantitation, which was expected, as trough samples were taken approx. 24 weeks after the ocrelizumab infusion. These samples were not included in model development. Attempts to include below lower limit of quantitation observations at the final stage and re-run the final model were not successful.[23]

Mean (standard deviation [SD]) body weight for RMS was 74.8 kg (17.9) and 72.4 kg (17.2) in the PPMS study. Mean (SD) age was 37.3 years (9.17) for patients with RMS and 44.6 years (7.85) for patients with PPMS. Mean (SD) B-cell count at baseline was 0.245×10^9/L (0.136) for patients with RMS and 0.232×10^9/L (0.148) for patients with PPMS.

The summary of model development is presented in Table 2. The concentration–time course of ocrelizumab in patients with RMS was accurately described (see goodness-of-fit, stratified visual predictive check, and normalized prediction distribution error plots in Figures S1–S3) by a 2-compartment model with time-dependent clearance. Total clearance was estimated as the sum of constant clearance and time-dependent clearance, which declined exponentially with time on treatment. Estimated time-independent PK parameters were typical for an immunoglobulin G1 mAb (Table 3).

For a reference patient (female, 75 kg, baseline B-cell count 0.225×10^9/L), ocrelizumab time-independent clearance and central volume were estimated at 0.17 L/d (95% CI: 0.166–0.174) and 2.78 L (95% CI: 2.71–2.85), respectively. Initial time-dependent clearance was estimated at 0.0489 L/d (95% CI: 0.0464–0.0514), comprising 20% of the total initial clearance, and declined with a half-life of 33 weeks. The estimated terminal half-life of ocrelizumab was 26 days.

Body weight was identified as the main covariate (Table 4). Peak concentration values were estimated to be 19% higher for patients weighing <60 kg and 13% lower for patients weighing >90 kg when compared with the 60–90 kg group. AUC_τ was estimated to be 26% higher for patients weighing <60 kg and 21% lower for patients weighing >90 kg when compared with the 60–90 kg group. Higher clearance was also identified in patients with a higher B-cell count at baseline (<7% increase at the 97.5th percentile), and central volume was higher (<12% increase) in males *vs* females.

All model parameters were estimated precisely (relative standard error <14%) and interindividual variability was low (coefficient of variation [CV] ≤35%, except for intercompartmental clearance [Q], for which CV was 50%).

The model developed based on the RMS data also accurately described ocrelizumab concentrations as well as effects of covariates in patients with PPMS (Figures S4–S6), thus, re-estimation of PK parameters and covariate effects was not performed for the PPMS data.

Ocrelizumab PK was independent of age and renal and hepatic function within the given data set, based on comparison of estimated PK parameters for these patients.

Only 1% of the population tested positive for treatment-emergent anti-drug antibodies during the controlled treatment period (3 patients in the RMS Phase III studies, 9 patients in the PPMS trial). Upon visual inspection, their PK data were comparable to anti-drug antibody-negative patients and therefore remained in the data set; no formal covariate testing was performed due to the small numbers.

Ethnicity and race had no impact on PK; the vast majority of patients was, however, categorized as White.

Since body weight was identified as the most relevant covariate, the obtained PK parameters from the 600-mg dose were used to simulate a body weight-based dosing regimen for the RMS and PPMS patient population. Table 5 shows that the dosing regimen equivalent to 600 mg but administered as a mg-per-kg-body-weight dose, i.e. 8 mg/kg, is predicted to result overall in slightly lower exposure compared to the 600-mg flat dose.

TABLE 2 Summary of NONMEM runs for relapsing multiple sclerosis model development

Run	Description	OFV	ΔNpar	Comment
Base model development				
101	Two-compartment linear model, etas to all parameters, combined (additive + proportional) error model	11 488.52	-	Additive residual error negligible
102	As 101, but exponential residual error (additive in log transformed variables)	−3040.53	−1	Accepted
112	As 102, but 3-comp model	−4425.20	+2	
111	As 102, but catenary 3-comp model	−4511.37	+2	
103	As 102 + time-dependent clearance (CLt = CL_{T0}*exp(−kdes*t)), τ (CL_{T0}), and separate CL_{T02} for study 21493 Part 2	−5126.21	+4	Accepted
104	As 103 + WT (CL_{inf};V_1;CL_{T0}) + WT(Q;V_2-fixed)	−5512.31	+3	Accepted
105	As 104 but eta(V_2) = 0	−5512.05	−1	Accepted
106	As 105 + correlation of CL_{inf} and V_1	−5587.68	+1	Accepted
107	As 106 + residual error for TAD < 1	−5595.39	+1	Final base model
108	As 107 but error for TAD < 1 fixed to 15%	−5584.73	−1	Reject
109	As 106 but additive + proportional error model, non-transformed variables	8684.93	+1	Reject
Covariate model development				
130	As 107 + CL_{inf} and V_1(SEX; Ethn; race) + CL_{inf} (BCD19) + WT (V_2; Q) + CL_{T0}(SEX; BCD19)	−5659.05	+11	Full model
131	As 130, but no CL_{inf} (SEX; Ethn; race) and CL_{T0}(SEX)	−5655.03	−4	Accepted
132	As 131, but no V_1 (Ethn; race); fixed Q (WT)	−5648.59	−3	Accepted
133	As 132, but no CL_{T0}(BCD19)	−5649.01	−1	Final covariate model
134	As 133, but no CL_{inf} (BCD19)	−5634.50	−1	Rejected
135	As 133, but no V_1(SEX)	−5614.89	−1	Rejected

ΔNpar, = additional number of estimated parameters compared with a reference model; CL_{inf}, constant clearance; CL_t, time-dependent clearance (L/day); CL_{T0}, initial time-dependent clearance (at time 0); CL_{T02}, initial time-dependent clearance at the start of OLE for Phase II study following partial B-cell recovery (time was reset to zero); NONMEM, nonlinear mixed-effect modeling software; OFV, NONMEM objective function value; Q, intercompartmental clearance; TAD, time after dose (days); V1, central volume; V2, peripheral volume.

3.2 | Analysis of the exposure–PD response relationship

3.2.1 | B-cell depletion and repletion during ocrelizumab treatment

Treatment with ocrelizumab led to rapid depletion of CD19-positive B cells in blood (14 days post-infusion, the first time point of assessment), and B-cell depletion was sustained for the duration of treatment for the majority (96%) of patients. B-cell repletion was defined as reaching the lower limit of the normal range (LLN) for B cells in blood, or the patient's respective baseline measurement if this was lower than the LLN. Only up to 4% of patients on ocrelizumab treatment showed B-cell repletion between the ocrelizumab doses given every 6 months. Indeed, the dosing interval of 6 months had been selected based on very few patients repleting B cells between doses, as observed in previous studies with ocrelizumab in patients with rheumatoid arthritis, to ensure in general continuous depletion of peripheral blood B cells throughout treatment.

Differences in B-cell depletion/repletion were observed across exposure quartiles for the proportion of patients achieving B-cell depletion in blood of ≤5 cells/μL (which is considered the cut-off for assay accuracy for B-cell count in blood[19]) at the assessed time points. The initial decrease in B cells was larger and the proportion of patients with a return of B cells before the next treatment lower in higher C_{mean} quartiles compared with the lower quartiles. Figure 1 shows the fraction of patients with RMS and PPMS with blood B-cell levels of ≤5 cells/μL over time by C_{mean} quartiles. Although all patients presented with extensive B-cell depletion in blood after treatment with ocrelizumab, this analysis showed more pronounced B-cell depletion in patients with higher exposure, and improved B-cell depletion over time with continued treatment. More than 90% of all patients with RMS or PPMS in the 2 top exposure quartiles achieved blood B-cell levels of ≤5 cells/μL by 96 weeks, whereas in the lowest exposure quartile <70% of all patients were in this category at week 96.

3.2.2 | B-cell repletion after discontinuation of ocrelizumab treatment

Time to repletion after treatment discontinuation could not be assessed from the pivotal studies as the majority of patients elected

TABLE 3 Parameter estimates of the population pharmacokinetic model in patients with relapsing multiple sclerosis

Parameter		Estimate	RSE	95% CI		
CL_{inf} (L/d)	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/d)	θ4	0.294	7.46	0.251–0.337		
κ_{des} (y^{-1})	θ5	1.11	5.95	0.979–1.24		
CL_{T0} (L/d)	θ6	0.0489	2.62	0.0464–0.0514		
CL_{T02} (L/d)	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		
$VL_{inf,BCD19}$[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%	31.3%
ω^2_{Q}	Ω(3,3)	0.239	8.91	0.197–0.281	CV = 48.9%	53.3%
ω^2_{CLT0}	Ω(4,4)	0.125	12.3	0.095–0.156	CV = 35.4%	47.2%
$\sigma^2_{TAD \leq 1}$	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 with the rest of the patients.
[c]Power coefficient of the power function with the reference value of 0.225×10^9/L.
%RSE, relative standard error; σ^2, sigma^2, residual variance; ω^2, omega^2, interindividual variance; CI, confidence interval; CL_{inf}, constant clearance; CL_{T0}, initial time-dependent clearance (at time 0); CL_{T02}, initial time-dependent clearance at the start of OLE for Phase II study following partial B-cell recovery (time was reset to zero); CV, coefficient of variation computed as 100% multiplied by the square root of the variance; NA, not applicable; OLE, open-label extension; Q, intercompartmental clearance; R, correlation coefficient; RSE, 100·SE/PE, where PE is parameter estimate; SE, standard error; TAD, time after dose (days); V_1, central volume; V_2, peripheral volume

to continue receiving treatment with ocrelizumab in the OLE. However, repletion data from the Phase II study show that, following the final infusion of 600 mg ocrelizumab, median time to B-cell repletion was 72 weeks (range 27–175), with LLN defined as 80 cells/μL. Sensitivity analyses of different LLN definitions showed median repletion times between 53 (LLN = 40 cell/μL, range 27–145) and 86 (LLN = 107 cells/μL, range 27–222) weeks. In 90% of patients B-cell levels returned to above the LLN (80 cells/μL) or baseline measurement (whichever was lower) by approximately 120 weeks (2.5 y) after the last infusion.

4 | DISCUSSION

The concentration–time course of ocrelizumab in patients with RMS was accurately described by a 2-compartment PK model with time-dependent clearance. The model was also able to accurately predict the PK of ocrelizumab in patients with PPMS.

The presence of a time-dependent clearance component is probably due to target-mediated drug disposition (TMDD). Clearance of ocrelizumab is mediated in part by its therapeutic target, CD20-positive B cells. As treatment continues and B cells are depleted, the contribution of TMDD to the overall clearance is reduced. Following a longer interruption in treatment, as was the case between the main treatment phase and the OLE in the Phase II study, partial restoration of B cells is observed; this is accompanied by a corresponding partial restoration of the time-dependent clearance, adding further evidence to the TMDD hypothesis. Population PK models developed to describe the PK of other anti-CD20 agents, such as obinutuzumab and rituximab, have shown that clearance of these molecules similarly consists of both time-dependent and time-independent components.[21,24,25] With the data presented here, the time-dependent clearance component accounted for approximately 20% of the total initial clearance. All estimated time-independent PK parameters were typical for an immunoglobulin G1 mAb.[26]

TABLE 4 Covariate effects for the population pharmacokinetic model in patients with relapsing multiple sclerosis

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]Values of the continuous covariates represent 2.5th and 97.5th percentiles of the values in the analysis data set.
CI, confidence interval; CL_{inf}, constant clearance; CL_{T0}, time-dependent clearance; Q, intercompartmental clearance; RMS, relapsing multiple sclerosis; V_1, central volume; V_2, peripheral volume

TABLE 5 Simulated exposure (C_{mean}) distribution for flat *vs* body weight-based dose

	C_{mean} (μg/mL)			
Dosing regimen	Mean	Median	5th percentile	95th percentile
600 mg	19.3	18.9	11.8	28.1
8 mg/kg	18.2	18.1	12.6	24.6

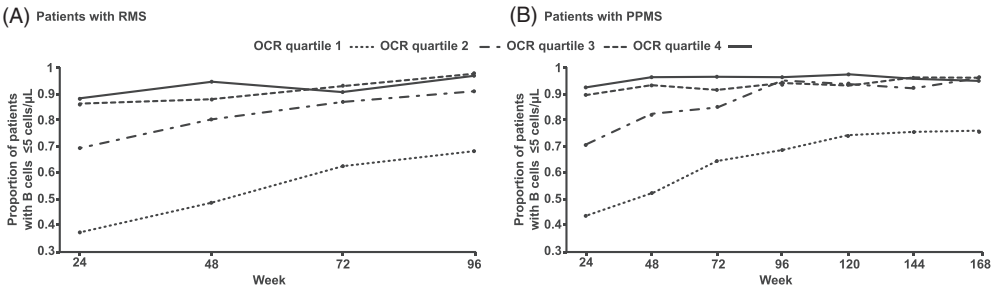

FIGURE 1 Proportion of: (A) patients with RMS (WA21092 and WA21093); and (B) patients with PPMS (WA25046) with a B-cell count of ≤5 cells/μL in blood by ocrelizumab C_{mean} exposure quartiles over time. In patients with RMS, C_{mean} quartile ranges (μg/mL) were: Q1: Min–15.38; Q2: 15.38–18.72; Q3: 18.72–22.17; Q4: 22.17–max, and median (range) body weights (kg) were: Q1: 89 (49–170); Q2: 79 (49–123); Q3: 67 (46–108); Q4: 60 (38–97). In patients with PPMS, C_{mean} quartile ranges (μg/mL) were: Q1: Min–15.83; Q2: 15.83–18.92; Q3: 18.92–23.15; Q4: 23.15–max, and median (range) body weights (kg) were: Q1: 84 (46–136); Q2: 74 (46–125); Q3: 68 (46–115); Q4: 56 (40–93). C_{mean}, mean concentration over time; OCR, ocrelizumab; PPMS, primary progressive multiple sclerosis; Q, quartile; RMS, relapsing multiple sclerosis

In the Phase III ORATORIO trial, patients with PPMS received the 600-mg ocrelizumab dose as 2 infusions of 300 mg 14 days apart throughout the study. The dosing regimen evaluated in the Phase III trials in MS had been chosen based on PK, PD, immunogenicity, safety and efficacy data obtained with ocrelizumab in prior rheumatoid arthritis studies and the Phase II study in patients with RRMS.[27] In the Phase III studies OPERA I and OPERA II in patients with RMS and the ORATORIO study in patients with PPMS, overall ocrelizumab exposure (AUC) was identical with the single-infusion (600 mg) and the split-infusion (2 × 300 mg) regimens. The observed B-cell depletion in blood, the pattern of only <4% patients with B-cell repletion between ocrelizumab doses administered every 6 months, and the PK–PD correlation was comparable in the RMS and PPMS trials, independent of the dosing regimen used. This indicated that there appears to be no benefit to administering ocrelizumab as double infusions after the first dose. The first dose is, however, maintained as

2 × 300-mg infusions given 2 weeks apart, intended to possibly reduce the risk for infusion-related reactions which occur most frequently upon the first ocrelizumab administration. A harmonized dosing regimen (with the first 600-mg dose always given as 2 × 300-mg infusions, and subsequent doses as single 600-mg infusions) has been approved by all health authorities for all patients with RMS and PPMS. No dose adjustment was considered necessary to account for the identified covariate effects.

Treatment with ocrelizumab 600 mg led to rapid and near-complete depletion of B cells in blood, which was sustained throughout treatment for the vast majority of patients. More patients in the 2 highest quartiles of ocrelizumab exposure had B-cell levels ≤5 cells/μL when compared with the lowest quartile. B-cell depletion in the lower exposure groups increased over time with further subsequent ocrelizumab dose administrations. These data indicate that the 600 mg every 24 weeks ocrelizumab dosing regimen achieves generally near-complete B-cell depletion overall, but patients in the highest exposure quartile had the lowest blood B-cell count. Several doses of ocrelizumab treatment may be required to achieve deeper depletion of B cells in blood and other body compartments over time, as only a minority of B cells are located in the blood, while the vast majority of B cells resides in tissues. There is no established specific blood B-cell depletion target, and it is unclear to what extent efficacy tracks with levels of B cells in blood. The relationship between B-cell depletion achieved with ocrelizumab in blood and in extravascular tissue compartments is also unknown. Further assessment is required to better understand any potential relationship between B-cell levels in blood and efficacy parameters. In addition, while the relationship of B-cell levels in blood based on exposure is informative at the population level in a highly harmonized clinical trial setting, individual patients' B-cell measurement can be variable at different time-points depending on the applied assay, and thus lacks sensitivity to inform treatment decisions.

Body weight was identified as the main covariate, and therefore PK simulations explored a body weight-based dosing regimen of 8 mg/kg *vs* the approved flat dose of 600 mg. Overall lower exposure was predicted with 8 mg/kg *vs* the 600-mg dose for the given patient population. Therefore, this body weight-based dosing approach would not add value, as exposure tended to be slightly lower, while a correlation of higher exposure with more complete B-cell depletion was observed. In addition, a body weight-based dosing regimen would add complexity for individual preparation of the infusion *vs* the approved flat dose of 600 mg for all patients.

In conclusion, the PK of ocrelizumab at the approved dose of 600 mg every 6 months was described with PK parameters typical for an immunoglobulin G1 monoclonal antibody, with body weight as the main covariate. PK simulations showed that a body weight-based dosing regimen is, however, not expected to add value compared to the approved 600-mg dosing regimen. The PK and B-cell depletion in blood were comparable across the RMS and PPMS trials, with the highest degree of blood B-cell depletion observed in patients with the highest ocrelizumab exposure.

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Ekaterina Gibiansky is a paid consultant for F. Hoffmann-La Roche Ltd.

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CONTRIBUTORS

Ekaterina Gibiansky and Yumi Yamamoto: PK analysis; Claire Petry: compilation of data sets, graphical data analyses; Ann Herman: B-cell data analysis; Heidemarie Kletzl, Francois Mercier, Andreas Guenther: planning, supervision and interpretation of PK and PD analyses; Ludwig Kappos, Stephen Hauser: investigators in the clinical studies, MS experts; Qing Wang, Fabian Model: statistical analyses. All authors provided critical input to the data generation and data interpretation of the work presented in this manuscript.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.

clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available at: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see: https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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