CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761238Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology (OCP) Review

Applicant	TG Therapeutics, Inc.
Product (Generic Name)	Ublituximab (TG-1101)
Product (Trade Name)	BRIUMVI® (ublituximab) injection
Link to EDR	\\CDSESUB1\evsprod\BLA761238\0001
BLA Submission	761238 (Sequence 0001)
Dosage Form (Strength)	Intravenous injection (25 mg/mL)
Route of Administration	Intravenous infusion
Proposed Dosing regimen	First and Second Infusions: 150 mg intravenous infusion (First Infusion), followed two weeks later by a 450 mg intravenous infusion (Second Infusion). Subsequent Infusions: 450 mg intravenous infusion every 6 months.
Indication	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.
Submission Date	09/24/2021
OCP Review Team	Anantha Ram Nookala, Ph.D., Vishnu Sharma, Ph.D., Atul Bhattaram, Ph.D., Gopichand Gottipati, Ph.D.
Final Signatory	Mehul Mehta, Ph.D.
OCP Division	Division of Neuropsychiatric Pharmacology (DNP)
OND Division	Division of Neurology II (DN2)

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1. Executive Summary

In this original Biologics License Application (BLA) 761238, the applicant, TG Therapeutics Inc., is seeking approval of Ublituximab for the treatment of relapsing forms of multiple sclerosis (RMS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. Ublituximab (Tradename: BRIUMVI®) is a New Molecular Entity (NME) and is not marketed in the US for any indication. It is a recombinant immunoglobulinG1 chimeric monoclonal antibody (mAb), which is presumed to target the cluster of differentiation (CD) 20 antigen expressed on the surface of pre-B and mature B lymphocytes triggering antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and complement-mediated lysis. Currently, there are two FDA approved (anti-CD20) B-cell targeted mAb therapies, namely ocrelizumab and ofatumumab for the treatment of MS.

The applicant is relying on two identical pivotal, multicenter, randomized, double-blind, active comparator-controlled phase 3 studies (TG1101-RMS301 and TG1101-RMS302) in subjects with RMS. The primary efficacy endpoint, reduction in the annualized relapse rate (ARR) compared to teriflunomide (active comparator), met the prespecified criteria for efficacy in both the studies, following 150 mg administered by intravenous (IV) infusion on Day 1, followed by 450 mg by IV infusion on Day 15. Subsequent infusions are 450 mg IV infusions administered every 6 months. Besides the two phase 3 studies in RMS patients, the applicant conducted a dose-ranging study (TG1101-RMS201) in RMS patients in the current BLA. The applicant also conducted additional studies in chronic lymphocytic leukemia or small lymphocytic lymphoma and filed under BLA 761207 with Division of Cancer Pharmacology I, but it was ultimately withdrawn.

The primary focus of this review is to evaluate (1) the appropriateness of the dosing regimen in the general population and (2) the need for dose optimization based on extrinsic and intrinsic factors.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) team reviewed the information submitted under this BLA 761238 and recommends approval of Ublituximab for the treatment of RMS in adults.

Key review issues with specific recommendations and comments are summarized below:

Review Issues	Recommendations and Comments
Pivotal evidence of effectiveness	The evidence of effectiveness for ublituximab for the treatment of RMS in adults is from two pivotal Phase 3, randomized, multicenter, double-blind, double-dummy, active-controlled studies (TG1101-RMS301 and TG1101-RMS302). The primary efficacy end point, reduction in ARR, met the prespecified statistical criteria. An additional Phase 2 placebo-controlled, dose-finding study in subjects with RMS provided supportive evidence.
General dosing instructions	The dosing regimen is 150 mg administered by IV infusion over 4 hours on Day 1, followed by 450 mg by IV infusion over 1 hour on Day 15. Subsequent infusions are 450 mg IV infusions over 1 hour administered every 6 months.
Dosing in patient groups (intrinsic and extrinsic factors)	No dose adjustments are needed based on age, race, sex, bodyweight, renal or hepatic impairment, food-intake or metabolic/transporter mediated interactions.
Bridge between the "to-be-marketed" and clinical trial formulations	The applicant conducted analytical comparability studies to establish a bridge between to-be-marketed product and the pivotal clinical trial formulation. The Office of Biotechnology Products (OBP) team confirmed that the two products are analytically comparable, and therefore, the scientific bridge is acceptable.

1.2 Post marketing requirements and commitments

A post-marketing study is required to meet the clinical pharmacology requirements of this application as indicated below.

1. **Evaluation of Neutralizing Antibodies**
   The original neutralizing antibody assay was not sensitive enough to detect low level of positive control in the presence of high concentrations of ublituximab. In communication by the sponsor dated 09/30/2022, the sponsor agreed to develop a neutralization assay and submit a full validation report of the newly developed

neutralization assay, re-analyze neutralizing antibody in patients enrolled in the pivotal clinical studies (TG1101-RMS301 and TG1101-RMS302), and evaluate the potential impact on the pharmacokinetics, pharmacodynamics, safety, and efficacy of Ublituximab.

2. Summary of Clinical Pharmacology Assessment

2.1 Pharmacology and Clinical Pharmacokinetics

Mechanism of Action

Ublituximab is a recombinant, glycoengineered mAb and the exact mechanism by which it exerts therapeutic effects in RMS is not known. It is presumed to target the CD20 antigen expressed on the surface of pre-B and mature B lymphocytes. Following cell surface binding to B lymphocytes, ublituximab triggers antibody-dependent cellular cytolysis, antibody-dependent cellular phagocytosis, and complement-mediated lysis resulting in the depletion of B cells.

Absorption

Since ublituximab is administered by IV infusion, absorption is not relevant.

Distribution

The volume of distribution of ublituximab is 3.2 liters.

Metabolism and excretion

Ublituximab is expected to be degraded to small peptides and amino acids via catabolic pathways in the same manner as endogenous IgGs. Monoclonal antibodies typically do not undergo metabolism by the cytochrome P450 system and unlikely to be affected by drug transporters; therefore, no drug interaction studies were conducted with ublituximab.

The mean clearance of ublituximab is 11.2 L/h and the mean terminal half-life was approximately 22 days.

Age, Race, Sex, and Weight

The covariate effects of age, race, sex, and weight are unlikely to be clinically relevant (please refer to Appendix 4.3 for further details). Therefore, no dose adjustments are recommended for ublituximab based on these covariates.

Specific Populations:

Patients with Renal or Hepatic Impairment

Generally, the IgG monoclonal antibodies undergo elimination via intracellular catabolism and therefore, hepatic impairment is not expected to significantly impact the disposition of ublituximab. Furthermore, renal elimination of monoclonal antibodies is generally considered low. Therefore, applicant did not conduct any dedicated studies to evaluate the impact of renal or hepatic impairment on the PK of ublituximab. There was no clinically relevant change in pharmacokinetics observed in patients with mild renal impairment, or in patients with mild hepatic impairment based on data from phase 3 studies. The impact

of renal or hepatic impairment is unlikely to be clinically relevant and therefore, no dose adjustments are recommended for ublituximab based on renal or hepatic impairment.

Immunogenicity:

Overall, the final immunogenicity database consisted of 534 subjects from two Phase 3 clinical studies (TG1101-RMS301 and TG1101-RMS302; shown in **Table *1***) from which anti-ublituximab antibody (ADA) results were available. Of these subjects, treatment-emergent ADAs (TE-ADAs) were detected in 434 subjects (81.3%). Clinical samples for potential neutralizing activity were characterized in 434 TE-ADA positive subjects and neutralizing antibodies (NAbs) were detected in 34 subjects (7.83%). However, the presence of TE-ADAs did not have a clinically meaningful impact on ublituximab exposure, percent change in B-lymphocytes from baseline, and efficacy. The assay used to measure NAbs is subject to interference from serum ublituximab, possibly resulting in an underestimation of the incidence of NAb formation. Due to the limitation of the assay conditions, the potential clinical impact of NAb to ublituximab is not known. Please refer to Appendix 4.2 and Office of Biotechnology Products review for additional details on immunogenicity assessments.

2.2 Dosing and Therapeutic Individualization

2.2.1 General Dosing

The general dosing regimen is 150 mg diluted in 250 mL of 0.9% sodium chloride administered as IV infusion over 4 hours on Day 1, followed by 450 mg diluted in 250 mL of 0.9% sodium chloride administered as IV infusion over 1 hour on Day 15. Subsequent infusions are 450 mg IV infusions over 1 hour administered every 6 months. The dosing regimen is identical to that evaluated in pivotal efficacy/safety studies in RMS subjects.

2.2.2 Therapeutic individualization

No therapeutic individualization is necessary for extrinsic/intrinsic factors. Ublituximab is administered by intravenous route, and therefore, food-drug interactions are not anticipated. In addition, its drug-drug interaction liability is considered low (See Section 2.1). No dedicated clinical studies were performed in subjects with renal or hepatic impairment; however, renal or hepatic impairment is not expected to impact the pharmacokinetics of ublituximab. Therefore, no dose adjustment is warranted in patients with hepatic or renal impairment.

2.3 Outstanding Issues

None

2.4 Summary of Labeling Recommendations

The applicant's labeling recommendations are generally acceptable.

3. Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

Ublituximab is supplied at a concentration of 25 mg/mL (150 mg/6 mL) in a single-use glass vial as a sterile, clear to opalescent, colorless to slightly yellow solution for dilution with 0.9% sodium chloride prior to intravenous infusion. Ublituximab is a IgG1 mAb that has 2 glycosylated heavy and light chains with 16 correctly paired disulfide bonds. The exact mechanism of action of ublituximab is unknown but is presumed to involve targeting the CD20 receptor expressed on the surface of pre-B and mature-B lymphocytes to trigger antibody-dependent cellular cytolysis, antibody dependent cellular phagocytosis and complement-mediated lysis.

Currently, there are several FDA approved disease-modifying therapies for the treatment of RMS consisting of small molecules (teriflunomide, monomethyl fumarate, dimethyl fumarate, fingolimod, siponimod, ponesimod, ozanimod, mitoxantrone and cladribine) and large molecules such as mAbs and small proteins (interferon beta-1a and interferon beta-1b, and glatiramer acetate). The approved mAbs include B-cell targeting therapies (ocrelizumab and ofatumumab) and T-cell targeting therapies (natalizumab and alemtuzumab).

In a Type C meeting held on 16 June 2020, the agency indicated that the use of a population pharmacokinetic approach to support labeling regarding drug-demographic and drug-disease interactions seemed reasonable and levels of anti-drug antibodies should be evaluated in the Phase 3 pivotal trials. Special protocol assessment agreement letters for the pivotal Phase 3 trials were issued by the FDA on 19 October 2020. A Type B pre-BLA meeting was held with FDA on 06 April 2021 to discuss the efficacy and safety data from Studies TG1101-RMS301 and TG1101-RMS302 that would support the BLA of ublituximab for the treatment of adult patients with RMS.

3.2 General Pharmacology and Pharmacokinetic Properties

A summary of pharmacology and PK characteristics of ublituximab are summarized in the table below.

Pharmacology	
Mechanism of Action	Ulituximab is a recombinant chimeric glycoengineered mAb. The exact mechanism by which ublituximab exerts therapeutic effects in MS is not completely understood. It is presumed to affect immunomodulation by binding to the CD20 receptors expressed on the surface of pre-B and mature B lymphocytes triggering antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and complement-mediated lysis. This process depletes circulating CD20 expressing B cells.
General Information	
Dose Proportionality	The exposure of ublituximab increased in a dose proportional manner over the dose range of 150-600 mg in subjects with RMS.
Accumulation	After repeated dosing with dosing regimen as indicated in section 1.1, the Cmax ratio at Week 48 to Week 24 was 1, indicative of minimal accumulation.
Immunogenicity	Anti-drug antibodies were evaluated in serum using Electrochemiluminescent Immunoassay validated at [redacted] (b) (4) From the two Phase 3 studies, TE-ADAs were detected in 81.3% subjects (434 out of 534) at one or more time points in either study, of which 7.83% (34 out of 434) subjects tested positive for NAbs. No clinically significant differences in the pharmacokinetics, efficacy, or safety profile of ublituximab were observed in patients who tested positive for TE-ADA.
Absorption	
Tmax	At the end of infusion
Distribution	

Volume of distribution	3.2 L
Elimination	
Terminal Elimination Half-life	The mean terminal half-life is 22 days.
Metabolism/Excretion	Monoclonal antibodies are not known to be metabolized by the cytochrome P450 system or affected by drug transporters. As a human IgG1 monoclonal antibody, ublituximab is expected to be degraded to small peptides and amino acids by ubiquitous proteolytic enzymes in the same manner as endogenous IgG.

3.3 Clinical Pharmacology Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The primary evidence of effectiveness is based on two randomized, multicenter, double-blind, double-dummy, active comparator-controlled Phase 3 studies, TG1101-301 and TG1101-302, in subjects with relapsing multiple sclerosis (RMS). The study design features are summarized in **Table *1*** below. The primary efficacy endpoint, the annualized relapse rate (shown in **Table *2***) met the prespecified statistical criteria compared with teriflunomide (active comparator) at week 96 in both the studies. Please refer to the statistical review by Drs John P Lawrence and Xiang Ling and clinical efficacy review by Drs. Laura Baldassari and Paul Lee for additional details statistical/safety/efficacy analyses of the pivotal phase 3 data.

Table 1:Overview of Study Design for Phase 3 Studies (TG1101-RMS301 and TG1101-RMS302)

Study ID	TG1101-RMS301 and TG1101-RMS302
Primary Endpoint	Annualized Relapse Rate
Study Design	A phase 3, randomized, multicenter, double-blinded, double-dummy, active-controlled study with 3 periods: 1. Screening (4 weeks) 2. Treatment Period (96 weeks) 3. Follow-Up (20 weeks)
Study Treatments	Ublituximab – 150 mg Day 1, 450 mg on Day 15, Week 24, 48, 72, and 96 Teriflunomide – 14 mg QD from Week 1 Day 1 until the last day of Week 95
No. of Randomized patients with at least one dose and one baseline and post-baseline efficacy assessment (n)	TG1101-RMS301 – ublituximab: 271; teriflunomide: 274 TG1101-RMS302 – ublituximab: 272; teriflunomide: 272
Key Inclusion Criteria	≥ 2 relapses in prior 2 years or 1 relapse in the year prior to screening and /or ≥ Gadolinium enhancing lesion Documented MRI of brain with abnormalities consistent with MS Expanded Disability Status Scale 0.5-5 (inclusive) at screening
Treatment Duration	120 weeks double blind

Source: Adapted from CSR TG1101-RMS301, Page 32-35 and 56, and TG1101-RMS302, Page 32-35 and 57

Table 2: Annualized Relapse Rate in Study TG1101-301 and 302 (mITT population)

	TG1101-RMS301		TG1101-RMS302	
	Ublituximab (N=271)	Teriflunomide (N=274)	Ublituximab (N=272)	Teriflunomide (N=272)
Duration of treatment (years)				
Mean (SD)	1.7 (0.37)	1.8 (0.31)	1.8 (0.20)	1.7 (0.37)
Cumulative treatment time (subject years)	464.52	479.44	485.90	465.70
Number of IRAP confirmed relapses during treatment				
Mean (SD)	0.162 (0.4507)	0.405 (0.8166)	0.195 (0.5848)	0.375 (0.7334)
Cumulative number of IRAP confirmed relapses	44	111	53	102
Raw annualized relapse rate	0.09	0.23	0.11	0.22
Least squares means (95% CI)	0.076 (0.042, 0.138)	0.188 (0.124, 0.283)	0.091 (0.049, 0.169)	0.178 (0.109, 0.291)
Rate ratio: ublituximab / teriflunomide	0.406 (0.268, 0.615)		0.509 (0.330, 0.784)	
Difference: ublituximab - teriflunomide	-0.111 (-0.166, -0.056)		-0.087 (-0.148, -0.027)	
p value	<0.0001		0.0022	

Source: CSR Study TG1101-RMS301, Table 20 (page 74) and CSR Study TG1101-RMS302, Table 20 (page 75)

3.3.2 Is the proposed dosing regimen appropriate for the general population for which the indication is being sought?

Yes. The proposed general dose and dosing regimen for the proposed indication in RMS is appropriate.

The applicant conducted the pivotal phase 3 trials with a fixed dosing regimen of 450 mg every 6 months, following a first dose of 150 mg on day 1 and second dose of 450 mg on day 15, and weeks 24, 48, 72, and 96. The dose was selected based on a phase 2 dose ranging study (TG1101-RMS201). The applicant assessed maintenance dose of 450 and 600 mg ublituximab doses and various infusion durations (1, 1.5, and 3 hours) in patients with RMS. No significant differences in the primary efficacy variable (responder rate of B-cell depletion at Week 4) and safety events in the 450 and 600 mg dose cohorts following the initial 150 mg dose were reported. Based on these results, the applicant selected 450 mg dose for the pivotal phase 3 trials in RMS patients. The B-cell reductions were sustained pre-dose at Week 24 and at Week 48; therefore, a dosing interval of 24 weeks was selected in the phase 3 trial.

The most common adverse events reported from phase 3 trials include infusion reactions, respiratory tract infections, Herpes virus-associated infections, and pain in extremities. Please refer the clinical review by Drs. Rui Li, Laura Baldassari, and Paul Lee for more details.

In conclusion, the ublituximab dosing regimen as indicated in section 1.1 is approvable from clinical pharmacology perspective.

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

No. Dose adjustment is not necessary based on the intrinsic factors such as bodyweight, age, race, sex, renal or hepatic impairment and extrinsic factor such as food-intake or drug-interactions as described below. Population pharmacokinetic analysis was conducted on data from 591 subjects to evaluate the impact of intrinsic and extrinsic factors.

Body Weight

Body weight was identified to be a statistically significant predictor of ublituximab clearance and volume of distribution; increase in the body weight decreased ublituximab exposures at steady state. Applicant has quantified these changes i.e. up to 24% increase and 22% decrease in PK exposures ($C_{max,ss}$, $C_{min,ss}$ and AUC_{ss}) for 5th percentile (50 kg) and 95th percentile (111 kg) of weight distribution, respectively as compared to a 73 kg typical subject based on the final population PK model. The changes in ublituximab exposure based on body weight are not expected to be clinically relevant. Additionally, it

should be noted that only fixed doses of ublituximab were administered in all the clinical studies. Therefore, no dose adjustment is warranted based on bodyweight.

Sex

PK data of 351 females and 204 males dosed with ublituximab were compared and the median PK parameters in males were lower than in females. However, based on the magnitude of the impact at the steady state (C_{max}, C_{min} and AUC were within 20% of the typical values), sex is unlikely to be clinically relevant covariate. Therefore, no dose adjustment is needed based on sex.

Renal impairment

No dedicated renal impairment studies were conducted. Based on the population pharmacokinetic analysis, the mean predicted exposures for mild renal impairment patients (n=101) at steady state were increased by 17% and 19% for Cmax,ss and Cavg,ss, respectively compared to normal renal function patients. In general, renal elimination of monoclonal antibodies is considered low, and given the minimal impact on exposures, no dose adjustment is recommended based on renal impairment.

Hepatic impairment

No dedicated hepatic impairment studies were conducted. Based on the population pharmacokinetic analysis, the mean predicted exposures at steady state for mild hepatic impairment patients (n=19) were comparable to normal hepatic function patients. The PK data from moderate hepatic impairment patients was limited (n=3) to draw meaningful conclusions. In general, hepatic elimination of monoclonal antibodies is considered low and given the minimal impact on exposures, no dose adjustment is recommended based on hepatic impairment.

Immunogenicity

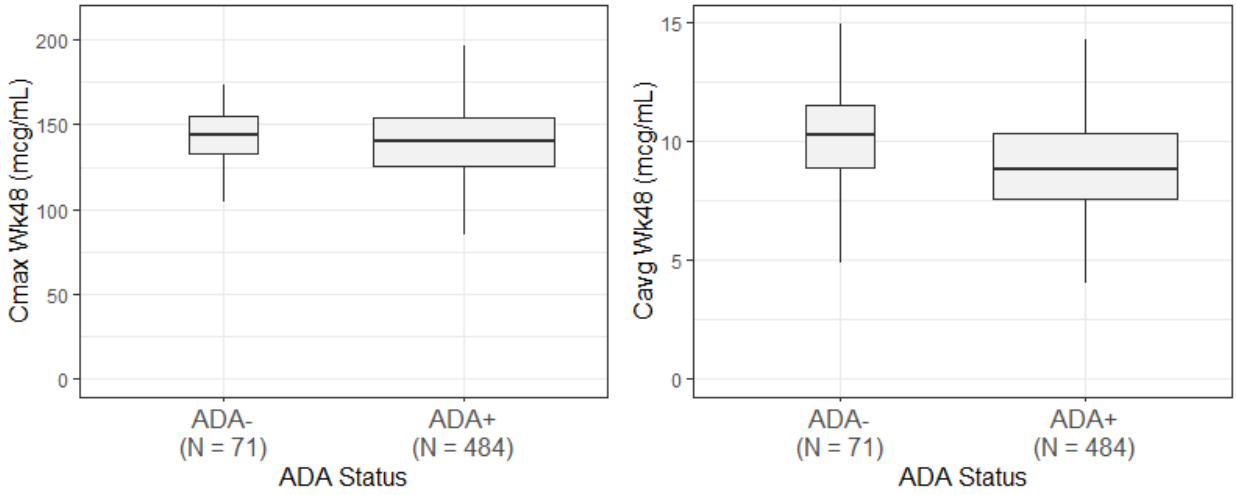
The clinical immunogenicity database for ublituximab includes results from three clinical studies comprising of a total of 574 evaluable subjects: 40 subjects from TG1101-RMS201 and 534 subjects from combined phase 3 studies (TG1101-RMS301 and TG1101-RMS302). It should be noted that only the subjects from phase 3 studies were included for evaluating the effect of immunogenicity on PD (mean percent change in B-lymphocytes from baseline), safety, and efficacy.

a. Effect of Immunogenicity on Ublituximab PK

The impact of TE-ADA status on ublituximab C_{max} and C_{avg} is shown **Figure *1***. The mean C_{trough} and C_{avg} values at week 48 were approximately 16% and 7.6% lower, respectively in TE-ADA positive subjects compared to TE-ADA negative subjects. The C_{max} values at week 48 were unchanged in TE-ADA positive subjects compared to TE-ADA negative

subjects. These findings suggest that the effect of TE-ADA on ublituximab PK is not expected to be clinically relevant.

Figure 1:Effect of TE-ADA status on PK



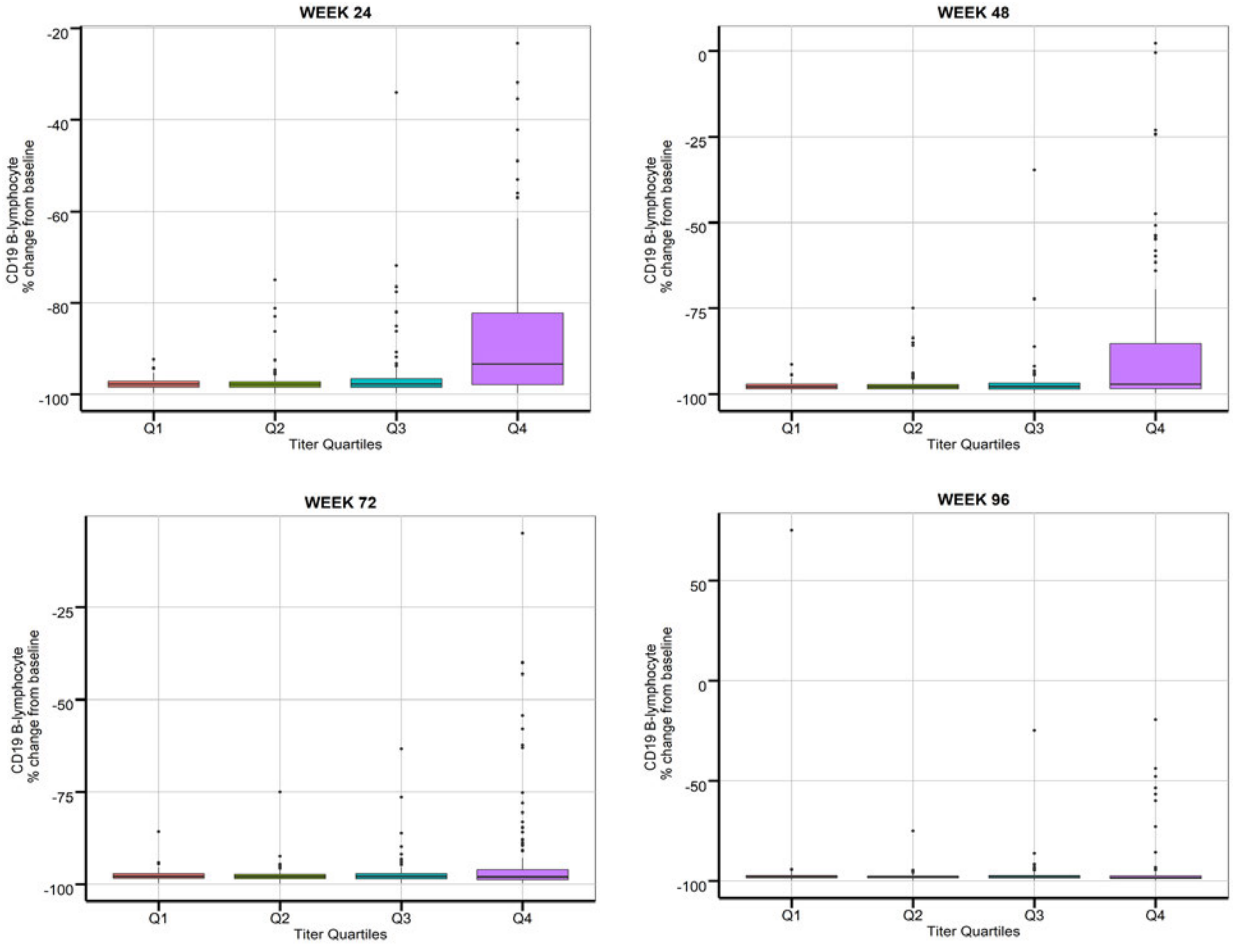
Source: Reviewer's independent analysis

b. Effect of Immunogenicity on Ublituximab PD

The impact of ADA status on PD (mean percent change in B-lymphocytes from baseline) was evaluated at 24, 48, 72 and 96 weeks as shown in **Table *3***. The results suggest that there were no significant differences in the percent B-lymphocyte count from baseline in TE-ADA positive subjects compared to TE-ADA negative subjects. Further correlation analyses at 24, 48, 72 and 96 weeks was conducted by dividing the TE-ADA positive subjects into 4 quartiles based on TE-ADA-titer values as shown in **Figure *2***. The results indicated that percent change in B-lymphocyte count from baseline was similar across all the quartiles at all the weeks, except for week 24 where the percent change in B-lymphocyte count from baseline was lower in TE-ADA-titer quartile 4. However, this change is not expected to be clinically relevant as there is no change in the primary efficacy endpoint (ARR) compared to other TE-ADA-titer quartiles. The assay used to measure NAbs is subject to interference from serum ublituximab, possibly resulting in an

underestimation of the incidence of NAb formation. Due to the limitation of the assay conditions, the potential clinical impact of NAb on ublituximab PD is not known.

Figure 2: Effect of TE-ADA status by quartiles on CD19 B-lymphocytes at week 24, 48, 72, and 96



Source: Reviewer's independent analysis

Table 3: B-lymphocyte Count (%) Decrease from Baseline by Post-baseline TE-ADA Status

Endpoint	TE-ADA Positive (n)	TE-ADA Negative (n)
Mean Percent Change B-Lymphocyte from Baseline at Week 24	-88.1 (423)	-90.2 (94)
Mean Percent Change B-Lymphocyte from Baseline at Week 48	-88.1 (415)	-90.1 (93)
Mean Percent Change B-Lymphocyte from Baseline at Week 72	-89.6 (410)	-90.6 (91)
Mean Percent Change B-Lymphocyte from Baseline at Week 96	-89.3 (396)	-89.7 (83)

Source: Adapted from Applicant Integrated Summary of Immunogenicity, Pg 126-132

c. Effect of Immunogenicity on Ublituximab Efficacy

The impact of ADA status on primary efficacy endpoint (ARR) was evaluated at week 96 and the results are summarized in ***Table 4***. The mean ARR in TE-ADA positive subjects was comparable to TE-ADA negative subjects. Further analyses were conducted by dividing the ADA positive subjects into 4 quartiles based on ADA-titer values (***Table 4***). There were no clinically relevant differences in the ARR in any of the TE-ADA-titer quartiles.

Table 4: Effect of Immunogenicity on Annualized Relapse Rate by Post-baseline TE-ADA Status

Endpoint	TE-ADA Positive (n)	TE-ADA Negative (n)
Mean Annualized Relapse Rate (ARR)	0.10 (434)	0.12 (100)
Titer Q1	0.18 (108)	N/A

Titer Q2	0.09 (109)	N/A
Titer Q3	0.08 (108)	N/A
Titer Q4	0.05 (109)	N/A

Source: Adapted from Applicant Integrated Summary of Immunogenicity, Pg-16

d. Effect of Immunogenicity on Ublituximab Safety

Incidence of treatment emergent adverse events and adverse events of special interest were similar in TE-ADA positive subjects compared to TE-ADA negative subjects. As no clinically relevant differences were noted, further analysis evaluating the impact of immunogenicity on ublituximab safety were not conducted.

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

Since ublituxmab is administered by intravenous infusion, food-drug interactions are not anticipated.

Ublituximab is a monoclonal antibody and is not a cytokine modulator, therefore it is unlikely to influence drug metabolizing enzymes/transporters. Therefore, no drug-drug or transporter-drug interaction studies were conducted in-vitro or in-vivo.

3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support approval of the to-be marketed formulation?

Yes. The applicant used two different concentrations of the ublituximab drug product (10 and 25 mg/mL) in the phase 3 trials while the concentration of the to-be-marketed formulation is 25 mg/mL. Both the drug product concentrations contained (b) (4) sodium citrate, (b) (4) sodium chloride, and (b) (4) polysorbate 80, pH 6.5. Since both the drug products were diluted in 0.9% sodium chloride before use and the other components remained the same, both the drug products were considered comparable. Please refer to the OBP review by Drs Xiaoshi Wang, and Yan Wang, and clinical efficacy review by Drs. Drs. Laura Baldassari and Paul Lee for additional details on the different drug product concentrations.

4 APPENDICES

4.1 Summary of Bioanalytical Method Validation

For the determination of plasma ublituximab concentrations, the applicant used a ligand binding electrochemiluminescent immunoassay (ECLIA) method. Briefly, anti-ublituximab polyclonal antibody was immobilized on a meso scale discovery plate to capture ublituximab present in the serum. Bound ublituximab was detected by an anti-ublituximab antibody that is labeled with ruthenium. Electrodes within the plates were stimulated resulting in emission of an Electrochemiluminescent signal from the ruthenium label, which is proportional to the amount of ublituximab that is bound by the capture antibody. This method was developed and validated (b) (4)
The ELISA method was validated in compliance with the standards set forth in the 2018 FDA Bioanalytical Method Validation guidance. Summary of the validation parameters is presented in the table below:

Table 5:Summary of Assay Validation Report

Analyte	TG-1101 (Ublituximab)
Source and Lot of Reagents	Ublituximab drug product, TG Therapeutics, Inc., Lot AJ0106 25 mg/mL
Biological Matrix	Human serum
Minimum Required Dilution	1:100
LLOQ	15.63 ng/mL
ULOQ	2000 ng/mL
MQC	187.5 ng/mL
Cumulative Accuracy (%Bias) of Standards	-2.10% - 1.90%
Cumulative Precision (%CV) of Standards	1.62% - 2.83%
Cumulative Inter-Assay Accuracy (%RE)	-8.71% - 13.95%
Intra-Batch Precision (%CV)	4.21 – 11.54
Hook Effect	No prozone/hook effect was observed; the dilutions with nominal concentrations above the ULOQ quantified greater than the ULOQ. The overall mean concentration across all the dilutions evaluated for the DC (1000- to 25,000-fold) and ULOQ (2- to 50-fold) had a precision of ≤20% CV.
Hemolysis Effect	Precision ≤25% CV and accuracy within ±25% RE of the nominal concentration

Source: Adapted from 1128004 validation report

Reviewer's comments:

The validated assay performance was reviewed for the pivotal phase 3 studies. Accuracy and precision of QC samples were ≤15% (and ≤20% at LLQ), and calibration curves for the LC-MS/MS bioanalytical assay were within acceptable limits.

4.2 Pharmacometrics Assessment: Population PK Analyses

4.2.1 Applicant's Population PK analysis:

Objectives: To update a previously developed pop PK model for ublituximab using data from subjects with RMS enrolled in Studies TG 1101-RMS201, TG1101-RMS301, and TG 1101-RMS302 and to assess the impact of potential covariates, including disease, on the PK of ublituximab.

Data: Pharmacokinetic data of 7485 samples from 895 subjects enrolled in 6 studies (TG 1101-RMS201, TG1101-RMS301, and TG 1101-RMS302, CD20-0703, TGTX-1101-101 and UTX-TGR-304) were used to develop Pop PK models for ublituximab. The baseline covariate characteristics of subjects is provided in the **Table *6***. Out of 859 subjects in the dataset, 591 subjects were subjects with RMS which represents 75% (5624/7485 samples) of the PK data.

Method: Nonlinear mixed effect modeling was used for PK model development using NONMEM v7.4.3 with FOCEI estimation method. The previously developed PopPK model (two-compartment model with linear first-order elimination) was the starting model for base model development using the combined dataset including data from subjects with RMS. Covariate modelling was performed using stepwise covariate model building procedure (p-value of 0.01 and 0.001 for forward and backward step respectively). The relationship of continuous covariates and PK parameter was described with power models; and categorical covariate-PK parameter relationship was described using a power structure with the most common level of the covariate being the reference. Impact of covariates on primary and secondary PK parameters were evaluated using final PK model.

Results: The PK of ublituximab was described by two-compartment model with first-order elimination. Covariates such as weight, and ADA were added on clearance; weight, sex and region were added on the volume of distribution in central compartment. The parameter estimates of the final population PK model for ublituximab are shown in ***Table 7***. The population PK model for ublituximab was assessed with diagnostics plots including goodness-of-fit and visual predictive checks (VPC) (***Figure 3***). Overall, the applicant's population PK model adequately describe the PK data of ublituximab. The effect of the covariates on the simulated steady-state secondary PK parameters i.e. Cmax,ss , Cmin,ss and AUC,ss of ublituximab is shown in ***Figure 4***.

The net multivariate effects of covariates were also assessed by using the final PopPK model to generate posthoc individual ublituximab exposure estimates for subjects in the analysis dataset and stratifying the exposure estimates by subpopulations of interest for

comparison (***Table 8***), which showed that $C_{max,ss}$ and $C_{avg,ss}$ varied by ≤20% between covariate categories for all covariates of interest. Cmin,ss was more variable, varying up to 65% between covariate categories.

Sensitivity analysis: The final pop PK model was re-estimated with the dataset including excluded outliers (15 PK samples, model UMS166) and including RMS subpopulation only (model UMS175). In both cases, similar structural parameters were estimated with similar precisions (***Table 9***), which suggested the robustness of the PK model and its estimated parameters.

Table 6: Summary of Baseline Covariates in the Ublituximab PK Dataset by Study

	TG1101-RMS201 (N=47)	TG1101-RMS301 (N=272)	TG1101-RMS302 (N=272)	Previous Dataset (N=304)	Overall (N=895)
Status					
RMS	47 (100%)	272 (100%)	272 (100%)	0 (0%)	591 (66.0%)
CLL/NHL	0 (0%)	0 (0%)	0 (0%)	304 (100%)	304 (34.0%)
Maximum Dose (mg)					
<150	0 (0%)	0 (0%)	0 (0%)	9 (3.0%)	9 (1.0%)
150	2 (4.3%)	5 (1.8%)	0 (0%)	3 (1.0%)	10 (1.1%)
300	0 (0%)	0 (0%)	0 (0%)	3 (1.0%)	3 (0.3%)
450	15 (31.9%)	267 (98.2%)	272 (100%)	21 (6.9%)	575 (64.2%)
600	30 (63.8%)	0 (0%)	0 (0%)	5 (1.6%)	35 (3.9%)
900	0 (0%)	0 (0%)	0 (0%)	257 (84.5%)	257 (28.7%)
1200	0 (0%)	0 (0%)	0 (0%)	6 (2.0%)	6 (0.7%)
Age (y)					
Mean (SD)	39.1 (9.59)	36.2 (8.41)	34.5 (8.76)	66.0 (9.14)	46.0 (16.9)
Median [Min, Max]	42.0 [20.0, 56.0]	36.0 [18.0, 55.0]	33.0 [18.0, 55.0]	66.0 [39.0, 88.0]	42.0 [18.0, 88.0]
Body weight (kg)					
Mean (SD)	89.3 (22.8)	71.1 (16.7)	70.2 (17.3)	82.5 (19.3)	75.7 (19.2)
Median [Min, Max]	91.0 [54.4, 145]	69.0 [43.0, 135]	67.0 [42.0, 137]	80.2 [45.1, 154]	73.0 [42.0, 154]
Sex					
Male	15 (31.9%)	105 (38.6%)	94 (34.6%)	205 (67.4%)	419 (46.8%)
Female	32 (68.1%)	167 (61.4%)	178 (65.4%)	99 (32.6%)	476 (53.2%)
Race					
White	38 (80.9%)	265 (97.4%)	269 (98.9%)	245 (80.6%)	817 (91.3%)
Black	7 (14.9%)	6 (2.2%)	2 (0.7%)	13 (4.3%)	28 (3.1%)
Other	2 (4.3%)	1 (0.4%)	1 (0.4%)	3 (1.0%)	7 (0.8%)
Missing	0 (0%)	0 (0%)	0 (0%)	43 (14.1%)	43 (4.8%)
Region					
North America/Western Europe	47 (100%)	26 (9.6%)	27 (9.9%)	234 (77.0%)	334 (37.3%)
Eastern Europe	0 (0%)	246 (90.4%)	245 (90.1%)	70 (23.0%)	561 (62.7%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hepatic Function Category					
Normal	44 (93.6%)	246 (90.4%)	238 (87.5%)	238 (78.3%)	766 (85.6%)
Mild	2 (4.3%)	10 (3.7%)	8 (2.9%)	55 (18.1%)	75 (8.4%)
Moderate	1 (2.1%)	1 (0.4%)	2 (0.7%)	7 (2.3%)	11 (1.2%)
Severe	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)	1 (0.1%)
Missing	0 (0%)	15 (5.5%)	24 (8.8%)	3 (1.0%)	42 (4.7%)
Renal Function Category					
Normal	45 (95.7%)	223 (82.0%)	220 (80.9%)	106 (34.9%)	594 (66.4%)
Mild	2 (4. 3%)	49 (18.0%)	52 (19.1%)	140 (46.1%)	243 (27.2%)
Moderate	0 (0%)	0 (0%)	0 (0%)	58 (19.1%)	58 (6.5%)
ADA					
Negative	21 (44.7%)	37 (13.6%)	30 (11.0%)	289 (95.1%)	377 (42.1%)
Positive	26 (55.3%)	235 (86.4%)	242 (89.0%)	15 (4.9%)	518 (57.9%)

Abbreviations: ADA = antidrug antibodies; CLL/NHL = hematological malignancies comprising chronic lymphocytic leukemia and non-Hodgkin's lymphoma; RMS = relapsing forms of multiple sclerosis.

Source: Applicant pop PK report 20 August 2021, Page 48, Table 5-2

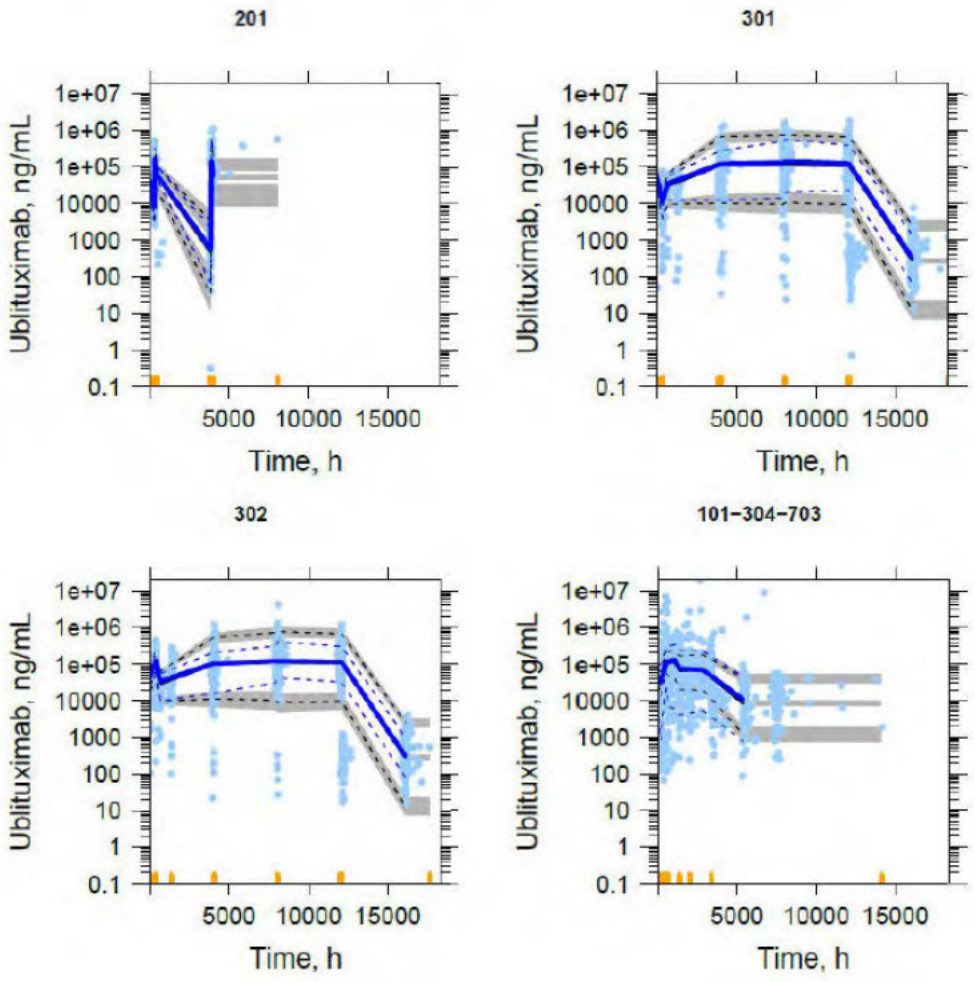
Table 7:Parameter estimates of the final population PK model for ublituximab

Parameter	Estimate	RSE[a] (%)	IIV[b] (CV%)	RSE (%)	Shrinkage[c] (%)
Clearance (CL, mL/h)	11.6	2.91	38.1	11.6	5.32
Volume of central compartment (V_c, L)	3.18	2.40	15.0	18.5	32.6
Inter-compartmental clearance (Q, mL/h)	11.6	10.5			
Volume of peripheral compartment (V_p, L)	3.60	3.55	21.3	27.1	40.0
Fractional change in CL for Study CD20-0703	3.06	17.5			
Fractional change in V_c for Study CD20-0703	1.68	6.25			
Fractional change in CL for Doses < 300 mg due to TMDD	4.89	17.4			
Fractional change in CL at Time > 10000 h (or 417 days)	0.875	0.41			
Effect of ADA on CL	1.14	3.12			
Effect of body weight on CL	0.524	10.8			
Effect of body weight on V_c	0.435	10.9			
Effect of Eastern Europe region on V_c	1.10	2.26			
Effect of female sex on V_c	0.931	1.75			
Covariance of CL and V_c[d]	0.0248	25.4			
Residual error					8.35
Proportional residual error (all studies except CD20-0703 (%)	31.7	2.35			
Proportional residual error – Study CD20-0703 (%)	60.3	6.57			

Abbreviations: CL = clearance; CV% = percent coefficient of variation; ETA = individual-specific random effect; IIV = inter-individual variability; Q = inter-compartmental clearance; RSE = relative standard error; SD = standard deviation; SE = standard error; U2 = ublituximab + umbralisib; V_c = volume of the central compartment; V_p = volume of the peripheral compartment

Source: Applicant pop PK report 20 August 2021, Page 56, Table 5-5

Figure 3: Prediction Corrected Visual Predictive Checks for the Final PK Model by Study



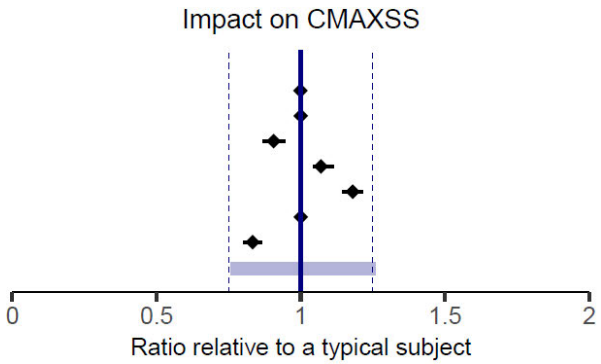
Abbreviations: pcVPC = prediction-corrected visual predictive check; PI = prediction interval; pred-corr = prediction-corrected; PopPK = population pharmacokinetic(s).

Note: The blue dots are prediction-corrected observed concentrations; the blue lines are the 50th (solid), 5th (dashed), and 95th (dashed) percentiles of observed concentrations; and the black lines are the 50th (solid), 5th (dashed), and 95th (dashed) percentiles of simulations. The gray bands are the 95% PIs for the corresponding black lines based on 500 simulations. The short yellow lines indicate bin intervals.

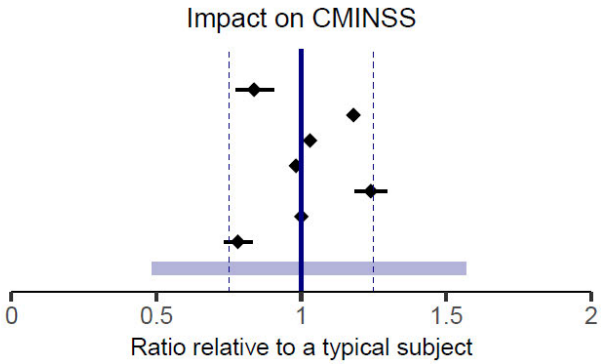
Source: Applicant pop PK report 20 August 2021, Page 59, Figure 5-4

Figure 4: Forest Plot of Covariate Effect in Final PK Model on PK Parameters of ublituximab

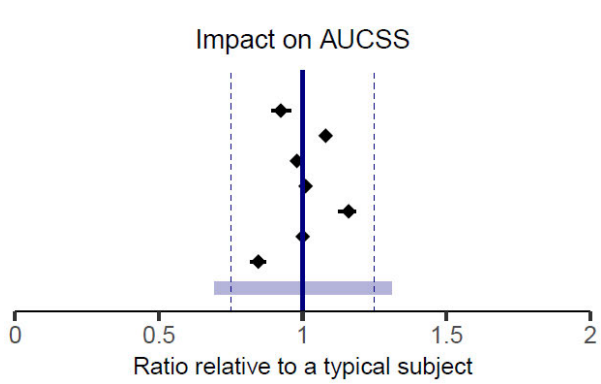
Covariate	Percentile	Value	Ratio [95% CI]
ADA		Positive	0.999 [0.999, 0.999]
Time		>416 days	1 [1, 1]
Region		Eastern Europe	0.906 [0.875, 0.942]
Sex		Female	1.07 [1.05, 1.11]
Weight	5%	50	1.18 [1.15, 1.21]
	50%	73	1 [1, 1]
	95%	111	0.833 [0.807, 0.859]
BSV	90% CI	N/A	1 [0.759, 1.26]



Covariate	Percentile	Value	Ratio [95% CI]
ADA		Positive	0.837 [0.78, 0.901]
Time		>416 days	1.18 [1.17, 1.19]
Region		Eastern Europe	1.03 [1.02, 1.04]
Sex		Female	0.982 [0.974, 0.989]
Weight	5%	50	1.24 [1.19, 1.29]
	50%	73	1 [1, 1]
	95%	111	0.781 [0.739, 0.826]
BSV	90% CI	N/A	1 [0.484, 1.57]



Covariate	Percentile	Value	Ratio [95% CI]
ADA		Positive	0.924 [0.896, 0.954]
Time		>416 days	1.08 [1.08, 1.08]
Region		Eastern Europe	0.98 [0.973, 0.988]
Sex		Female	1.01 [1.01, 1.02]
Weight	5%	50	1.16 [1.13, 1.18]
	50%	73	1 [1, 1]
	95%	111	0.846 [0.825, 0.865]
BSV	90% CI	N/A	1 [0.695, 1.31]



Source: Applicant pop PK report 20 August 2021, Page 60, Figure 5-5

Table 8: Summary of Model-Predicted Steady-State Ublituximab Exposures Stratified by Covariates of Interest

Covariate	Category	N	$C_{min,ss}$ (µg/mL)	$C_{min,ss}$ ratio	$C_{max,ss}$ (µg/mL)	$C_{max,ss}$ ratio	$C_{avg,ss}$ (µg/mL)	$C_{avg,ss}$ ratio
All		555	0.139 (0.127, 0.154)		139 (137, 141)		8.94 (8.73, 9.14)	
Weight	< 80 kg	401	0.164 (0.148, 0.181)	0.559	147 (145, 149)	0.823	9.51 (9.29, 9.73)	0.799
	≥80 kg	154	0.0917 (0.0736, 0.114)		121 (118, 123)		7.6 (7.25, 7.97)	
Age	<35y	273	0.156 (0.136, 0.178)	0.801	141 (138, 143)	0.979	9.13 (8.85, 9.43)	0.958
	≥35y	282	0.125 (0.109, 0.144)		138 (135, 140)		8.75 (8.47, 9.04)	
Sex	M	204	0.123 (0.103, 0.146)	1.22	125 (123, 128)	1.18	8.16 (7.86, 8.46)	1.15
	F	351	0.15 (0.134, 0.168)		148 (146, 150)		9.42 (9.16, 9.69)	
Race	White	542	0.142 (0.129, 0.156)	0.463	139 (137, 141)	1.04	8.95 (8.75, 9.15)	0.943
	All Others	13	0.0657 (0.0235, 0.184)		145 (133, 157)		8.44 (6.42, 11.1)	
Region	Nth Am/WEu	68	0.114 (0.0833, 0.156)	1.25	141 (136, 147)	0.986	8.69 (8.04, 9.39)	1.03
	EEu	487	0.143 (0.13, 0.159)		139 (137, 141)		8.97 (8.76, 9.19)	
ADA	Negative	71	0.211 (0.16, 0.277)	0.621	143 (139, 148)	0.972	10.2 (9.57, 10.9)	0.859
	Positive	484	0.131 (0.118, 0.145)		139 (137, 140)		8.76 (8.55, 8.97)	
WBC	< 7	398	0.147 (0.131, 0.164)	0.837	140 (138, 142)	0.979	9.07 (8.84, 9.3)	0.948
	≥ 7	157	0.123 (0.101, 0.149)		137 (134, 141)		8.6 (8.19, 9.04)	
Platelet Count	< 211	170	0.153 (0.13, 0.18)	0.876	137 (134, 140)	1.02	9.08 (8.73, 9.45)	0.977
	≥ 211	385	0.134 (0.119, 0.151)		140 (138, 142)		8.87 (8.63, 9.12)	
Hemoglobin	< 134	199	0.16 (0.138, 0.185)	0.806	146 (144, 149)	0.925	9.52 (9.19, 9.86)	0.907
	≥ 134	356	0.129 (0.114, 0.147)		135 (133, 137)		8.63 (8.38, 8.88)	
Renal Impairment	Normal	454	0.127 (0.114, 0.142)	1.65	135 (134, 137)	1.17	8.65 (8.44, 8.87)	1.19
	Mild	101	0.209 (0.171, 0.256)		158 (154, 161)		10.3 (9.86, 10.8)	
Hepatic Impairment	Normal	494	0.142 (0.128, 0.156)	0.678	139 (137, 141)	1.02	8.95 (8.74, 9.16)	0.962
	Mild	19	0.0963 (0.0325, 0.286)		142 (130, 155)		8.61 (7.02, 10.6)	
	Moderate	3	0.134 (0.0369, 0.49)	0.559	127 (109, 148)	0.823	8.59 (7.33, 10.1)	0.799

Abbreviations: Cat = category; N = number of subjects.
Values are geometric mean (90% confidence interval). Ratios are geometric mean ratio.

Source: Applicant pop PK report 20 August 2021, Page 63, Table 5-7

Table 9:Parameter Estimates of the Final Ublituximab PopPK Model for All Data (Run UMS166) and RMS Subpopulations (Run UMS175)

	Final Model (Run UMS165)			Final Model with All Data (Run UMS 166)		Final Model – RMS Subjects Only (Run UMS175)	
Parameter	**Estimate**	**RSE[a] (%)**	**95% CI**	**Estimate**	**RSE (%)**	**Estimate**	**RSE (%)**
Clearance (CL, mL/h)	11.6	2.91	11.0, 12.3	11.5	2.99	11.2	2.86
Volume of central compartment (V_c, L)	3.18	2.40	3.03, 3.33	3.24	2.24	3.13	2.43
Inter-compartmental clearance (Q, mL/h)	11.6	10.5	9.23, 14.0	9.82	7.47	12.3	9.06
Volume of peripheral compartment (V_p, L)	3.60	3.55	3.35, 3.85	3.40	2.60	3.62	2.71
Fractional change in CL for Study CD20-0703	3.06	17.5	2.01, 4.12	3.02	19.8	-	-
Fractional change in V_c for Study CD20-0703	1.68	6.25	1.47, 1.88	1.58	7.45	-	-
Fractional change in CL for Doses < 300 mg due to TMDD	4.89	17.4	3.22, 6.55	5.44	17.1	-	-
Fractional change in CL at Time > 10000 h (or 417 days)	0.875	0.41	0.868, 0.882	0.872	0.42	0.877	0.39
Effect of ADA on CL	1.14	3.12	1.07, 1.21	1.13	3.73	1.14	3.06
Effect of body weight on CL	0.524	10.8	0.413, 0.635	0.477	15.3	0.499	10.9
Effect of body weight on V_c	0.435	10.9	0.341, 0.528	0.392	13.2	0.407	12.6
Effect of Eastern Europe region on V_c	1.10	2.26	1.05, 1.15	1.09	2.37	1.11	2.52
Effect of female sex on V_c	0.931	1.75	0.899, 0.963	0.928	1.75	0.926	1.71
Interindividual Variability (%)							
CL	38.1	11.6	33.5, 42.2	54.8	12.2	22.2	12.8
V_c	15.0	18.5	12.0, 17.5	20.0	18.6	12.6	20.9
V_p	21.3	27.1	14.6, 26.4	38.6	23.9	18.0	20.0
Covariance of CL and V_c[d]	0.0248	25.4	0.0125, 0.0371	0.0655	20.8	0.0144	24.0
Correlation for CL and V_c	0.434	-	-	0.599	-	0.515	-
Residual error							
Proportional residual error (all studies except CD20-0703 (%)	31.7	2.35	30.2, 33.1	33.7		30.5	2.36
Proportional residual error – Study CD20-0703 (%)	60.3	6.57	52.5, 68.1	59.8		-	-

Abbreviations: - – not estimated; CL = clearance; CV% – percent coefficient of variation; ETA – individual-specific random effect; IIV = inter-individual variability; Q = inter-compartmental clearance; RSE = relative standard error; SD – standard deviation; SE = standard error; U2 = ublituximab + umbralisib; V_c = volume of the central compartment; V_p = volume of the peripheral compartment.

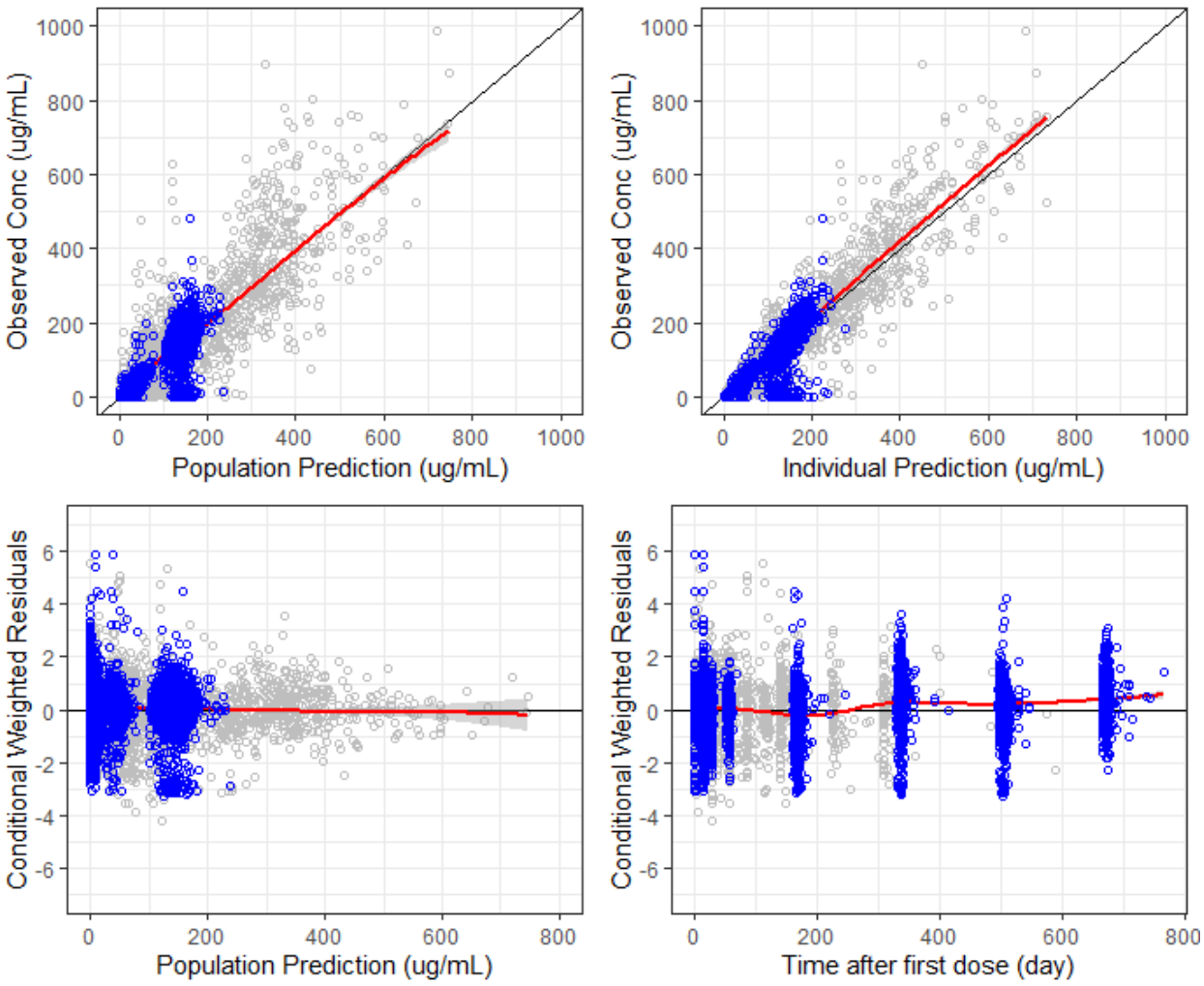
Source: Applicant pop PK report 20 August 2021, Page 127, Table 8-7

4.2.2 Reviewer's Analysis

Sponsor's Pop PK model evaluation

The reviewer was able to run the applicant's final PK model and obtained similar results as reported by the applicant. Model diagnostics for ublituximab are shown in ***Figure 5***.

Figure 5: Goodness-Of-Fit Plots of the Final Population PK Model for Ublituximab



Blue and grey circle represents subjects with RMS and CLL/NHL respectively

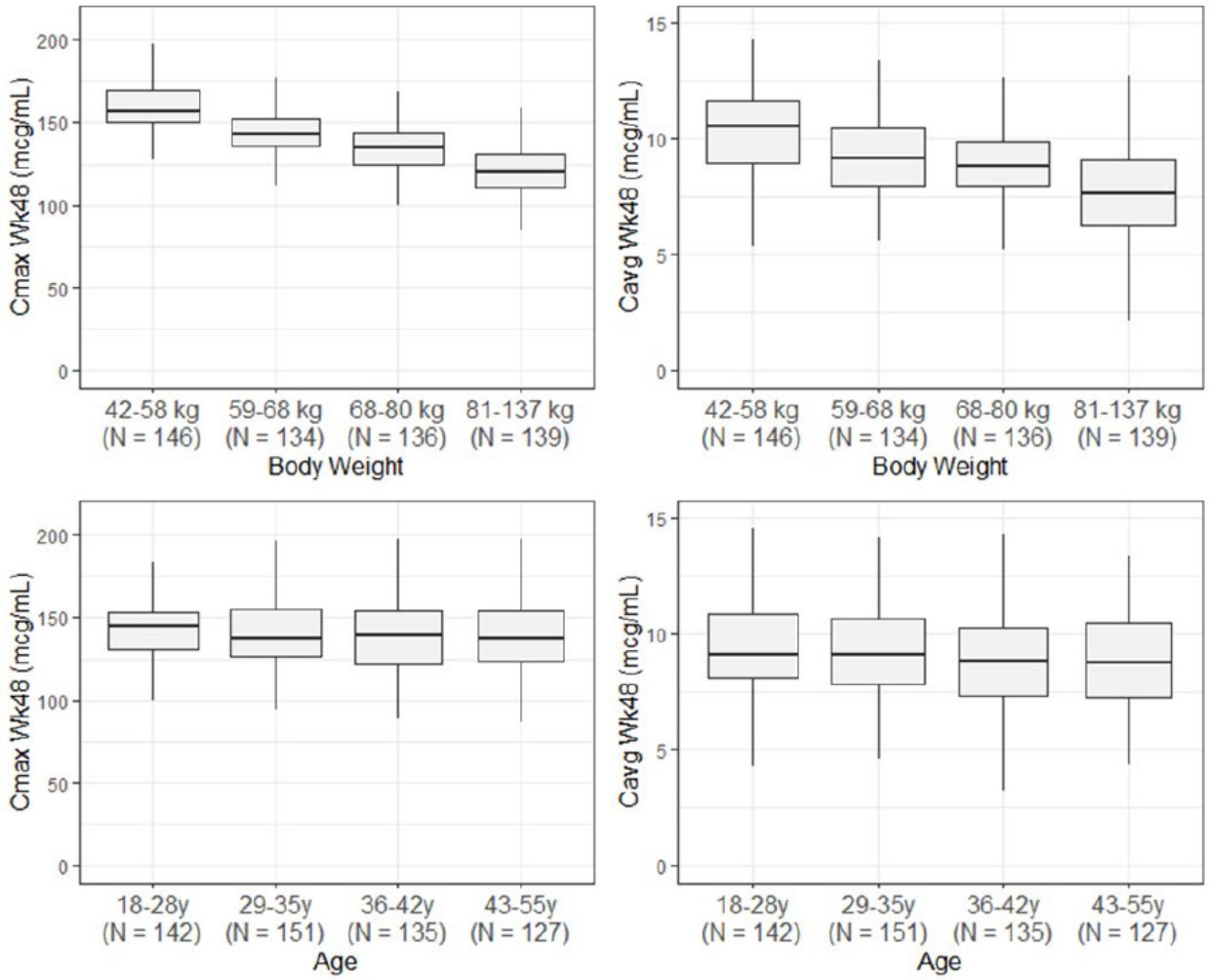
Source: Reviewer's independent analysis

The impact of covariate on PK of ubilitxuimab was evaluated by comparing the PK parameters (Cavg,ss, and Cmax,ss) of ublitixumab across covariate of interest in RMS subjects. These PK parameters were derived from simulated ublituximab concentration-time profiles, based on the final PK model, for RMS subjects [Study 201 (N= 15); Study 301 (N=268); Study 302 (n=272)] following treatment with the reference dosing regimen (450 mg every 24 week).

Body weight effect: Pharmacokinetic data of 555 subjects dosed with ubtlixumab were distributed into quartiles (i.e. first quartile: n=146, 42-58 kg; second quartile: n=134, 59-68 kg; third quartile: n=136, 68-80 kg; and fourth quartile: n=139, 81-137 kg) based on their weight distribution and compared (***Figure 5***). Overall, increase in body weight resulted in lower PK exposure of ubtlixumab. Applicant has quantified these changes i.e. up to 24% increase and 22% decrease in PK exposures ($C_{max,ss}$, $C_{min,ss}$ and AUC_{ss}) for 5^{th} percentile (50 kg) and 95^{th} percentile (111 kg) of weight distribution respectively as compared to the typical values of subjects (***Figure 4***). Of note, the applicant has studied fixed doses in Phase-3 trials.

Age effect: Pharmacokinetic data of 555 subjects dosed with ubtlixumab were distributed into quartiles (i.e. first quartile: n=142, 18-28y; second quartile: n=151, 29-35y; third quartile: n=135, 36-42y; and fourth quartile: n=127, 43-55y) based on their age distribution and compared (***Figure 6***). Overall, PK parameters of all quartiles were similar and thus did not suggest any clinically relevant impact on the PK of ublituximab.

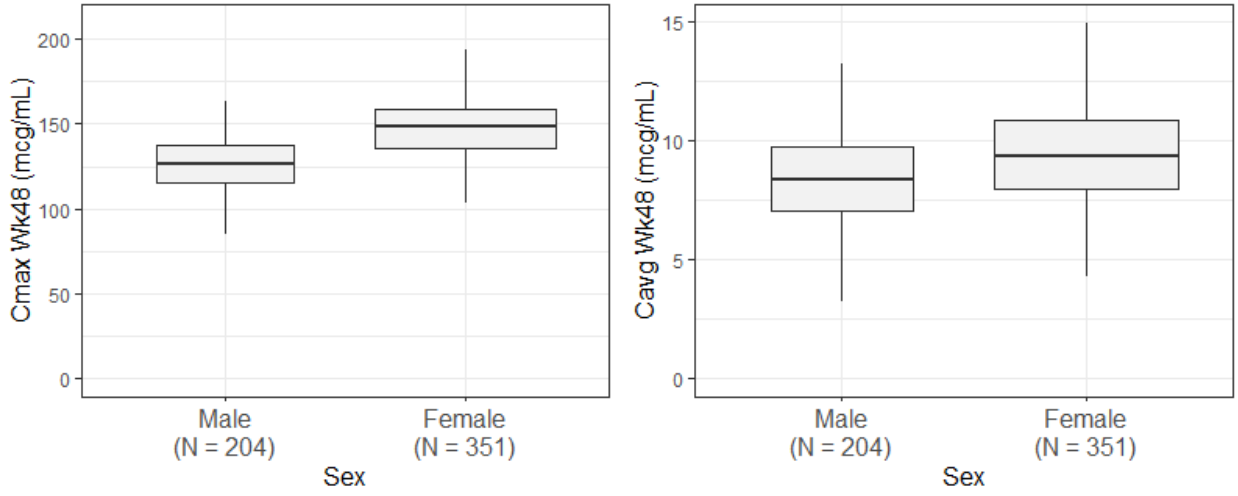
Figure 6: Boxplots of Cmax and Cavg of Ublituximab at Week 48 by Weight Quartiles (Top Row) and Age Quartiles (Bottom Row)



Source: Reviewer's independent analysis

Sex effect: Pharmacokinetic data of 351 females and 204 males dosed with ublituximab were compared and compared (***Figure 7***). Overall, median PK parameters in males were lower than in females. However, the relevant changes in steady-state C_{max}, C_{min} and AUC were within 20% of the typical values (***Figure 4***) and thus did not suggest any clinically relevant impact of gender on the PK of ublituximab.

Figure 7: Boxplots of Cmax and Cavg of Ublituximab at Week 48 by Sex

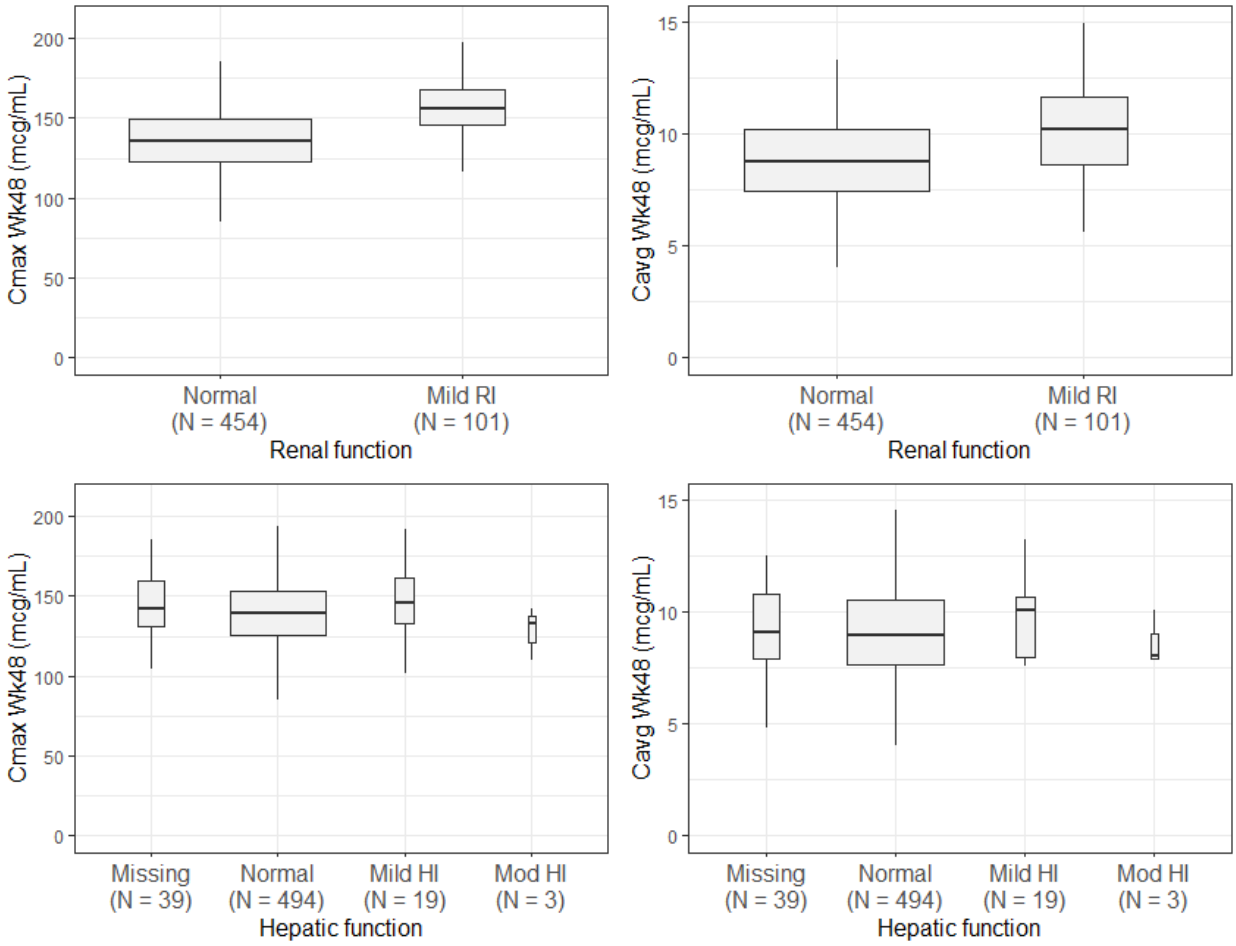


Source: Reviewer's independent analysis

Renal Impairment: Pharmacokinetic data of 454 healthy subjects and 101 subjects with mild renal impairment dosed with ublituximab were compared (***Figure 8***). Overall, subjects with renal impairment have shown <20% increase in Cmax and Cavg as compared to the healthy subjects, and thus did not suggest any clinically relevant impact of mild renal impairment on the PK of ublituximab. Data from subjects with moderate and severe renal impairment was not available.

Hepatic Impairment: Pharmacokinetic data of 494 healthy subjects, 19 subjects with mild hepatic impairment and three subjects with moderate hepatic impairment dosed with ublituximab were compared (***Figure 8***). Overall, PK parameters of healthy subjects and subjects with mild hepatic impairment were similar and thus did not suggest any clinically relevant impact on the PK of ublituximab. Of note, limited data (n=3) was available for subjects with moderate hepatic impairment and no data was available for subjects with severe hepatic impairment.

Figure 8: Boxplots of Cmax and Cavg of Ublituximab at Week 48 by Renal function (Top Row) and Hepatic function (Bottom Row)



Source: Reviewer's independent analysis

Conclusions:

The following population characteristics do not have a clinically meaningful effect on the pharmacokinetics of ublituximab: body weight, sex, age, ADA status, mild renal impairment or mild hepatic impairment.

1. Listing of Analysis Codes and Output Files

File Name	Description	Location
pk_analysis_ublituximab.R tgtubli_rms_exposures_subpop_v3.R	Exploratory PK analysis	\\Reviews\ Ublituximab_BLA761238_VS\Rscripts

2. References

1. Population pharmacokinetic and exposure-response analysis of efficacy and safety of ublituximab in multiple sclerosis, Document# TGTX-PMX-TG 1101-2920-002, 20 Aug 2021

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VENKATESH A BHATTARAM
11/29/2022 12:13:03 PM

SREEDHARAN N SABARINATH
11/29/2022 12:39:09 PM

MEHUL U MEHTA
11/29/2022 06:36:13 PM