CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761149Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY

BLA- 761149 (Enspryng)

CLINICAL PHARMACOLOGY REVIEW

BLA Number	761149
Link to EDR	\\CDSESUB1\evsprod\BLA761149\0001
Submission Date(s)	08/15/19
Submission Type	Type 1- New Molecular Entity (Standard Review)
Brand Name	Enspryng
Generic Name	Satralizumab
Formulation and Strength	Solution for injection (120 mg/mL)
Route of Administration	Subcutaneous injection
Proposed Indication	Neuromyelitis optica spectrum disorders (NMOSD)
Applicant	Genentech, Inc.
Associated IND	IND-118183
Reviewers	Dawei Li, Ph.D., Michael Bewernitz, Ph.D., Manuela Grimstein, Ph.D.
Team Leader	Atul Bhattaram, Ph.D., Yuching Yang, Ph.D., Angela Men, MD., Ph.D.
OCP Division	Division of Neuropsychiatric Pharmacology
Division Director	Mehul Mehta, Ph.D.

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1 Executive Summary

This original Biologics License Application (BLA) 761149 is for Enspryng (satralizumab) subcutaneous injection solution with proposed indication for the treatment of adults (b) (4) with neuromyelitis optica spectrum disorder (NMOSD). Satralizumab has been granted Breakthrough Therapy Designation for treatment of neuromyelitis optica (NMO) and neuromyelitis optica spectrum disorders (NMOSD) by the FDA in December 2018.

Satralizumab is a humanized IgG2 monoclonal antibody (mAb) that specifically binds to soluble and membrane-bound human IL-6 receptor (IL-6R), and thereby prevents IL-6 downstream signaling through these receptors. IL-6 functions have been implicated in the pathogenesis of NMOSD.

The Applicant's proposed dosing regimen is 120 mg subcutaneous (SC) injection at weeks 0, 2, and 4, followed by a maintenance dose of 120 mg SC every 4 weeks.

The efficacy and safety of satralizumab is supported by results from two pivotal Phase 3 clinical trials BN40898 and BN40900 in patients with NMOSD. In study BN40898, treatment with satralizumab reduced the risk of an adjudicated relapse by 62% when administered in combination with immunosuppressive therapy compared to placebo. In study BN40900, treatment with satralizumab led to a 55% reduction in the risk of experiencing an adjudicated relapse compared to placebo. However, the effectiveness of satralizumab treatment in AQP4-IgG seronegative population and pediatric population 12 years of age and older are not supported by the results from these pivotal trials.

The clinical pharmacology review focuses on the appropriateness of the proposed dosing regimen of satralizumab and the impact of immunogenicity on pharmacokinetics (PK), pharmacodynamics (PD), efficacy and safety of satralizumab.

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the information contained in BLA 761149. This BLA is approvable for the treatment of adults with neuromyelitis optica spectrum disorder (NMOSD) from a clinical pharmacology perspective. The key review issues with specific recommendations and comments are summarized below.

Review Issues	Recommendations and Comments
Evidence of effectiveness	Two pivotal Phase 3 trials provide primary evidence.
General dosing instructions	The recommended dose regimen is 120 mg SC injection at weeks 0, 2, and 4, followed by a maintenance dose of 120 mg SC injection every 4 weeks.
Dosing in patient Subgroups (intrinsic and extrinsic factors)	No dose adjustments are needed based on age, race, sex, bodyweight, renal or hepatic impairment, or drug/transporter mediated interactions.
Immunogenicity	ADAs were detected in 52% in NMO and NMOSD patients receiving satralizimab as add-on therapy (BN40898); and 73% in NMO and NMOSD patients receiving monotherapy (BN40900). The development of ADAs was correlated to higher bodyweight, lower satralizimab exposure. The impact of ADA on satralizumab efficacy is inconclusive. Immunogenicity does not have a clinically-relevant impact on safety.

Labeling	Generally acceptable. The review team made recommendations for specific content and formatting changes.

1.2 Post-marketing Requirements

None

2 Summary of Clinical Pharmacology Assessment

2.1 The Pharmacology and Clinical Pharmacokinetics

Mechanism of Action

Satralizumab is a humanized engineered monoclonal antibody that targets soluble and membrane-bound human IL-6 receptor (IL-6R) and thereby prevents IL-6 downstream signaling through these receptors. IL-6 is a pro-inflammatory cytokine with pleiotropic functions, which is potentially involved in the pathophysiology of NMOSD, including production of pathological autoantibodies against Aquaporin-4 (AQP4).

Pharmacokinetics

Following SC administration of satralizumab at the recommended dosing schedule, steady state was achieved at week 8 with the mean Cmin of 19.7 (±12.2) mcg/mL, Cmax of 31.5 (±14.9) mcg/mL and AUC(0-t) of 737 (± 386) mcg.mL/day, respectively. The bioavailability was 85%.

Satralizumab undergoes biphasic distribution, the estimated typical central and peripheral volume of distribution was 3.46 L and 2.07 L, respectively.

The total clearance of satralizumab is described by a linear clearance process operating in parallel with a concentration-dependent elimination process. The linear clearance component is estimated to be 0.0601 L/day. The associated terminal t1/2 is approximately 30 days.

Based on population pharmacokinetic analysis, bodyweight was a significant covariate.

Specific Populations

No formal clinical studies have been conducted to investigate the effect of renal/ hepatic impairment on satralizumab.

Immunogenicity

Due to the interference between satralizumab and the neutralizing antibody assay, neutralizing antibody were not determined, binding antibody measures are the only interpretable immunogenicity assessments in this submission. In study BN40898, the double-blind period, ADA was detected in 17 out of 41 patients (41%) treated with satralizumab as add on to immunosuppressant therapy, including 2 patients with treatment boosted ADAs (ADA positive at baseline, >4-fold increased ADA titer post-baseline) and 15 patients with treatment-induced ADAs (ADA negative at baseline, ADA positive post-baseline). In the overall period, ADA was positive (at least once) during the study in 34 of 65 patients (52.3%). In study BN40900, the double-blind period, ADA was detected in 45 out of 63 (71%) patients treated with satralizumab monotherapy. In the overall period, ADA was positive (at least once) during the study in 58 of 80 patients (72.5%).

PopPK analysis suggested that the development of ADAs was associated with 13% lower SC

bioavailability and ~20% higher total clearance. In addition, patients who went on to develop ADAs generally had higher body weight.

It is not clear whether the development of ADA has a clinically-relevant effect on satralizumab efficacy. The development of ADAs does not have a clinically-relevant effect on safety.

2.2 Dosing and Therapeutic Individualization

2.2.1 General Dosing

The recommended dose regimen is 120 mg SC injection at weeks 0, 2, and 4, followed by a maintenance dose of 120 mg SC injection every 4 weeks.

2.2.2 Therapeutic Individualization

No therapeutic individualization for intrinsic or extrinsic factors is recommended.

2.3 Outstanding Issues

None.

3 Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

Satralizumab injection for subcutaneous administration is supplied as a sterile, colorless to slightly yellow, preservative-free solution of approximately pH of 6. Satralizumab is supplied in a single-dose prefilled syringe, which delivers 1ml of solution containing 120 mg of satralizumab, L-arginine (26.1 mg), L-histidine (3.1 mg), poloxamer 188 (0.5 mg), (b) (4) (pH adjustment), and Water for Injection, USP.

The satralizumab clinical program is composed of two phase 1 studies (SA-001JG in healthy volunteers; SA-105JG in RA patients) and two phase 3 pivotal safety and efficacy studies in subjects with NMOSD (Study BN40898 in adult and adolescent patients with satralizumab in addition to background immunosuppressive therapy; Study BN40900 in adult patients with satralizumab as a monotherapy).

The key aspects of these clinical studies are summarized in table below.

Table 1: Satralizumab Clinical Trials

Trial	Description	Population	Dose
SA-001JG	Phase 1, Parts A and B: placebo-controlled, randomized, double-blind, dose escalation study (single SC dose) Part C: open-label (single IV dose)	Healthy subjects (n=84)	Parts A and B: satralizumab SC 30/60/120/240 mg; Placebo Part C: satralizumab IV 60/120mg
SA-105JG	Phase 1, Open-label, randomized, parallel-group, multiple-dosing study	Adult subjects with RA (n=33)	Satralizumab 120 mg at Week 0, 2 and 4, then 30/60/120 mg SC Q4W until Week 16 extension period: satralizumab 120 mg

BN40898	Phase 3, randomized, double-blind, add-on to background immunosuppressive treatment, placebo-controlled followed by OLE	Adult and adolescent patients with NMO or NMOSD (Satralizumab n=41; Placebo n=41)	DB period: 120 mg SC at Week 0, 2, 4, and Q4W thereafter OLE: 120 mg SC at Week 0, 2, 4, and Q4W thereafter
BN40900	Phase 3, randomized, double-blind, monotherapy, placebo controlled followed by OLE	Adult patients with NMO or NMOSD (Satralizumab n=63; Placebo n=32)	DB period: 120 mg SC at Week 0, 2, 4, and Q4W thereafter OLE: 120 mg SC at Week 0, 2, 4, and Q4W thereafter

3.2 General Pharmacology and Pharmacokinetic Characteristics

The clinical pharmacology and pharmacokinetics information of satralizumab are summarized below.

Table 2: Summary of Satralizumab Clinical Pharmacology Information

Pharmacology	
Mechanism of Action	Satralizumab is a humanized engineered monoclonal antibody that targets soluble and membrane-bound human IL-6 receptor (IL-6R) and thereby prevents IL-6 downstream signaling through these receptors.
QT Prolongation	No formal QT evaluation has been conducted for satralizumab. As a large molecule, satralizumab has a low likelihood to directly interact with ion channels.
General Information	
Bioanalysis	Satralizumab was determined in human serum using an Enzyme-Linked Immunosorbent (ELISA) method.
Drug total exposure following the therapeutic dosing regimen	Steady state pharmacokinetics were achieved after the loading period (8 weeks) for Cmin, Cmax and AUC(0-t) as follows: Cmin: 19.7 (±12.2) mcg/mL, Cmax: 31.5 (±14.9) mcg/mL and AUC(0-t): 737 (±386) mcg.mL/day.
Dose Proportionality	The pharmacokinetics of satralizumab have been shown to be non-linear, with increased clearance at lower doses due to target-mediated drug disposition (TMDD). For single SC administration of satralizumab ranging from 60 to 240 mg, the point estimates for the slopes of AUCinf and Cmax were 1.67 and 1.24, respectively.
Immunogenicity	Due to the interference between satralizumab and the neutralizing antibody assay, neutralizing antibody were not determined, binding antibody measures are the only interpretable immunogenicity assessments in this submission. In NMO and NMOSD patients receiving the recommended regimen, 52% of patients and 73% of patients developed ADAs when given as add on to immunosuppressant therapy (Study BN40898) and as monotherapy (Study BN40900), respectively. Lower satralizumab exposure

	was observed in ADA positive patient, which was also associated with higher bodyweight. It is not clear whether the presence of ADA has a clinically-relevant impact on satralizumab efficacy. The development of ADA does not have a clinically-relevant effect on satralizumab safety.
Inhibitor/Inducer	As a monoclonal antibody inhibiting IL-6 signaling, the impact on CYP activity was investigated using PBPK modeling and simulation. Although this analysis was considered exploratory, based on the low baseline IL-6 levels seen in NMOSD patients in the Phase 3 studies, the IL-6 mediated suppression of CYP enzymes is expected to be low. Accordingly, the impact of satralizumab treatment on the exposure of CYP substrates is expected to be minor. Other potential interactions (e.g., with transporters) are not expected.
Distribution	
Volume of Distribution	Estimated central and peripheral volume of distribution were 3.46 L and 2.07 L, respectively.
Elimination	
Terminal Elimination Half-life	Approximately 30 days with associated linear clearance of 0.0601 L/day.
Metabolism / Excretion	As a humanized IgG2 monoclonal antibody, satralizumab is expected to be degraded into small peptides and amino acids by proteolytic enzymes widely distributed in the body.

3.3 Clinical Pharmacology Review Questions

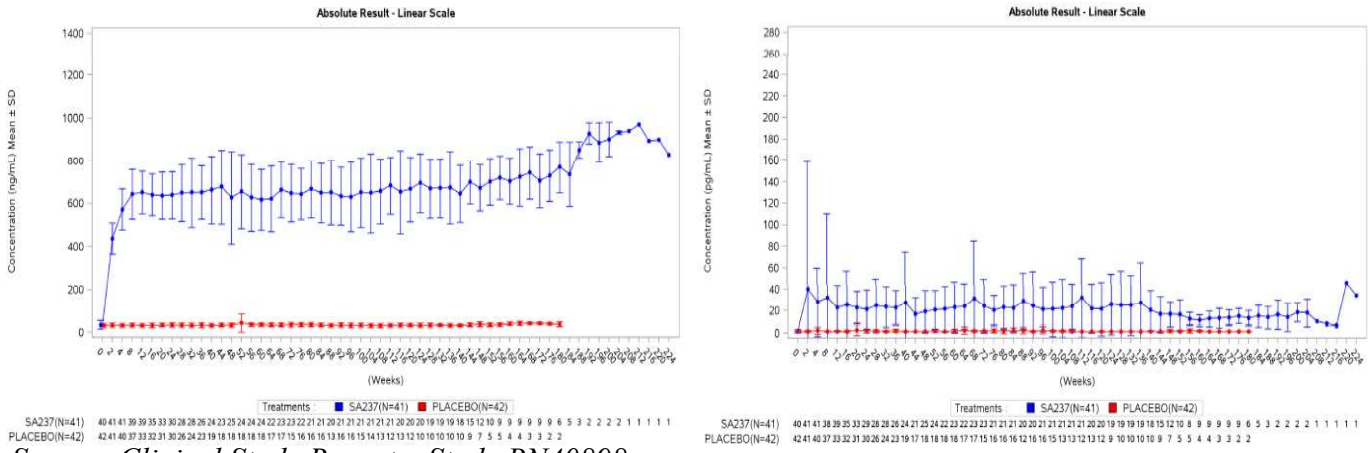
3.3.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

The evidence of effectiveness of satralizumab is supported by the efficacy results from two Phase III studies BN40898 and BN40900. Study BN40898 is a Phase III, multicenter, double-blind, placebo-controlled study to assess the efficacy and safety of satralizumab as an add-on therapy for the treatment of NMO and NMOSD in adult and adolescent (12 to 17 years old) patients. Study BN40900 is a Phase III, multicenter, double-blind, placebo-controlled study to assess the efficacy and safety of satralizumab as monotherapy for the treatment of NMO and NMOSD in adult patients.

Per the Applicant's analysis, both studies achieved the primary endpoint; treatment with satralizumab led to significant reduction in the risk of experiencing a protocol-defined relapse by 62% (HR [95% CI]: 0.38 [0.16, 0.88] and 55% (HR [95% CI]: 0.45 [0.23, 0.89]) compared to placebo in studies BN40898 and BN40900, respectively. The hazard ratios for the two studies were similar, showing that satralizumab provides comparable efficacy whether administered as monotherapy or add-on therapy. However, current data do not support the effectiveness of satralizumab in AQP4-IgG seronegative population (n=28, study BN40898; n=31, study BN40900) and adolescent (n=7, study BN40898) with NMO and NMOSD. (Please refer to the clinical review and biostatistics review for additional details).

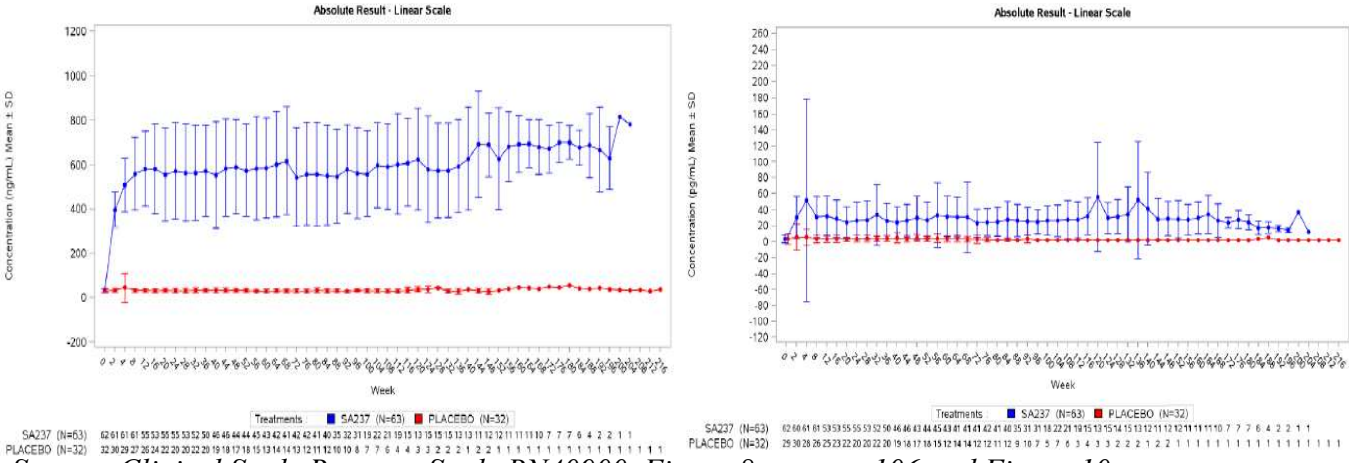
The following PD makers were evaluated for Studies BN40898 and BN40900: serum sIL-6R and serum IL-6 concentration as Markers of Target Engagement; C-reactive protein and complement components (C3-complement component 3, C4-complement component 4 and CH50-total complement activity) as Markers of Inflammation. Increased mean levels of the target engagement markers sIL-6R and IL-6 were observed in both satralizumab-treated groups in parallel with the concentration-time profile (see Figure 1 and Figure 2). Mean levels of CRP and immune complement components (C3, C4, and CH50) declined in the satralizumab group compared with placebo and then remained constant.

Figure 1. Time Course of Mean Serum sIL-6R and Mean IL-6 Absolute Concentrations (Linear Scale), DB Period (Study BN40898)



Source: Clinical Study Report – Study BN40898, Figure 8 on page 110 and Figure 10 on page 114

Figure 2. Time Course of Mean Serum sIL-6R and Mean IL-6 Absolute Concentrations (Linear Scale), DB Period (Study BN40900)



Source: Clinical Study Report – Study BN40900, Figure 8 on page 106 and Figure 10 on page 110.

The relationship between satralizumab exposure and pharmacodynamic markers, efficacy variables was evaluated for Studies BN40898 and BN40900. However, due to use of a single dosing regimen in both trials, the findings from the exposure-response analyses for efficacy over

the resulting exposure range are unlikely to be useful for informing efficacy at other dose levels. As such, the Applicant's exposure-response analyses for efficacy was not reviewed.

Overall, support for the efficacy of satralizumab as add-on and monotherapy for the treatment of NMO and NMOSD in adults comes from the clinical efficacy results from Study BN40898 and Study BN40900.

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

The recommended regimen for satralizumab, as a loading dose of 120 mg SC Q2W for a total of three doses, followed by maintenance doses of 120 mg SC Q4W in patients with NMO/NMOSD is supported by the results of two Phase III studies (Study BN40898 and study BN40900), demonstrating significant reduction of risk of relapse as both monotherapy and as add-on therapy, and acceptable safety and tolerability.

3.3.3 Does the immunogenicity affect the PK, PD, efficacy and safety?

It is not clear whether the presence of ADA has a clinically-relevant impact on satralizumab efficacy. The development of ADA does not have a clinically-relevant effect on satralizumab safety.

Due to the interference between satralizumab and the neutralizing antibody assay, neutralizing antibodies were not determined, binding antibody measures are the only interpretable immunogenicity assessments in this submission.

Immunogenicity incidence

In study BN40898, during the DB period, ADA was detected in 17 out of 41 patients treated with satralizumab. Of the 17 patients with ADA, 2 patients had ADA at baseline that increased by more than 4-fold post-baseline (treatment boosted ADA). The remaining 15 ADA-positive patients were negative at baseline and developed ADA on treatment (treatment-induced ADAs). Twelve patients had persistent treatment induced ADA.

In study BN40900, during the DB period, ADA was detected in 45 out of 63 patients treated with satralizumab. All 45 ADA positive patients were ADA negative at baseline and developed ADA on treatment (treatment-induced ADAs). Thirty-five patients had persistent treatment induced ADA.

Immunogenicity impact on PK, PD, efficacy and safety

PopPK analysis of the data from the Phase III trials suggest that development of ADAs is associated with lower satralizumab exposure, higher body weight. Compared to ADA- negative patients, ADA-positive patients appear to have higher IL-6, lower sIL-6R levels and comparable levels on other PD markers (CRP, fibrinogen, C3, C4, and CH50).

While the Applicant's post-hoc analyses of ADA effect on protocol-defined relapse (PDR) indicate the satralizumab efficacy benefit appears greater in ADA- subjects than for ADA+ subjects, these assessments were confounded by body weight. Applicant reports that, in the untreated patient, if the patient's weight is above the median then there is an increased risk of PDR, irrespective and independent of treatment. In addition, the applicant reports a correlation between higher bodyweight and increased probability of developing ADAs. Furthermore, satralizumab plasma exposure is generally lower in subjects with higher body weight. Therefore,

the current data do not support direct conclusions being drawn on whether the development of ADA have a clinically-relevant impact on the efficacy of satralizumab. Please refer to sections **4.4 Effect of Immunogenicity** for additional details.

The Applicant indicates that the main adverse events associated with immunogenicity include injection-related reactions and adverse-events leading to dose interruption. There were 19.79 injection-related reaction events per 100 patient-years in ADA positive patients (7 patients, 11.3%) vs. 13.33 events per 100 patients-years in ADA negative patients (6 patients, 14.3%). There were 24.28 "AE leading to dose interruption" events per 100 patient-years in ADA positive patients (13 patients, 21.0%) vs. 16.96 events per 100 patients-years in ADA negative patients (10 patients, 23.8%). The most common AE leading to dose interruption in both ADA positive as well as ADA negative subjects were infections. Overall, the development of ADA does not have a clinically-relevant effect on safety. Please refer to the medical officer's review for additional details regarding safety.

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

No.

No in-vivo studies were conducted to assess the effect of intrinsic or extrinsic factors. Satralizumab is a monoclonal antibody and therefore no significant effect of renal impairment and hepatic impairment on satralizumab pharmacokinetics is anticipated. No relationship was found between satralizumab clearance and creatinine clearance based on graphical examination. Similarly, no relationship was found between satralizumab clearance and AST/ALT based on visual examination. Though popPK analysis indicates that body weight is a covariate on satralizumab PK, the efficacy data from Study BN40898 and study BN40900 provide support for the flat dosing regimen (please see the medical officer's review for details).

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

As satralizumab is a biologic administered by SC injection, a food-drug interaction is not applicable.

Based on the available PK data and analyses provided in the submission, the impact of commonly-used small molecule drugs on satralizumab PK remains inconclusive (please refer to **4.2.2 Population PK Model** for details).

Elevated baseline IL-6 levels observed in patients with inflammatory diseases may down-regulate the synthesis of CYP enzymes. Accordingly, inhibition of IL-6 signaling in patients treated with anti-IL-6 mAb may restore CYP expression to higher levels than those in the absence of treatment, leading to increased metabolism of CYP substrate drugs. Current evidence suggests the baseline IL-6 level in the target patient population is likely the key factor for estimation of the interaction effect of an anti-IL-6 therapy with CYP substrates.

Applicant applied PBPK analysis to investigate the potential of satralizumab to reverse IL-6-mediated suppression of CYP enzymes; however, this analysis was considered exploratory (See PBPK review, **Appendix 4.5**). Based on the low baseline IL-6 levels seen in NMOSD patients in the Phase 3 studies, the IL-6 mediated suppression of CYP enzymes is expected to be low. Accordingly, the impact of satralizumab treatment on the exposure of CYP substrates is expected to be minor.

The team recommends, upon initiation or discontinuation of satralizumab, monitoring the therapeutic effect of sensitive CYP substrates with narrow therapeutic index, and adjusting the dose or regimen as recommended in their label.

The primary elimination pathway for satralizumab is clearance by the reticuloendothelial system that is likely similar to endogenous IgG clearance. Overall, based on the known mechanisms of satralizumab elimination, the potential risk of PK interactions between satralizumab and other drugs is expected to be low.

4 Appendices

4.1 Summary of Bioanalytical Method Validation and Performance

For the determination of satralizumab concentrations, the applicant developed an enzyme-linked immunosorbent assay (ELISA) in human serum. The ELISA method was validated in observance of the FDA Guidance for Industry Bioanalytical Method Validation.

The accuracy and precision were within acceptable ranges. Sample stability studies demonstrated that satralizumab in human serum was stable up to 24 hours at ambient room temperature; during 1 to 5 freeze-thaw cycles and up to 733 days at -20.0°C and -80.0°C.

Summary of the method validation parameters are presented in the table below:

Validation Report No.	Assay Range (ng/mL)	QCs (ng/mL)	Relative Error (%)		Precision (%)	
			Intra-Assay	Inter-Assay	Intra-Assay	Inter-Assay
ADM10-5053 (Chugai)[a]	200-6400	200, 400, 1200, 3200, 6400	-11.1 to 9.3	-12.8 to 6.9	4.9 to 12.6	3.9 to 12.6
45N093B ([(b) (4)])[b]	200-6400	200, 400, 800, 1200, 3200, 6400	-9.5 to 2.0	-5.0 to 7.5	2.1 to 7.8	8.4 to 12.2

a Assay performed for Studies SA-001JP, SA-105JP, and BN40898
b Assay performed for Study BN40900

4.2 Population Pharmacokinetic Analyses

The Applicant submitted reports poppk-stage1.pdf and poppk-stage2.pdf to sequence 0004 module 5335. Report poppk-stage1.pdf describes population pharmacokinetic (PPK) analyses and pharmacokinetic-pharmacodynamic (PKPD) analyses based on data obtained from the subset of the subjects enrolled before the clinical cutoff date in the then-ongoing Phase 3 Trial BN40900. Report poppk-stage2.pdf describes the extension of the poppk-stage1.pdf analyses using the full dataset from the Phase 3 Trial BN40900. As the poppk-stage2.pdf report contains the finalized analyses, poppk-stage1.pdf will not be further discussed in this review.

4.2.1 Summary of PK Data

Subjects enrolled in Studies SA-001JP, BN40898, and BN40900 provided PK data for population PK analyses. Subjects enrolled in Trial BN40900 provided data for exposure-response analyses. A summary of the key attributes of these studies is found in the table below.

Table 3: Clinical Studies Which Provided Data Used in PPK and PKPD Modeling

Study ID	Design	Dosing	Subjects	PK Sampling
SA-001JP	Phase 1, placebo-controlled, randomized, double-blind study to assess the safety, tolerability, and PK of satralizumab single doses in different racial groups.	Parts A and B: (DB) 30/60/120/ 240 mg SC Part C: (OL) 60/120 mg IV	Healthy volunteers placebo: n=12 SC satralizumab: n=60 IV satralizumab: n=12	pre-dose, and 1 (IV only), 4, 8, 12, 18, 24, 48, 56, 72, 80, and 96 hours post-dose. Weekly up to 10 weeks post-dose
BN40898	Phase 3, randomized, double-blind, placebo-controlled trial to assess efficacy and safety of satralizumab as an *add-on* to existing immunosuppressive therapy. Followed by OLE.	DB period: 120 mg SC at Week 0, 2, 4, and Q4W thereafter OLE: 120 mg SC at Week 0, 2, 4, and Q4W thereafter	Patients with NMO or NMOSD placebo: n=42 SC satralizumab: n=41	DB Period: Weeks 0, 2, 4, 5*, 6*, 8, every 4 weeks thereafter. OL Period: every 4 weeks (Weeks 0-48), every 24 DB/OL: At visit after relapse, at withdrawal
BN40900	Phase 3, randomized, double-blind, placebo-controlled trial to assess efficacy and safety of satralizumab *monotherapy*. Followed by OLE.		Patients with NMO or NMOSD placebo: n=32 SC satralizumab: n=63	PK samples: Same as BN40898 PD samples: Weeks 0, 2, 4, every 4 weeks thereafter Immunogenicity: Weeks 0,4, every 4 weeks thereafter

*DB=double-blind, OL=open-label, OLE = OL extension. *=optional PK sample.*

Source: sequence 0004, module 27, synopses-indiv-studies.pdf, pages 2-6 of 10, sequence 0004, module 5335, poppk-stage2.pdf, pages 24-25 of 380

Phase 3 Trial BN40898 is also referred to as Trial SA-307JG as well as Trial 307. Phase 3 Trial BN40900 is also referred to as SA-309JG as well as Trial 309.

4.2.2 Population PK Model

The Structural model includes two-compartments, first-order absorption for SC administration, and parallel linear and non-linear elimination pathways. A Michaelis-Menten model was used to characterize the non-linear pathway which is expected to represent target-mediated clearance. Key attributes of the model are described below.

Allometric Scaling: Linear clearance (CL), volume of distribution of the central compartment (Vc), intercompartmental clearance (Q), and volume of distribution of the peripheral compartment (Vp) were scaled with body weight (normalized to 60 kg body weight) according to a power model. The power model exponents were fixed to 1 for clearance terms (CL and Q) and 0.75 for volume terms (Vc and Vp).

Inter-Individual Variability: exponential

Residual Variability: exponential

Covariates: Disease status (healthy volunteer vs. NMO/NMOSD patient), body weight, time-varying immunogenicity, and subcutaneous formulation are covariates on CL. Body weight is the only covariate on Q, Vc, and Vp. Time-independent immunogenicity response (detection of ADAs at ≥ 1 one time point) is a covariate on absolute subcutaneous bioavailability.

Parameter estimates for the final PPK model (denoted as Run 224) are found in the table below.

Table 4: Parameter estimates for final PPK Model (Run 224) – Structural and Covariate Parameters

Fixed Effect Parameter		Estimate	RSE (%)	95%CI
CL (L/day)	θ_1	0.0601	7.46	0.0513 - 0.0689
V_C (L)	θ_2	3.46	6.04	3.05 - 3.87
Q (L/day)	θ_3	0.336	12.6	0.253 - 0.419
V_P (L)	θ_4	2.07	9.84	1.67 - 2.47
V_{max} (µg/mL/day)	θ_5	0.455	3.67	0.422 - 0.488
K_M (µg/mL)	θ_6	0.462	8.47	0.385 - 0.539
k_a (1/day)	θ_7	0.251	6.99	0.216 - 0.285
F_{SC}	θ_8	0.854	6.09	0.752 - 0.956
σ_{IV}	θ_9	0.417	30.7	0.166 - 0.668
σ_{HV}	θ_{10}	0.84	10.2	0.672 - 1.01
σ_{ST309}	θ_{11}	1.66	8.83	1.37 - 1.94
CL, Q ~ WT	θ_{12}	0.75	Fixed	
CL ~ HV	θ_{13}	1.96	7.37	1.67 - 2.24
CL ~ ADA_T	θ_{14}	1.45	8.76	1.2 - 1.7
CL ~ FORM	θ_{15}	1.09	1.04	1.06 - 1.11
V_C, V_P ~ WT	θ_{16}	1	Fixed	
F_{SC} ~ ADA (NMO/NMOSD)	θ_{17}	0.866	2.42	0.825 - 0.907

CL = clearance, V_c = volume of distribution of central compartment, Q=intercompartmental clearance, V_p=volume of distribution of peripheral compartment, V_{max} = maximum target-mediated elimination rate, K_m=Michaelis-Menten EC_{50} term, k_a = first-order rate constant for SC absorption, F_{sc} = bioavailability for sub-cutaneous administration, σ_{IV} = the effect of intravenous route on residual variability, σ_{HV} = the effect of being a healthy volunteer (vs patient) on residual variability, σ_{ST309} = the effect of participation in Trial 309 (aka Phase 3 Trial BN40900) versus other studies on residual variability, the ~ symbol denotes a structural PK parameter (left side of ~) and it's covariate (right side of the ~), ADA_T is time varying anti-drug antibody status, ADA is time-independent anti-drug antibody status, FORM = IV formulation or SC formulation.

Source: sequence 0004, module 5335, poppk-stage2.pdf, pages 68 of 380

Table 5: PK Parameter estimates for the final PPK Model (Run 224) – Variability Parameters

Variance Parameter		Estimate	RSE (%)	95%CI	Variability	Shrinkage
ω^2_{CL}	Ω(1,1)	0.0894	16.6	0.0603 - 0.118	CV=29.9%	21.2%
ω^2_{Vc}	Ω(2,2)	0.0296	19.5	0.0183 - 0.041	CV=17.2%	24.8%
ω^2_{Q}	Ω(3,3)	1.13	19.3	0.7 - 1.55	CV=106%	25.2%
ω^2_{Vp}	Ω(4,4)	0.28	16.2	0.191 - 0.369	CV=52.9%	15.8%
ω^2_{KA}	Ω(5,5)	0.329	21.7	0.189 - 0.47	CV=57.4%	29.3%
$\omega^2_{ADA\_T}$	Ω(6,6)	0.284	23.3	0.154 - 0.414	CV=53.3%	11.3%
ω^2_{σ}	Ω(7,7)	0.212	11.2	0.165 - 0.258	CV=46.0%	-2.7%
σ^2	Σ(1,1)	0.0307	15.4	0.0214 - 0.04	CV=17.5%	1.2%

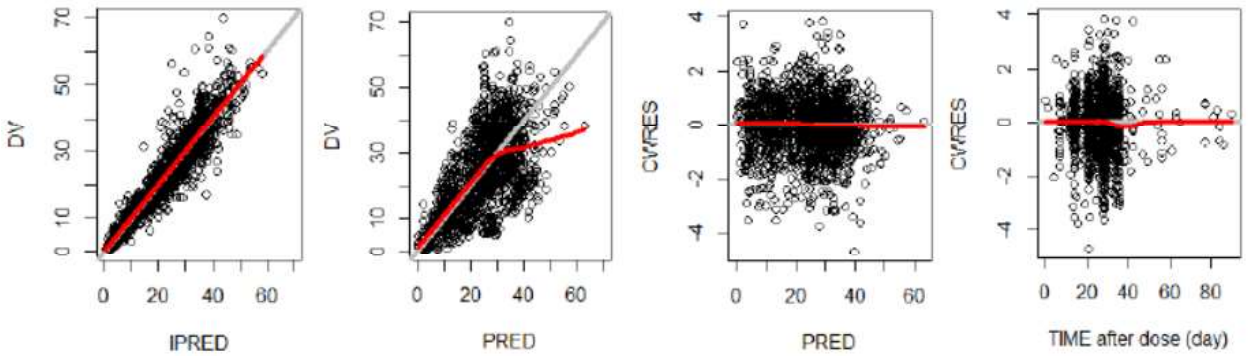
*SE=standard error; RS=relative standard error; %RSE=100·SE/PE, where PE is a parameter estimate; 95% CI=95% confidence interval; SD= standard deviation; CV=coefficient of variation, CV=100*SD %*

Source: sequence 0004, module 5335, poppk-stage2.pdf, pages 68 of 380

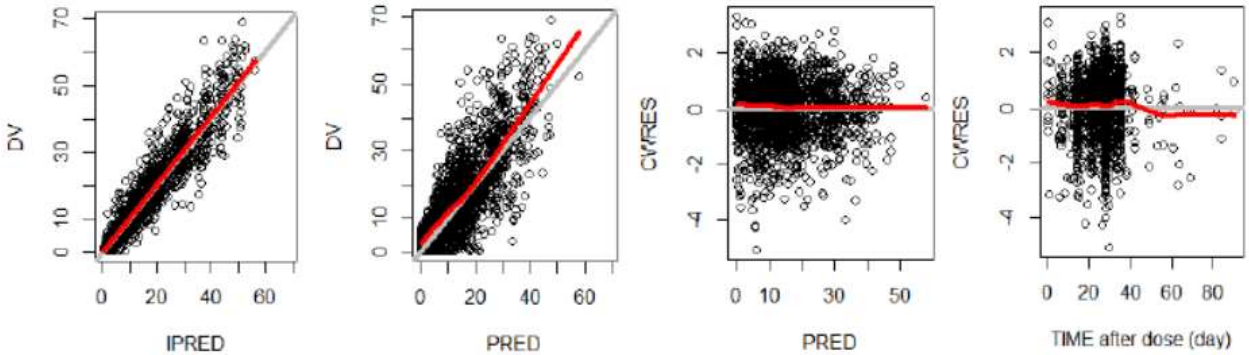
Model diagnostics are presented in the figures below.

Figure 3: Diagnostic Plots for Final Population PK Model – By Phase 3 Trial

Trial BN40898 (Trial 307)



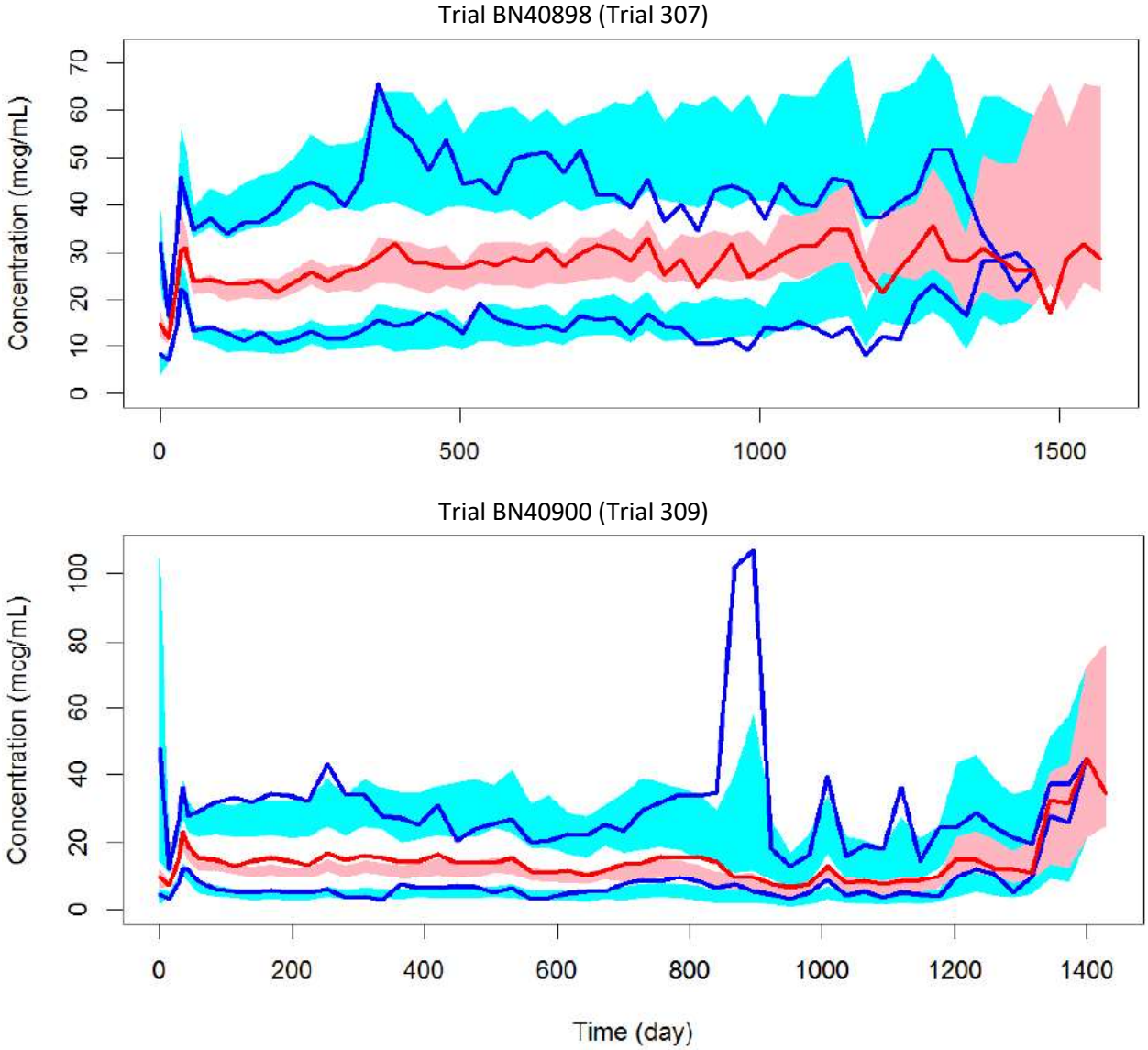
Trial BN40900 (Trial 309)



DV: observed concentrations; PRED: population predictions of the model; IPRED: individual predictions of the model; CWRES: conditional weighted residuals; IWRES: individual weighted residuals; TIME: time after the first 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: sequence 0004, module 5335, poppk-stage2.pdf, pages 136-137 of 380

Figure 4: Prediction-Corrected Visual Predictive Check normalized to 120 mg – By Phase 3 Trial



The lines show median (red), and the 5th and 95th percentiles (blue) of the observed concentrations (with prediction-correction). The shaded regions show the 90% confidence intervals of the median (red shaded band), and the 5th and 95th percentiles (blue shaded bands) of the simulated concentrations. The simulated values were computed using the final model from 1000 virtual trials with dosing, sampling, and covariate values obtained from the analysis dataset.

Source: sequence 0004, module 5335, poppk-stage2.pdf, pages 190-191 of 380

[*Reviewer comment: According to* ***Table 4****, the precision for* σ_{IV} *(the effect of intravenous route on residual variability) was the parameter estimated with the lowest precision (30.7% RSE). The lower precision for this parameter is likely due to the IV formulation being administered to a total of n=12 subjects (n=6 received 60 mg IV, n=6 received 120 mg IV) in the Phase 1 SA-001JP study. As the Phase 3 trials used the SC formulation and the proposed label includes only an SC*

formulation, the precision of the effect of IV on residual unexplained variability will not be further discussed.

*The diagnostic plots in **Figure 3** involving CWRES demonstrate no apparent bias of the model with respect to PRED or time after dose. Overall, it is not clear whether the DV vs PRED plots indicate bias in the model.*

*The prediction-corrected visual prediction check (pc-VPC) plots (**Figure 4**) indicate that, for both trials, uncertainty is greater (wider band) for the 95th percentile than for the lower exposures. The pc-VPC for Trial BN40900 (Trial 309) shows a transient increase in the 95th percentile of observed exposures at ~900 days. The reason for this transient increase is not clear.*

Overall, the final model (Run 224) appears to represent the PK profile well.

Satralizumab was administered along with concomitant immunotherapy in both Phase 3 studies. In the PK dataset, baseline treatment of azathioprine (AZT), mycophenolate mofetil (MMF), and oral corticosteroids (OCS) were by adult subjects in Trial BN40898 (Trial 307) and Trial BN40900 (Trial 309). Concomitant medication use information in the PK dataset is presented in the table below.

Table 6: Number of Adult Subjects Receiving Each Concomitant Medication at Baseline in Satralizumab Arm in Trial BN40898 (Trial 307) and Trial BN40900 (Trial 309)

Co-medication	Taken	Not Taken
Azathioprine	24 (16.4%)	122 (83.6%)
Mycophenolate Mofetil	9 (6.2%)	137 (93.8%)
Oral Corticosteroids	33 (22.6%)	113 (77.4%)

Source: sequence 0004, module 5335, poppk-stage2.pdf, pages 63-64 of 380

Applicant performed an assessment of co-meds on satralizumab PK as part of the PPK analyses. Applicant generated plots, not shown in this review, of the eta CL estimate for subjects receiving each co-med in Table 6 versus that for subjects that did not receive each co-med (not shown in review; figure 34, 35, and 36 of on pages 154-156 poppk-stage2.pdf). Based on these plots, the Applicant concludes that the dependency of the random effects on AZA, MMF, and OCS use do not show any trends unaccounted for by the final model. As such, the Applicant did not include concomitant AZA, MMF, or OCS use in the final PPK model. From a mechanistic perspective, satralizumab is not expected to be the victim of interaction perpetrated by AZA, MMF, or OCS.

As the Applicant did not include AZA, MMR, or OCS in the PPK model, parameter estimates for AZA, MMF, or OCS are not available. In addition, the majority of subjects enrolled in the Phase 3 program did not receive AZA, MMF, or OCS (see Table 6). ***Overall, the impact of these frequently-used small molecule drugs on satralizumab PK remains inconclusive.*** (b) (4)

The effect of anti-drug anti-bodies (ADA) on satralizumab PK was assessed as part of the PPK analyses. Over all studies, ADAs were detected in 132 subjects (58%) after receiving satralizumab. ADAs were detected in 54%, 52%, and 73% of subjects treated satralizumab in studies SA-001JP, BN40898, and BN40900, respectively. The Applicant determined the development of ADAs (in terms of time-varying ADA status) resulted in ~20% increase in total clearance (defined as the combination of linear clearance process and non-linear clearance process at steady-state concentration of 25.7 μg/mL). In addition, lower SC bioavailability was observed at baseline

(prior to ADA detection) and at all subsequent timepoints in patients that demonstrated ≥ 1 positive ADA sample (time-independent ADA status).

The Applicant states that the effect of ADA on bioavailability manifested itself starting from the first dose, even before ADA were detected or had a chance to develop. The Applicant indicates that an attempt to model the immunogenicity effect as starting at the second dose (that is, assume that the first dose is not affected) resulted in a higher objective function value. Applicant states that it is possible that patients with lower exposure are more likely to develop ADAs. Overall, It is not clear how ADAs could be present in subjects prior to treatment with satralizumab.

Additional information on the effects of immunogenicity can be found in section 4.4 of this review.]

4.2.3 Label Statements Based on Population PK Modeling

The Applicant proposes the following label statements in section 12.3 based on PPK-modeling results. For each proposed statement based on PPK-modeling, the reviewer provides a determination as to whether the PPK analyses support the statement.

The final labeling language will reflect the ongoing discussions within the Agency and with the Sponsor after this review has been archived.

12.3 Pharmacokinetics

(b) (4)

[*Reviewer comment: Based on the available PK data and analyses provided in the submission,* (b) (4) *As such, OCP recommends modifying the label statement to reflect the inconclusive analysis results. Please refer to section 4.3.2 Population PK Model for details.*]

Absorption

(b) (4) The bioavailability was 85%."

[*Reviewer comment: The proposed statements for the Absorption section are supported by the population PK analyses. However, OCP recommends removing the statement regarding* (b) (4).]

Distribution

"Satralizumab undergoes biphasic distribution. The central volume of distribution was 3.46 L the peripheral volume of distribution was 2.07 L. The inter-compartmental clearance was 0.336 L/day."

[*Reviewer comment: The proposed statements for the Distribution section are supported by the population PK analyses.*]

Elimination

"The total clearance of satralizumab is concentration-dependent. Linear clearance (accounting for approximately half of the total clearance at steady state using the recommended dose in NMOSD patients) is estimated to be 0.0601 L/day. The associated terminal t½ is approximately 30 days (range 22-37 days) based on data pooled from (b) (4)

[*Reviewer comment: The proposed statements for the Elimination section are supported by the population PK analyses.*]

Specific Populations

"Population pharmacokinetic analyses in (b) (4) patients with NMOSD showed that age, gender, and race did not meaningfully influence the pharmacokinetics of satralizumab."

[*Reviewer comment: The proposed sentence regarding the effect of age, gender, and race on ENSPRYNG PK is supported by the PK analyses. We propose including weight in this statement.*]

(b) (4)

Drug Interaction Studies

(b) (4)

[*Reviewer comment: Based on the available PK data and analyses provided in the submission, the impact of commonly-used small molecular drugs on satralizumab PK remains inconclusive. As such, OCP recommends modifying the label statement to reflect the inconclusive analysis results. Please refer to section 4.3.2 Population PK Model for details.*]

4.3 Exposure-Response Analyses

The Applicant conducted exposure-response analyses of satralizumab plasma exposure on risk of protocol-defined relapse (PDR). The results of the exposure-response analyses are presented in poppk-stage-2.pdf (sequence 0004, module 5335).

4.3.1 Exposure-Response for Efficacy

There was a single dose level that was administered at the same dosing intervals in both Phase 3 trials (Satralizumab 120 mg subcutaneous administration at Weeks 0, 2 and 4, and Q4W thereafter in Phase 3 trials BN40898 and BN40900). Due to use of a single dosing regimen in

both trials, the findings from the exposure-response analyses for efficacy over the resulting exposure range are unlikely to be useful for informing efficacy at other dose levels. As such, the Applicant's exposure-response analyses for efficacy will not be reviewed.

4.3.2 Exposure-Response for Safety

At the time this review was archived, the main safety concerns for satralizumab are not expected to preclude approval (please refer to the review of the medical officer, Dr. Larry Rodichok for details). Due to use of a single dosing regimen in both trials, the findings from the exposure-response analyses over the resulting exposure range are unlikely to be useful for informing safety at other dose levels. As such, the Applicant's exposure-response analyses for safety will not be reviewed.

4.4 Effect of Immunogenicity

The Applicant assessed the effect of immunogenicity via comparisons study measurements in subjects with ≥ 1 positive anti-drug-antibody (ADA) test result versus subjects that were always ADA negative. A summary of the key results of the Applicant's comparisons between ADA+ and ADA- subjects are described below.

ADA+ subjects have:

1. Higher body weight, lower exposures
2. Higher IL-6 levels
3. Lower sIL-6R concentrations

, compared to ADA- negative subjects

The ADA+ subjects and ADA- subjects appear to have comparable C-reactive protein (CRP), fibrinogen, complement component 3 (C3), complement component 4 (C4), and total complement activity (CH50) (figures 131 through 135 on pages 253 through 257 of poppk-stage2.pdf; figures not shown in review).

Based on post-hoc analyses, Applicant computes protocol-defined relapse (PDR) risk reduction compared to placebo (i.e. higher % means greater risk PDR risk reduction compared to placebo) as:

1. BN40898: 32% and 80% in ADA+ and ADA- subjects
2. BN40900: 50% and 57% in ADA+ and ADA- subjects
3. BN40900 + BN40898: 68% and 50% in ADA+ and ADA- subjects

The post-hoc analyses of ADA effect on PDR risk indicate that in both trials, satralizumab efficacy benefit appears greater in ADA- subjects than for ADA+ subjects. Applicant concludes that while post-hoc analyses suggest treatment benefit is less in ADA+ patients, such analyses are confounded by the correlation between higher body weight and probability of developing ADAs. In particular, based on Applicant's analyses, Applicant concludes that higher body weight has been shown to be a negative prognostic factor. In other words, the Applicant concludes that, in the untreated patient, if the patient's weight is above the median then there is an increased risk of PDR, irrespective and independent of treatment.
Please refer to the Clinical review and biostatistics review for additional details regarding the effect of ADA on efficacy.

[*Reviewer comment: ADA+ Subjects appear to have higher IL-6, lower sIL-6R levels, and lower satralizumab exposure than ADA- negative subjects. In addition, ADA appears to have no effect on CRP, fibrinogen, C3, C4, CH50. Fatigue (via FACIT score) appears to be higher in ADA- subjects and VAS pain appears to be higher in ADA+ subjects (figures 138 and 139, pages 260 and 261 of poppk-stage2.pdf; figures not shown in review).*

The Applicant's post-hoc analyses indicate less benefit from satralizumab treatment (compared to placebo) in ADA+ subjects vs ADA- subjects. However, as the Applicant points out, the higher body weight in ADA+ subjects may be associated with a greater relapse risk (based on the Applicant's conclusion that higher body weight appears present higher relapse risk in the placebo group). Due to the breaking of randomization such that ADA+ tends to have higher weight than ADA- subjects, it is not clear that the post-hoc analyses of ADA status on efficacy are reliable. Please refer to the clinical review for additional details.

Overall, it is not clear whether development of ADA has a clinically-relevant effect on efficacy.]

4.5 Physiologically-based Pharmacokinetic Modeling

Executive Summary

The aim of this review is to evaluate the adequacy of the Applicant's PBPK report 1096878, titled "Evaluation of the Potential Impact of Changing IL-6 Levels on Disposition of Various Cytochrome P450 Substrates in Virtual Subjects with Demographic Characteristics Typical of Patients with Neuromyelitis Optica (NMO)" to support the intended use. Specifically, the Applicant applied the PBPK modeling and simulation approach to evaluate a potential disease drug-interaction between satralizumab and CYP substrates.

The Division of Pharmacometrics has reviewed the PBPK report, supporting modeling files, and response to request for information (dated 17 October 2019) to conclude the following:

- PBPK analyses cannot be used to prospectively estimate the magnitude of change on the exposure of CYP probe substrates by the indirect effect of satralizumab on CYP enzyme activity in patients with NMO/NMOSD.
- Reviewer's analysis suggests the baseline IL-6 levels in the target patient population is likely the key factor for estimation of satralizumab interaction potential with CYP substrates.

Background

Satralizumab is a humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody (mAb). Satralizumab targets the human IL-6R preventing IL-6 from binding to membrane-bound and soluble IL-6R. Cytokines, including IL-6, are known to modulate CYP activities in vitro. Elevated baseline IL-6 levels, observed in patients with inflammatory diseases, may modulate the expression of CYP enzymes. Accordingly, inhibition of IL-6 signaling in patients treated with an anti-IL-6 mAb may restore CYP expression to higher levels than those in the absence of treatment. As a result, an anti-IL-6 mAb therapy may lead to increased metabolism of CYP substrate drugs and changes in drug exposure.

Applicant conducted PBPK analysis to investigate IL-6-mediated CYP modulation effect, and its reversal upon administration of an anti-IL-6 therapy such as satralizumab in patients with NMO

or NMOSD (NMO Spectrum Disorders).

The Applicant's proposed label stated "(b) (4) *suppression of IL-6 signaling by treatment with ENSPRYNG from the low baseline levels seen in* (b) (4) *will have* (b) (4) *a minor impact on exposure of* (b) (4) *CYP450* (b) (4) (b) (4)

The aim of this review is to evaluate Applicant's PBPK model (b) (4)

Methods

PBPK modeling was conducted using the Simcyp simulator (V16.R1, Sheffield, UK). A previously published (Machavaram et al., 2013) PBPK model was used to simulate the impact of blockade of IL-6 signaling in virtual patients with NMO or NMOSD on the exposure of several orally administered CYP index substrates: simvastatin (CYP3A4), S-warfarin (CYP2C9), omeprazole (CYP2C19), caffeine (CYP1A2), dextromethorphan (CYP2D6) and midazolam (CYP3A4). The disease effect on CYP activities was modeled under the assumption that increased plasma IL-6 levels, reported in patients with NMO or NMOSD (Uzawa et al., 2010, Barros et al., 2016), is solely responsible for the suppression of CYP enzymes.

Specifically, a semi-mechanistic dynamic model incorporating the effects of enzyme suppression on the level of individual CYP proteins in the liver was used. The key assumptions in the model is that the unbound liver concentration of IL-6 is in rapid equilibrium with the unbound plasma concentration of IL-6, and unbound liver concentrations of IL-6 affect the rate of CYP synthesis in the liver according to the following equation:

$$\underbrace{\frac{d[Enzyme]t}{dt}}_{\text{Rate of synthesis}} = \underbrace{k_{deg} * [Enzyme]_0 * \left(1 + \frac{(Emin \ - 1) \text{ x } [I]t}{\text{EC50} \ + \ [I]t}\right)}_{\text{Suppression factor}} - \underbrace{k_{deg} * [Enzyme]t}_{\text{Rate of degradation}}$$

where [Enzyme]t is the amount of active CYP enzyme at any given time in the liver; [Enzyme]0 is the basal amount of CYP enzyme in the liver; [Enzyme]t =[Enzyme]$_0$ at t=0; Emin is the minimum CYP enzyme activity (i.e. the maximum suppression) expressed as a fraction of basal level; EC50 is the concentration that results in half of the maximum suppressive effect; [I]t is the perpetrator (IL-6) concentration at time t; kdeg is the degradation rate constant of each respective CYP enzyme in the liver. The suppression in the intestine was assumed to be the same as that in the liver, adjusted by intestinal enzyme abundance. Values of the intrinsic turnover (kdeg) of hepatic CYP 3A4, 2C19, 1A2, 2C9 and 2D6 used in the simulations were 0.0193/h, 0.0267/h, 0.0183/h, 0.0067/h and 0.0099/h, respectively (Rowland Yeo et al., 2011; Yang et al., 2008).

PBPK model for IL-6

The model for IL-6 was based on a previously published model (Machavaram et al., 2013). The IL-6 pharmacokinetic parameters clearance (CLiv =1.0 L/h) and volume of distribution at steady-state (Vdss=0.43 L/kg) were used as input parameters for IL-6 (Table 7). To cover the

exposure of IL-6 in the NMO population reported in the literature (Barros et al., 2016, Uzawa et al.,2010), simulations were run at various steady-state plasma IL-6 concentrations (10, 50, 100 pg/mL). IL-6 was administered as an intravenous infusion (0.00926–0.0926 μg/h) for the duration of the simulation (18 days).

Suppression of CYP3A4, 2C19, 1A2, 2D6 and 2C9 by IL-6 was evaluated using hepatocytes in vitro system (Dickman et al., 2011). The enzyme suppression data, i.e., Emin and EC50 concentrations, were used in the simulations (Table 7). In the absence of in vitro data describing the Emin and EC50 in enterocytes, it was assumed that the same degree of maximal suppression in both gut and liver (Machavaram et al., 2013).

Table 7. Input parameters for IL-6 PBPK modeling

Parameter	Value	Method/Reference
Molecular weight (g/mol)	21000	
Log P	0.01	Assumed
Compound Type	Neutral	
B/P	1	Assumed
Fu	1	Assumed
Main plasma binding protein	Human serum albumin	
Distribution model	Minimal PBPK Model	
Vss (L/kg)	0.43	Machavaram et al., 2013
CLiv (L/h)	1	Machavaram et al., 2013
CLR (L/h)	0	Assumed
CYP1A2 Emin	0.23	Dickman et al., 2011
CYP1A2 EC50 (μM)	5.96E-05	Dickman et al., 2011
CYP2C9 Emin	0.053	Dickman et al., 2011
CYP2C9 EC50 (μM)	5.76E-06	Dickman et al., 2011
CYP2C19 Emin	0.214	Dickman et al., 2011
CYP2C19 EC50 (μM)	3.4E-06	Dickman et al., 2011
CYP2D6 Emin	0.302	Dickman et al., 2011
CYP2D6 EC50 (μM)	7.19E-06	Dickman et al., 2011
CYP3A4/5 Emin	0.24	Dickman et al., 2011
CYP3A4/5 EC50 (μM)	3.48E-06	Dickman et al., 2011

(Source: PBPK Report 1096878, Table 6)

Virtual population

The Applicant conducted a literature searches about information on covariates (age, gender, height, weight, liver weight, CYP abundance, plasma binding protein levels, B/P) that may affect the clearance of compounds cleared by CYP-mediated metabolism in patients with NMO or NMOSD. Although there was no relevant information identified for most of these co-variates; information was found related to the age and gender of patients with NMO or NMOSD. The median age of onset of NMO/NMOSD across the studies ranged from 29.5 to 45.7 years-old with no relationship to ethnicity. The studies comprised a total of 1323 subjects of which 1085 were female (female subjects =82% of the total population).

The Applicant stated that there was limited information describing the plasma/serum levels of IL-6 in patients with NMO or NMOSD (Barros et al., 2016, Uzawa et al.,2010) and the maximum value seen in any of the subjects was 80 pg/mL (Uzawa et al., 2010). The Applicant noted that this IL-6 level is within the range of values reported for subjects with rheumatoid arthritis (Machavaram et al., 2013, Jiang et al 2016). The observed baseline serum IL-6 levels in

NMO/MNOSD patients enrolled in the phase 3 trials (BN40898 and BN40900) were approximately 2- 4 pg/mL (range: 1.6-37.2 pg/mL) (Clinical Pharmacology Summary Report).

The Applicant noted that in one study serum albumin levels were reported to be lower in NMO/NMOSD patients than in healthy controls. Average values in those patients were around 41 g albumin/L (range: 19.7 – 67.9 g/L, n = 89 subjects), whereas the albumin levels are around 50 g/L in healthy Caucasian subjects (PBPK Report 1096878). The Applicant evaluated the effect of lower albumin concentrations on the pharmacokinetics of probe CYP substrates and the interaction effect with IL-6, using a sensitivity analysis approach.

In the current analysis, the defaults virtual population models for North European Caucasian and Chinese (Simcyp V16) were used in the simulations. For Japanese population, changes were made to the default model in the Simcyp V16. These changes included the age-height and height-weight relationships, hepatic and intestinal CYP abundance, serum creatinine and kidney volume variability (of note, these changes have been incorporated into the default Japanese population model in V17).

To represent a patient with NMO/NMOSD, simulations were run to achieve steady-state plasma IL-6 levels (10, 50, 100 pg/mL) covering the range of IL-6 exposure observed in NMO patients (Barros et al., 2016, Uzawa et al.,2010). The North European Caucasian, Japanese, and Chinese populations were adjusted to represent the demographics of the NMO/NMOSD patients in terms of age (30 to 46 years) and gender distribution (82% female).

To represent a patient with RA, simulations were run to achieve steady-state plasma IL-6 levels (10, 50, 100 pg/mL) representative of IL-6 exposure and demographics matching those of the subjects in the study reported by Schmitt et al. (2011). The default North European Caucasian population with subjects aged between 28 and 72 years and 66.7% of female were used.

Simulation of IL-6–Mediated effect on CYPs in patients with NMO or NMOSD
Ten virtual trials of 10 subjects receiving a single oral dose of caffeine (150 mg), S-warfarin (10 mg), omeprazole (20 mg), dextromethorphan (30 mg), simvastatin (40 mg), or midazolam (5 mg) on day 15, co-administered with steady-state IL-6 concentrations of 0, 10, 50, or 100 pg/mL from day 1 to day 18. The interaction effect was measured as the fold change of AUC of the victim drug in the presence versus absence of IL-6 levels.

The defaults models for the CYP substrates (Simcyp V16) were used (midazolam, simvastatin, s-warfarin, omeprazole, dextromethorphan and caffeine).

Verification of the performance of IL-6 PBPK model
For the CYP3A pathway, the predicted PK changes of simvastatin (40 mg single-dose), in the absence (IL-6=0) and presence of steady state IL-6 concentrations of 10, 50 and 100 pg/mL (IL-6 infused for 24 days) were compared to the reported data in RA patients before and after treatment with tocilizumab (an anti-IL-6 mAb) (Schmitt et al., 2011). The Applicant also compared the observed (Zhuang et al., 2015) and predicted PK changes of midazolam before and after treatment with sirukumab (an anti-IL-6 mAb) in RA patients (Machavaram et al., 2019). For the CYP1A2, CYP2C9 and CYP2C19 pathways, a comparison of observed (Zhuang et al.,

2015) and predicted PK changes of a specific CYP substrate (caffeine, s-warfarin, and omeprazole) before and after treatment with sirukumab in RA patients was carried out.

Reviewer's comments

Given the higher IL-6 concentration reported in RA patients and known IL-6 mediated CYP suppression, the bridging of increased clearance of CYP substrate following co-administration of tocilizumab and sirukumab to the reversal IL-6-mediated CYP suppression is mechanistically reasonable for an anti-IL-6 mAb. However, the current modeling approach did not include a detailed mechanistic description on the actual reversal of CYP suppression in liver.

Observed CYP substrate data (for example, CYP3A4 substrate simvastatin) collected 1 week after a single dose of tocilizumab in RA population was used to represent "observed data with 0 pg/mL IL-6". The data collected at baseline (1 week before tocilizumab treatment) was used to represent "observed data with 100 pg/mL IL-6", as shown in Table 8. Reviewer noted that the current TP-DI data did not evaluate the interaction effects of anti-IL-6 mAb on the PK of a CYP substrate after multiple doses of an anti-IL-6 mAb. Additionally, the observed simvastatin AUC (44.5 ng.h/mL) might not represent the scenario of 0 pg/mL IL-6 in RA patients.

Table 8. Predicted and observed AUC for simvastatin based on steady-state IL-6

	Simvastatin $AUC_{(0-t)}$ (ng*h/mL)			
IL-6 Concentration (pg/ml)	**0**	**10**	**50**	**100**
Simulated Population Mean and SD (N=120)	30.6 ± 24.0	35.8 ± 26.7	53.45 ± 38.2	70.4 ± 48.3
Observed mean and SD (n=12)*	44.5 ± 19 Observed at D7 after tocilizumab 10 mg/kg SD		Observed at RA subject before tocilizumab dosing	105 ± 46
Predicted mean fold change (trial range)		1.17 (1.14-1.21)	1.75 (1.62 – 1.90)	2.30 (2.07 – 2.57)
Observed mean fold change				2.36

(Source: PBPK Report 1096878, Table 9B)

Results

Q1. Can PBPK analysis be used to address the concern of potential indirect effect of satralizumab on CYP activity?

The Applicant's analysis provided information on potential changes in the PK of various CYP substrates as a result of the reversal of IL-6 mediated CYP suppression upon administration of satralizumab in NMO/NMOSD patients. The predicted geometric mean AUC ratios for simvastatin (CYP3A4 substrate), S-warfarin (CYP2C9 substrate), dextromethorphan (CYP2D6 substrate), caffeine (CYP1A2 substrate), and omeprazole (CYP2C9 substrate), at various steady-state IL-6 levels, for the three ethnic groups, are shown in Table 9.

Table 9. Predicted AUC ratios for CYP substrates in the absence and presence of steady-state IL-6

IL-6 (pg/mL)	AUC ratio* GM (95% CI)				
	Simvastatin	**S-warfarin**	**Dextromethorphan**	**Caffeine**	**Omeprazole**
North European Caucasian					
0	1	1	1	1	1
10	1.15 (1.14-1.16)	1.04 (1.04-1.05)	1.05 (1.05-1.05)	1.01 (1.01-1.01)	1.13 (1.12-1.14)

50	1.65 (1.59-1.67)	1.18 (1.16-1.20)	1.21 (1.19-1.2)	1.03 (1.03-1.04)	1.56 (1.52-1.60)
100	2.08 (2.01-2.15)	1.29 (1.25-1.33)	1.37 (1.35-1.40)	1.07 (1.06-1.07)	1.97 (1.91-2.03)
Chinese					
0	1	1	1	1	1
10	1.15 (1.14-1.15)	1.04 (1.04-1.05)	1.05 (1.04-1.05)	1.01 (1.01-1.01)	1.12 (1.11-1.13)
50	1.62 (1.58-1.65)	1.17 (1.15-1.19)	1.20 (1.18-1.21)	1.03 (1.03-1.04)	1.54 (1.50-1.57)
100	2.05 (1.99-2.11)	1.28 (1.24-1.31)	1.34 (1.32-1.37)	1.07 (1.06-1.06)	1.92 (1.87-1.98)
Japanese					
0	1	1	1	1	1
10	1.15 (1.14-1.16)	1.04 (1.04-1.05)	1.05 (1.05-1.05)	1.01 (1.01-1.01)	1.12 (1.11-1.13)
50	1.62 (1.58-1.66)	1.18 (1.16-1.20)	1.22 (1.21-1.24)	1.03 (1.03-1.03)	1.51 (1.48-1.55)
100	2.06 (1.99-2.13)	1.29 (1.26-1.33)	1.39 (1.36-1.42)	1.06 (1.06-1.06)	1.88 (1.83-1.94)

*Ratio is calculated as AUC with IL-6 / AUC without IL-6. Simvastatin (40 mg SD), S-warfarin (10 mg SD), dextromethorphan (30 mg SD), caffeine (150 mg SD), and omeprazole (20 mg SD) (Source: PBPK Report 1096878, Tables 13, 15, 17, 18 and 20).

In summary, when baseline IL-6 concentrations decrease from 10 to 0 pg/mL as a surrogate for satralizumab treatment, the predicted mean change in AUC would be less than 15% for simvastatin, omeprazole, and dextromethorphan; and less than 5% for S-warfarin and caffeine. A similar interaction effect was observed in all three ethnic groups (North European Caucasians, Chinese, and Japanese).

The simulations also showed higher interaction effect on CYPs with 100 pg/mL IL-6, with the extent of effect on the different enzymes in the following order:
CYP2C19~CYP3A4>CYP2C9>CYP2D6>CYP1A2.

Reviewer's comments
The Reviewer has identified limitations in the prediction of the effect of elevated IL-6 levels on CYP activity, as described below.

1. *Uncertainty on in-vitro-in-vivo extrapolation of IL-6 suppression data*

A range of in-vitro IL-6-mediated suppression parameters has been reported in the literature (Table 10). For example, the parameters derived using either mRNA or substrate's formation rate were different (Dickman et al. 2011, Klein et al., 2015). Additionally, a time-dependent decrease in EC50 values was reported for the CYP3A pathway, while an increase in EC50 were reported for the CYP1A2 pathway.

Although the Applicant's analysis was based on the suppression parameters reported in vitro (Dickman et al. 2011); it did not rule out the possibility that a different set of in-vitro parameters (from Dickman et al., 2011 or other reference) could have also captured the observed interaction effect but yielding different predictions. For example, Jian and colleagues (Jiang et al., 2016) proposed different EC50 and Emin (or Emax) values for IL-6 modulation of CYP enzymes. Re-analysis of the in vitro dose-response curve (reported by Dickmann et al., 2011) suggested the suppression effect of IL-6 on CYP1A2 did not become significant until its concentration reached

250 pg/mL. Different Emin and EC50 values for IL-6 towards CYP3A4 activity were also derived by reanalysis of the in vitro data. The resulting IL-6 model was qualified using the clinical TP-DI of sirukumab in RA patients (Zhuang et al., 2015). In this case, prospective predictions using the different IL-6 suppression parameters may be different. Machavaram et al., (2013) also concluded that the predicted interaction effect (i.e., AUC ratio) is highly sensitive to the in vitro CYP suppression parameters used.

Table 10. Summary in-vitro IL-6-mediated CYP suppression parameters in literature

Reference	In-vitro Assay	CYP marker	Incubation time (hour)	IL-6 concentration	Emin
CYP3A4					
Dickmann (2011) (Table 2)	Primary hepatocyte	6 - testosterone	48, 72, 96	EC50: [56.3, 20.6, 17.1] pg/mL	[0.416, 0.286, 0.215]
Dickmann (2011) (Table 3)	Primary hepatocyte	CYP3A4 mRNA CYP3A5 mRNA	72	EC50: 3.23 pg/mL EC50: 51.0 pg/mL	<0.03
Klein (2015) (Figure 6)	Primary hepatocyte	OH-atorvastatin formation	48, 72	NA (media conc 10 ng/mL)	[0.36, 0.1]
Klein (2015) (Figure 1)	Primary hepatocyte	mRNA	24	NA (media conc 0.1 pg/mL - 50 ng/mL)	~0.3
CYP1A2					
Dickmann (2011) (Table 2)	Primary hepatocyte	Acetaminophen formation	48, 72, 96	EC50: [409, 443, 1260] pg/mL	[0.107, 0.125, 0.233]
Dickmann (2011) (Table 3)	Primary hepatocyte	mRNA	72	EC50: 271 pg/mL	~0.15
Klein (2015) (Figure 6)	Primary hepatocyte	Acetaminophen formation	48, 72	NA (media conc 10 ng/mL)	[0.6, 0.35]
Klein (2015) (Figure 1)	Primary hepatocyte	mRNA	24	NA (media conc 0.1 pg/mL - 50 ng/mL)	~0.25

(Source: Reviewer's compilation of data presented in the references Dickmann et al. (2011) and Klein et al. (2015), as noted).

2. *Uncertainty on verification of response curve for CYP suppression using anti-IL-6 mAb data in patient population*

The elevation of systemic IL-6 concentration following the administration of an anti-IL-6 mAb is considered to reflect the displacement of IL-6 from its receptor by the anti-IL-6 mAb. The systemic IL-6 profile in the presence of an anti-IL-6 mAb was not used to simulate the reverse effect of IL-6-mediated CYP suppression. In other words, the model did not describe the relationship between elevated plasma IL-6 levels and decreased IL-6 suppression in the liver due to the occupied IL-6 receptor by an anti-IL-6 mAb. The Applicant used the patient's baseline plasma IL-6 levels as a surrogate for hepatic IL-6 concentration to simulate CYP suppression in the population. The interaction effect in both the absence and presence of an anti-IL-6 mAb was used to verify the response curve for CYP suppression. As previously stated (Methods section, Reviewer's comment), the substrate PK data observed 1 week after an anti-IL-6 mAb treatment may not represent the scenario of 0 pg/mL IL-6.

In addition, the clinical TP-DI data used for the model verification were collected after a single dose of the anti-IL-6 mAb, tocilizumab or sirukumab. The interaction effect after multiple-dose of an anti-IL-6 mAb is unknown. This added further uncertainty when assigning data towards presenting the scenario of 0 pg/mL IL-6.

Lastly, steady-state IL-6 concentrations of 100 pg/mL in liver/plasma in RA population were required to capture the observed interaction effects with tocilizumab or sirukumab on

simvastatin. However, there is a lack of clinical data at different steady-state IL-6 concentrations to verify the slope of the response curve and the CYP suppression level. Nevertheless, based on in-vitro data and limited in-vivo data (hepatic CYP3A4 activity determined using erythromycin breath test as a surrogate marker, in post-surgery patients), a dose-dependent CYP suppression level is expected.

3. The disease-interaction effect: differences on IL-6 levels among disease populations

The clinical TP-DI of tocilizumab (10 mg IV) with simvastatin (40 mg SD) in patients with RA (Schmidt et al., 2011) was used in the IVIVE of IL-6-mediated effect on CYP3A4 activity. In this clinical study, the observed mean fold difference in simvastatin exposure in RA patients post- and pre- treatment with tocilizumab was less than 2-fold (Table 11).

Similarly, in the clinical TP-DI study of sarilumab (200 mg single SC dose) with simvastatin (40 mg SD) in RA patients, administration of sarilumab resulted in reduced exposure to simvastatin (45% reduction) and simvastatin acid (36% reduction) (Lee et al., 2016) (Table 11).

Table 11. Effect of anti-IL-6 therapies on simvastatin AUC in RA patients

	Tocilizumab (RA)[#]	**Sarilumab (RA) [&]**	**Satralizumab (RA Japanese)^**	**Satralizumab (NMOSD)**
Dosing	10 mg/kg SD IV infusion	200 mg SD SC injection	NA	NA
Baseline IL-6 level (pg/mL)	~50	47.5	~32	~2-4
IL-6 level after anti-IL-6 therapy (pg/mL)	256 (after 1 day)	220 (after 1 wk) 138 (after 2 wks)	~132	~40
Baseline simvastatin AUC in healthy subjects (ng.h/mL)	18 -29	NA	-	-
Observed baseline simvastatin AUC in patients (ng.h/mL)	105 (46)*	84.3 (68.7)**	-	-
Observed simvastatin AUC in patients 1 week after anti-IL-6 therapy (ng.h/mL)	44.5 (19)*	47.9 (37.6)**	-	-
Observed simvastatin AUC in patients 5 weeks after anti-IL-6 therapy (ng.h/mL)	65 (34)*	NA	-	-

Data are *Arithmetic mean or **Geometric mean. [#] Source: Schmitt et al. 2011. [&]Reference: Lee et al 2016. Study INT12684, BLA 761037, Clinical Pharmacology Review. ^Reference: BLA 761149, Clinical Pharmacology Summary-Report.

In the current analysis, the predicted interaction effects on CYP substrates with steady state IL-6 concentrations in NMO/ NMOSD patients (as shown in Table 9) were comparable to the reported values in RA patients receiving anti-IL-6 therapies (Schmitt et al., 2011, Zhang et al. 2005).While simulations by the Applicant and similar work by others (Machavaram et al 2019, Jiang et al 2016) appear to describe the effect of elevated IL-6 on CYP activity reported in RA patient populations; information on clinical CYP modulation effect by lower or higher plasma IL-6 levels is scarce. As such, the current analysis cannot be verified on the effect of lower IL-6 levels, as reported in NMO/MMOSD patients compared with RA patients (Table 11).

In fact, sensitivity analysis evaluating the impact of steady-state systemic IL-6 levels on modulation of CYP substrate exposure showed a higher impact on the predicted interaction effect (AUC ratio) when baseline IL-6 levels increased from 25 to 100 pg/mL; while minimal effect was predicted when baseline IL-6 levels were less than 5 pg/mL (Jiang et al., 2016).

Further, a recent review (Jing et al., 2020) of TP-DIs of several interleukin antagonists concluded that the impact of an anti-IL mAb on CYP substrate exposure appeared to be disease-related. A

greater extent of inflammation, i.e., higher IL levels, appears to result in larger interaction potential.

A careful estimate of baseline systemic IL-6 levels in the target patient population is critical for the application of this analysis since the interaction effect between an anti-IL-6 mAb and a CYP substrate drug is directly dependent on the assumption of IL-6 levels. For example, the observed baseline serum IL-6 levels in NMO/MNOSD patients enrolled in the phase 3 trials (BN40898 and BN40900) were lower [2- 4 pg/mL (range: 1.6-37.2 pg/mL)] than previously reported [median value around 60 pg/mL] (Barros et al., 2016). Similarly, systemic IL-6 levels in RA patients highly varied among different studies ranging from 3.51 to 119 pg/mL, with an estimated average (±SD) value of 49.3 (± 48.5) pg/mL (pooled analysis conducted by Jiang et al., 2016).

In conclusion, the current evidence suggested that baseline IL-6 level is likely the key factor of an anti-IL-6 mAb interaction. Confidence in the baseline IL-6 levels in the NMO/NMOSD population is needed for estimation of the interaction potential of satralizumab.

Sensitivity analysis on serum albumin in NMO/NMOSD Subjects
The Applicant noted that the serum albumin concentrations were reported lower in NMO/NMOSD patients (around 41 g albumin/L) compared to healthy volunteers (around 50 g/L). The Applicant conducted sensitivity analysis to investigate the effect of lower albumin concentrations on the pharmacokinetics of probe CYP substrates and the DDI with IL-6. The SA predicted a less than 10% difference in AUC and Cmax ratio when varying serum albumin levels (14.8-76.6 g/L) on the exposure of CYP450 substrates with and without a given IL-6 level (0-100 pg/mL).

Conclusion
The Applicant's PBPK modeling approach, although it was mechanistically reasonable, did not include a detailed mechanistic description on the actual reversal of CYP suppression in liver. Thus, this PBPK analysis was deemed exploratory.

Reviewer's analysis suggests the baseline IL-6 levels in the target patient population is likely the key factor for estimation of satralizumab interaction potential with CYP substrates.

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