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APPLICATION NUMBER:

761142Orig1s000

CLINICAL PHARMACOLOGY
REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY
BLA- 761142 (UPLIZNA)
CLINICAL PHARMACOLOGY REVIEW

BLA Number	761142
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Submission Date(s)	June 11, 2019
Submission Type	Type 1- New Molecular Entity (Standard Review)
Brand Name	Uplizna
Generic Name	Inebilizumab
Formulation and Strength	Solution for injection (100 mg/10 mL)
Route of Administration	Intravenous infusion
Proposed Indication	Neuromyelitis optica spectrum disorders (NMOSD)
Applicant	Viela Bio, Inc.
Associated IND	IND-117295
Reviewers	Dawei Li, Ph.D., Michael Bewernitz, Ph.D.
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Table of Contents

Table of Contents	2
1 Executive Summary.....	3
1.1 Recommendation	3
1.2 Post-marketing Requirements.....	4
2 Summary of Clinical Pharmacology Assessment	4
2.1 The Pharmacology and Clinical Pharmacokinetics	4
2.2 Dosing and Therapeutic Individualization.....	5
2.2.1 General Dosing	5
2.2.2 Therapeutic Individualization	5
2.3 Outstanding Issues.....	5
3 Comprehensive Clinical Pharmacology Review	5
3.1 Overview of the Product and Regulatory Background.....	5
3.2 General Pharmacology and Pharmacokinetic Characteristics	6
3.3 Clinical Pharmacology Review Questions.....	7
3.3.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?	7
3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?	8
3.3.3 Does the immunogenicity affect the PK, PD, efficacy and safety?	9
3.3.4 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic/extrinsic factors?.....	12
3.3.5 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?	13
4 Appendices	13
4.1 Summary of Bioanalytical Method Validation and Performance	13
4.2 Population Pharmacokinetic Analyses.....	14
4.2.1 Population Summary of PK Data.....	14
4.2.2 Population PK Model	15
4.2.3 Label Statements Based on Population PK Modeling.....	20
4.3 Exposure-Response Analyses	22
4.3.1 Summary of PK and Efficacy Data	22
4.3.2 Exposure-Response Models	23
4.3.3 Applicant’s Conclusions from Exposure-Response Analyses.....	26
4.3.4 Reviewer’s Assessment of ADA Development.....	28

1 Executive Summary

This original Biologics License Application (BLA) 761142 is for inebilizumab IV solution with the proposed indication for the treatment of adults with neuromyelitis optica spectrum disorders (NMOSD) (b) (4). The FDA has granted an Orphan Designation for inebilizumab for the treatment of NMOSD on 02/10/2016 (#15-4904).

Inebilizumab is a monoclonal antibody that specifically binds to CD19. Following cell surface binding to CD19, inebilizumab supports antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). The precise mechanism by which inebilizumab exerts its therapeutic effects in NMOSD is unknown.

The Applicant's proposed dosing regimen is 300 mg intravenous infusion followed 2 weeks later by a second 300 mg intravenous infusion, and a single 300 mg intravenous infusion every 6 months thereafter, starting 6 months from the first infusion.

The efficacy and safety of inebilizumab is supported by the results obtained from the pivotal Phase 2/3 trial CD-IA-MEDI-551-1155. In this trial, treatment with inebilizumab at the recommended dosage statistically significantly reduced the risk of an Adjudication Committee (AC)-determined NMOSD attack as compared to treatment with placebo. The Hazard Ratio (HR) of AC-determined attacks with inebilizumab treatment relative to placebo was 0.227 (95% CI: [0.1214, 0.4232]) for the AQP4-IgG seropositive population and was 0.272 (95% CI: [0.1496, 0.4691]) for the total ITT population ($p < 0.0001$ for each comparison). However, the effectiveness of inebilizumab treatment in AQP4-IgG seronegative population is not supported by the results from this pivotal trial.

The clinical pharmacology review focuses on the appropriateness of the proposed dosing regimen of inebilizumab and the impact of immunogenicity on PK, PD, efficacy and safety of inebilizumab.

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the information contained in BLA 761142. This BLA is approvable 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	A phase 2/3 randomized, double-blind, placebo-controlled trial provides primary evidence of effectiveness.
General dosing instructions	The recommended dose regimen is 300 mg IV infusion on day 1 followed by 2 weeks later; 300 mg IV infusion every 6 months starting 6 months from the first infusion.
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	There was no apparent impact of ADA on the PK, PD (CD19+ B-cell depletion) or efficacy of inebilizumab. Safety profiles are comparable based on ADA status.
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

Inebilizumab is a humanized IgG1 monoclonal antibody targeting CD19+ B cells. The molecular weight is approximately 149 kDa. Following cell surface binding to B cells, inebilizumab supports antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). B-cells are believed to play a central role in the pathogenesis of NMOSD. The precise mechanism by which inebilizumab exerts its therapeutic effects in NMOSD is unknown.

Pharmacokinetics

Following IV administration of inebilizumab at the recommended dosing schedule (300 mg on day 1 and day 15) in patients with NMOSD, the concentration versus time profile was biphasic with a mean terminal half-life of 18 days.

Based on population pharmacokinetic analysis, the estimated typical central and peripheral volume of distribution of inebilizumab was 2.95 L and 2.57 L, respectively; the estimated systemic clearance of the first-order elimination pathway was 0.19 L/day. At low PK levels, inebilizumab may be subject to (CD19) receptor-mediated clearance.

Based on population pharmacokinetic analysis, the effects of body weight, age, gender and race are unlikely to be clinically significant. Therefore, no dose adjustments are recommended for inebilizumab based on these covariates.

Specific Populations

No formal clinical studies have been conducted to investigate the effect of renal/ hepatic impairment on inebilizumab. Based on population pharmacokinetic analysis, markers of renal function (creatinine clearance and estimated glomerular filtration rate) were not covariates of inebilizumab clearance in NMOSD patients. Though Child-Pugh hepatic impairment scores were not available, bilirubin (one of the four components of the Child-Pugh score of hepatic impairment) was not a covariate on inebilizumab clearance. Hepatic impairment is not expected to affect inebilizumab clearance. Overall, no dose adjustments are recommended for inebilizumab based on renal or hepatic impairment.

Immunogenicity

In study 1155, in the randomized-controlled period (RCP), the ADA incidence in inebilizumab-treated subjects at any time point was 9.8% (17 of 174 subjects, 2.9% at baseline 5 of 174 subjects, 7.0% post-treatment 12 of 174 subjects). The treatment-emergent ADA incidence was 2.9% (5 of 174 subjects). In the open-label period (OLP), the ADA prevalence in inebilizumab-treated subjects at any time point was 13.0% (30 of 230). The treatment-emergent ADA incidence was 5.3% (12 of 225 subjects). Additionally, the ADA incidence in placebo subjects at any timepoint was 14.3% (8 of 56 subjects, 7.1% at baseline 4 of 56 subjects). The detected ADA positive in inebilizumab treatment subjects at baseline and in placebo treatment subjects is

mainly due to the super-sensitivity of the assay and the cut-points was statistically set and biased towards false positive results rather than false-negatives. Overall, the presence of ADA is unlikely to have a clinically-relevant impact on PK, PD (CD20+ B-cell depletion, used in lieu of CD19+ B-cells as inebilizumab interferes with CD19-based B-cell detection methods), efficacy or safety of inebilizumab.

2.2 Dosing and Therapeutic Individualization

2.2.1 General Dosing

The recommended dose regimen is 300 mg IV infusion on day 1 followed by 2 weeks later; 300 mg IV infusion every 6 months starting 6 months from the first infusion.

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

Inebilizumab injection for intravenous use is supplied in three (3) single-use vials per dose, each containing 100 mg of inebilizumab in 10 mL. Each mL contains inebilizumab (10 mg), L-histidine (1.4 mg), L-histidine hydrochloride monohydrate (2.3 mg), α,α -trehalose dihydrate (40.1 mg), sodium chloride (4.1 mg), polysorbate 80 (0.1 mg) and Water for Injection, USP.

The inebilizumab clinical program composed of two phase 1 studies (one in subjects with systemic sclerosis [SSc], Study MI-CP200; one in subjects with relapsing forms of multiple sclerosis [MS], Study 1102) and one phase 2/3 pivotal safety and efficacy study in subjects with NMOSD.

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

Table 1: Inebilizumab Clinical Trials

Trial	Description	Population	Dose
MI-CP200	Phase 1, randomized, placebo-controlled, blinded, SAD study to evaluate safety, tolerability, PK and PD	Adult subjects with Systemic sclerosis (SSc) (n=28)	Single ascending doses of 0.1, 0.3, 1.0 3.0 and 10 mg/kg
CD-IA-MEDI-551-1102	Phase 1, randomized, placebo-controlled, blinded, dose escalation study to evaluate safety tolerability, PK and PD	Adult subjects with relapsing forms of MS (n=28)	Fixed IV dose on Day 1 and Day 15: 30, 100 and 600 mg; Single SC dose: 60 and 300 mg
CD-IA-MEDI-551-1155	Phase 2/3, randomized, double-blind, placebo-controlled with an open-label extension to evaluate efficacy	Adult subjects with NMOSD (Inebilizumab n=174; Placebo	RCP: 300 mg IV on Day 1 and Day 15; OLP: 300 mg on Day 1 and Day 15, then Q26W

	and safety	n=56)	thereafter

3.2 General Pharmacology and Pharmacokinetic Characteristics

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

Table 2: Summary of Inebilizumab Clinical Pharmacology Information

Pharmacology	
Mechanism of Action	Inebilizumab is a humanized IgG1 monoclonal antibody targeting CD19+ B cells. By binding to B cells (also known as B lymphocytes), inebilizumab supports antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP).
QT Prolongation	No formal QT evaluation has been conducted for inebilizumab. As a large molecule, inebilizumab has a low likelihood to directly interact with ion channels.
General Information	
Bioanalysis	Inebilizumab was measured using validated Enzyme Linked Immunosorbent Assay (ELISA) methods.
Drug total exposure following the therapeutic dosing regimen	The mean maximum concentration was 108 µg/mL, and the cumulative AUC of the 26-week treatment period was 2980 µg·d/mL following two IV administrations (300 mg, 2 weeks apart).
Dose Proportionality	The systemic exposures increased approximately proportionally with an increase in dose from 30 mg to 600 mg.
Immunogenicity	In study 1155, the ADA incidence in inebilizumab-treated subjects at any timepoint was 9.8% (17 of 174 subjects). The presence of ADA does not have a clinically-relevant impact on PK parameters, PD parameters, or the efficacy of inebilizumab.
Inhibitor/Inducer	Not evaluated. As a large recombinant protein, inebilizumab is not expected to be an inhibitor or inducer of drug metabolism enzymes or transporters.
Distribution	
Volume of Distribution	Central and peripheral volume of distribution was 2.95 L and 2.57 L, respectively.
Elimination	

Terminal Elimination Half-life	Approximately 18 days.
Metabolism / Excretion	As a humanized IgG1 monoclonal antibody, inebilizumab is expected to be degraded into small peptides and amino acids by proteolytic enzymes widely distributed in the body.

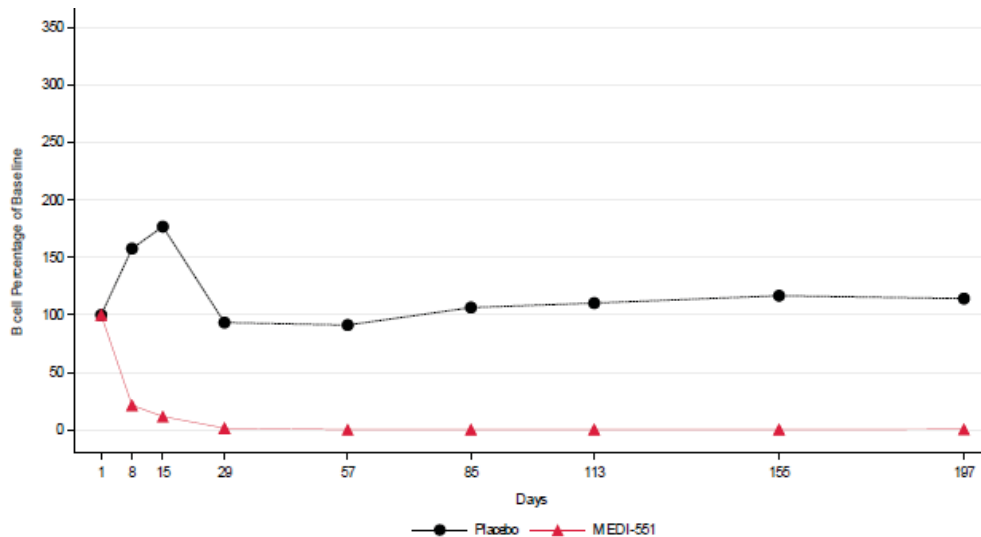
3.3 Clinical Pharmacology Review Questions

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

The evidence of effectiveness of inebilizumab is based on one placebo-controlled, randomized, double-blind, efficacy and safety phase 2/3 study in adult patients with NMOSD (study 1155). This study met its primary endpoint: subjects treated with inebilizumab (300 mg administered IV on Days 1 and 15) had a statistically significant reduction in the risk of Adjudication Committee-determined NMOSD attack in the AQP4-IgG seropositive population compared to subjects treated with placebo. However, current data do not support the effectiveness of inebilizumab in AQP4-IgG seronegative population. (Please refer to the clinical review and biostatistics review for further details).

CD20+ B cells were measured, rather than CD19+ B cells, because the presence of inebilizumab interferes with the recognition of cell surface CD19 in the CD19 assay. In study 1155, following treatment with inebilizumab, CD20+ B cells were below the lower limit of normal in 100% of inebilizumab-treated subjects at 4 weeks and 94% of subjects at the end of the 28-week randomized controlled period (RCP). Aside from a transient increase lasting ~1 month post-infusion, CD20+ B-cell counts in the placebo group were generally close to the baseline level throughout the RCP (see Figure 1).

Figure 1: Median Values for CD20 B-cell Count as Percentage of Baseline Over Time, Randomized-controlled Period (ITT Population) (Study 1155)



ITT = intent-to-treat; MEDI-551 = inebilizumab.
Median blood CD20+ B-cell count as a percentage of baseline over time in inebilizumab and placebo-treated subjects plotted on a linear scale.

Source: Applicant's Summary of Clinical Pharmacology (M 2.7.2), Figure 6 on page 20

However, the relationship between CD20+ B-cell changes and efficacy in an NMOSD population is not established. It is not clear that changes in the CD20+ B-cell profile can be used to support effectiveness of inebilizumab at this time.

The relationship of PK exposure and efficacy response (primary and key secondary endpoints) was evaluated for Study 1155. The key secondary endpoints included in exposure-response analyses are Expanded Disability Status Scale (EDSS) score, visual acuity, active magnetic resonance imaging (MRI) lesions, and number of hospitalizations. Though inebilizumab met the primary efficacy endpoint and showed improvement EDSS, active MRI lesions, and number of hospitalizations compared to placebo, an exposure-response relationship is not apparent for the primary efficacy endpoint nor any of these secondary endpoints.

Overall, the exposure-response (E-R) analysis does not provide additional evidence of the effectiveness of inebilizumab for the treatment of adults with NMOSD. Support for the inebilizumab for this indication comes from the clinical efficacy from Study 1155 (see Table 3).

Table 3. Primary Analysis of Time to Adjudication Committee-determined Attack, Randomized-controlled Period (Study 1155)

	AQP4-IgG sero+ N = 213		AQP4-IgG sero- N = 17		Total N = 230	
	Placebo N = 52	Inebilizumab N = 161	Placebo N = 4	Inebilizumab N = 13	Placebo N = 56	Inebilizumab N = 174
Number of subjects with an attack	22 (42.3%)	18 (11.2%)	0	3 (23.1%)	22 (39.3%)	21 (12.1%)
Number of censored subjects	30 (57.7%)	143 (88.8%)	4 (100%)	10 (76.9%)	34 (60.7%)	153 (87.9%)
Hazard ratio ^a		0.227		NA		0.272
95% CI ^a		(0.1214, 0.4232)		(NA, NA)		(0.1496, 0.4961)
p-value ^a		< 0.0001		0.9977		< 0.0001

AQP4-IgG = autoantibodies against aquaporin-4; CI = confidence interval; ITT = intent-to-treat; NA = not applicable; sero- = seronegative; sero+ = seropositive.

^a Based on Cox regression method, with Placebo as the reference group.

Source: Clinical Study Report – CD-IA-MEDI-551-1155, Table 20 on page 95

Reviewer’s comments: Due to the insufficient data for AQP4 sero- patients, the clinical effectiveness for AQP4 sero- patients is inconclusive. Please refer to the clinical review and biostatistics review for additional details.

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

The proposed dosing regimen is supported by the efficacy and safety in Study 1155.

Based on E-R analysis, there was no apparent relationship of PK exposure to inebilizumab and the outcome of the primary or key secondary efficacy endpoints. Overall, the exposure-response analyses do not clearly inform the dose selection.

The presence of ADA is not likely to have a clinically-relevant impact on inebilizumab PK or on CD20+ B-cell levels in subjects with NMOSD. There was no apparent impact of ADA on inebilizumab efficacy or safety. Please refer to sections **Error! Reference source not found.** and **4.3.2 Exposure-Response Models** for additional details.

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

The presence of ADA is unlikely to have a clinically-relevant impact on PK, PD, efficacy or safety of inebilizumab.

Immunogenicity incidences

In study 1155, a total of 2022 serum samples from 230 patients were tested for the presence of ADA to inebilizumab. In the RCP phase, the ADA incidence in inebilizumab-treated subjects at any time point was 9.8% (17 of 174 subjects). The treatment-emergent ADA incidence was 2.9% (5 of 174 subjects). In the OLP phase, the overall ADA prevalence in inebilizumab-treated subjects at any time point was 13.0% (30 of 230). The treatment-emergent ADA incidence was 5.3% (12 of 225 subjects).

Additionally, 8/56 (14.3%) of placebo-treated subjects had ADA at any timepoint (including 4 of 56 subjects at baseline) as compared to 17/174 (9.8%) of subjects treated with inebilizumab (including 12 of 174 subjects at baseline). The sponsor provided the following explanation for the observed ADA incidence in the placebo treatment arm and in the inebilizumab treatment arm at baseline:

ADA method cut-points are statistically set and biased towards false positive samples rather than false-negative samples as an assurance that true low positive samples can be detected. The process involves sequential assessments to identify and remove outliers, and for assumption of normality. This approach was used for both screening and confirmatory tier cut-point determination in order to avoid cut-point inflation and potentially miss true ADA positive samples. The applicant stated that the targeted false positive rate has been shown to generate an observed false positive rate of 2-11% in previous publications.

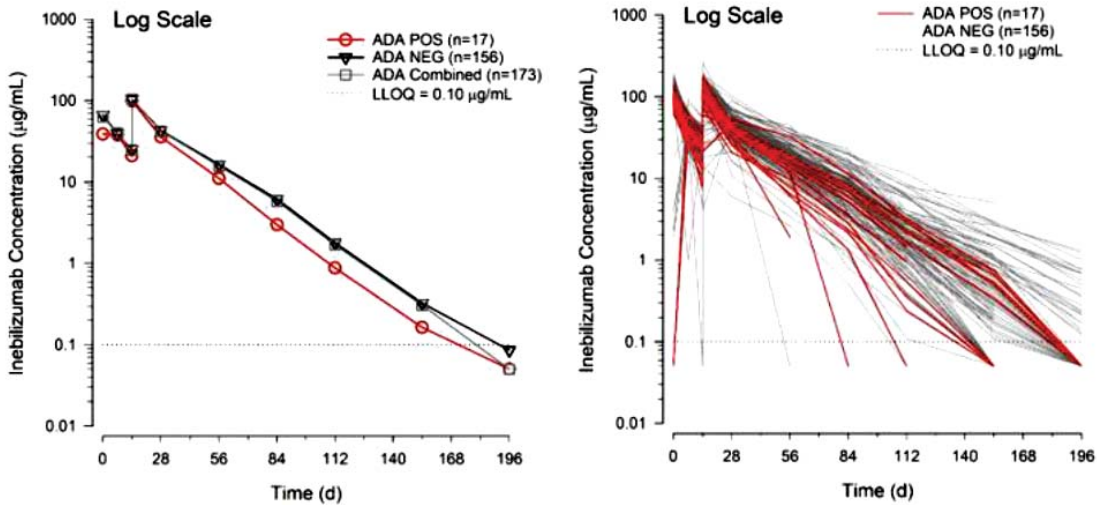
The inebilizumab ADA method has a sensitivity of 8.79 ng/mL using the goat polyclonal antibody positive control and is 10x more sensitive than the current guidance recommendations. These supersensitive assays typically lead to higher numbers of ADA positive patients with low titers that often have no clinical relevance.

Reviewer's comments: The sponsor provided justification indicated that observed ADA positive in placebo-treated subjects and in inebilizumab-treated subjects at baseline was mainly due to statistical cut-points setting approach caused false positive. According to the OBP reviewer, the developed analytical assay and validation results are acceptable, and the sponsor provided justification appears reasonable from the assay perspective.

Immunogenicity impact on pharmacokinetics

The inebilizumab PK profiles are similar for ADA-positive and negative (**Error! Reference source not found.**). Box plots comparing overall PK exposure (cumulative area under the concentration-time curve from Time 0 of Dose 1 to infinity [$AUC_{inf,cum}$]), CL, and $t_{1/2}$ in ADA-positive and ADA-negative subjects in the RCP, are presented in **Error! Reference source not found.**

Figure 2: Inebilizumab Serum Concentration-Time Profiles by ADA Status (Study 1155)



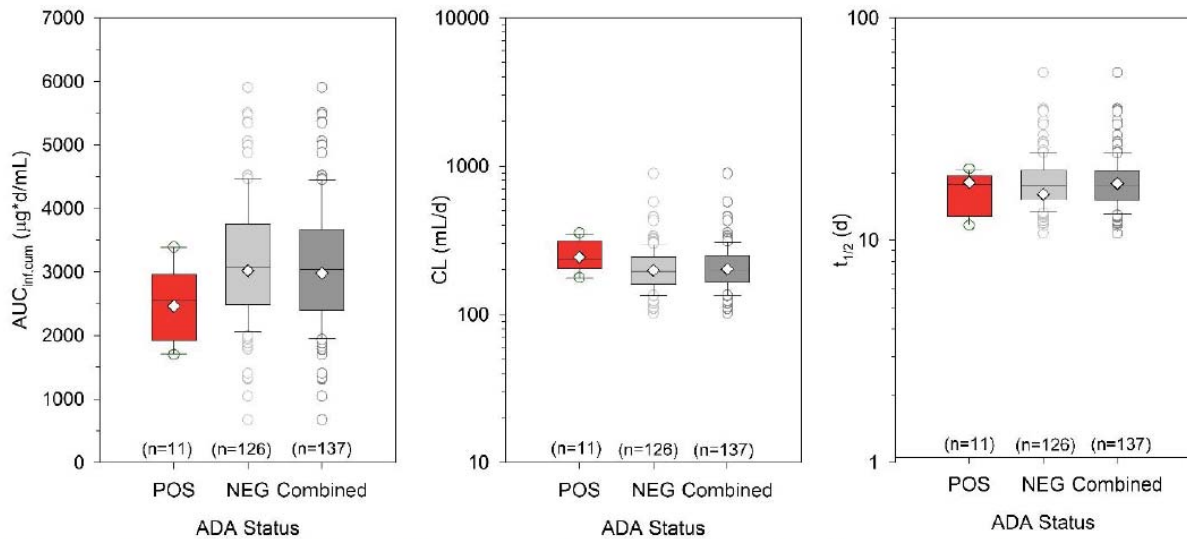
ADA = anti-drug antibodies; ADA NEG = ADA-negative subject, titer < 50; ADA POS = ADA-positive subject with titer $\geq$ 50; IV = intravenous; LLOQ = lower limit of quantitation; n = sample size.

Left panel: geometric mean serum concentration of inebilizumab; right panel: individual serum concentrations of inebilizumab.

Data below LLOQ are plotted at $\frac{1}{2}$ LLOQ (0.05 $\mu\text{g/mL}$; as shown by dotted line) for illustrative purposes only.

Source: 5353-integrated-summary-immunogenicity.pdf, Figure 5 on page 19

Figure 3: Impact of ADA on PK Exposure, Clearance and Terminal half-life (Study 1155)



ADA = anti-drug antibodies; NEG = ADA-negative subjects, titer < 50; POS = ADA-positive subjects with titer $\geq$ 50; IQR = inter-quartile range; n = sample size.

The boxes indicate the first and third quartiles. The black horizontal bar within the box illustrate the median (or second quartile). The whiskers are the minimum and maximum observation within the 1.5 IQR of the first and third quartiles, respectively. Circles = outliers; Diamond = geometric mean.

Source: 5353-integrated-summary-immunogenicity.pdf, Figure 6 on page 20

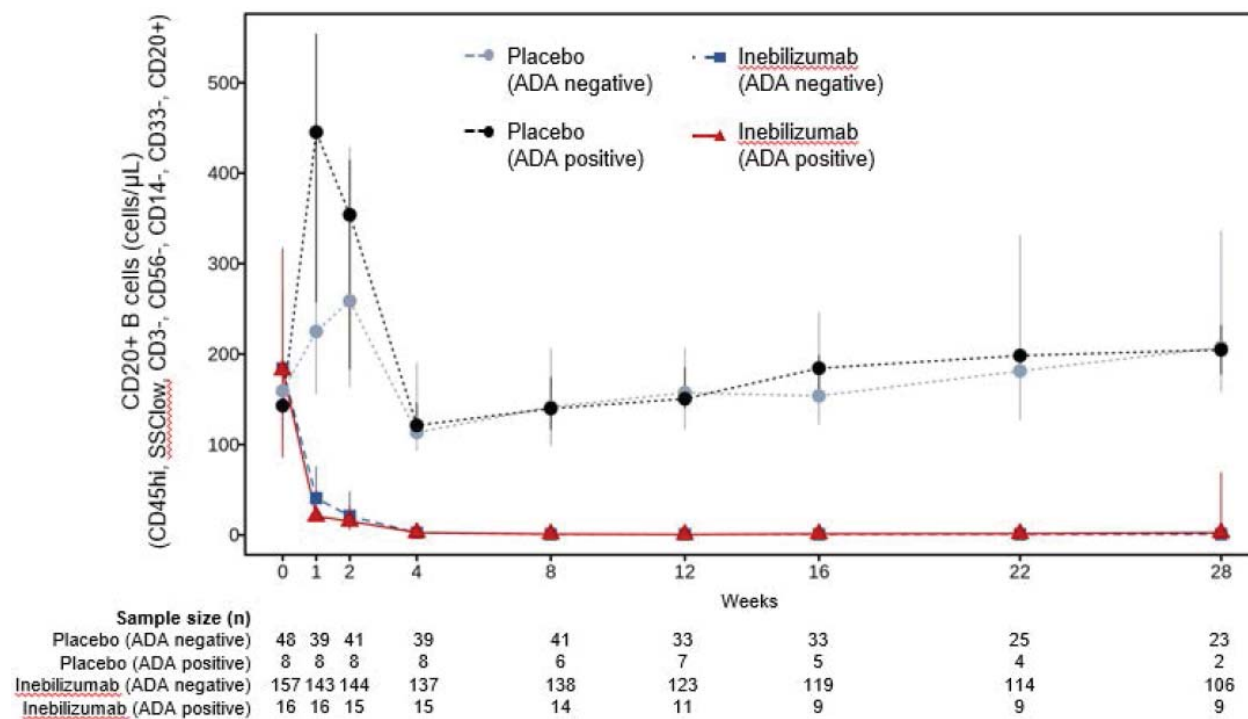
The mean CL in subjects with ADA status appears to be $\sim$ 22% higher in ADA-positive subjects versus ADA-negative subjects (243 mL/day versus 198 mL/day, respectively; from page 19 of

Applicant’s integrated summary of immunogenicity). However, the coefficient of variation for CL in these two groups is comparable to ADA effect on CL (25.4% CV and 34.6% CV in ADA-positive and ADA-negative subjects, respectively). Overall, considering the magnitude of the observed ADA effect on CL ADA status is not expected to produce a clinically-relevant effect on inebilizumab PK.

Immunogenicity impact on pharmacodynamics

The effect of ADA on pharmacodynamics was measured by CD20+ B-cell counts in inebilizumab and placebo-treated patients in RCP. As shown in **Error! Reference source not found.**, CD20+ B-cells are > 90% depleted by Week 2 and do not increase through Week 28 in both ADA positive and ADA negative inebilizumab-treated subjects.

Figure 4: Peripheral Blood Median Absolute CD20+ B-cell Count in Inebilizumab and Placebo-Treated Subjects in RCP by ADA Status (Study 1155)



Source: Clinical Study Report – CD-IA-MEDI-551-1155, Figure 16 on page 128

Immunogenicity impact on efficacy

The comparison of hazard ratios for AC-determined NMOSD attacks are summarized in **Error! Reference source not found.** The results indicate that there was no apparent effect of ADA on the efficacy of inebilizumab.

Table 4. Hazard Ratio of AC-Determined NMOSD Attack During the RCP by ADA Status (Study 1155)

ADA Status	Inebilizumab (n)	Placebo (n)	Hazard Ratio	95% CI

ADA Negative Inebilizumab vs Placebo	157	48	0.274	0.143 - 0.528
ADA Positive Inebilizumab vs Placebo	17	8	0.272	0.061 - 1.220

Source: 1155 Exposure-Response Report, Table 5, on page 29

Immunogenicity impact on safety

The comparison of Treatment-emergent Adverse Events (TEAE) based on ADA status are summarized in **Error! Reference source not found.** Overall, there was no apparent impact of ADA on the safety profile of inebilizumab.

Table 5: Summary of Treatment-emergent Adverse Events, Randomized-controlled Period by ADA status

Subjects with:	ADA Positive		ADA Negative	
	Placebo N = 8	Inebilizumab N = 17	Placebo N = 48	Inebilizumab N = 157
At least one TEAE	5 (62.5%)	12 (70.6%)	36 (75.0%)	113 (72.0%)
Blood and lymphatic system disorders	0	2 (11.8%)	4 (8.3%)	10 (6.4%)
General disorders and administration site conditions	0	2 (11.8%)	6 (12.5%)	16 (10.2%)
Infections and infestations	2 (25.0%)	9 (52.9%)	21 (43.8%)	57 (36.3%)
Injury, poisoning and procedural complications	1 (12.5%)	4 (23.5%)	10 (20.8%)	23 (14.6%)
Investigations	0	1 (5.9%)	5 (10.4%)	12 (7.6%)
Metabolism and nutrition disorders	1 (12.5%)	1 (5.9%)	3 (6.3%)	3 (1.9%)
Musculoskeletal and connective tissue disorders	0	3 (17.6%)	12 (25.0%)	35 (22.3%)
Nervous system disorders	1 (12.5%)	1 (5.9%)	11 (22.9%)	31 (19.7%)
Psychiatric disorders	0	2 (11.8%)	8 (16.7%)	10 (6.4%)

Source: Reviewer's summary based on Clinical Study Report – CD-IA-MEDI-551-1155, Table 14.3.1.4.6.1 on page 1803 and 14.3.1.4.6.2, on page 1807

Overall, development of ADA is not expected to have a clinically-relevant effect on the efficacy and safety of inebilizumab.

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. The assessment of intrinsic and extrinsic factors on inebilizumab PK was conducted using population PK (PPK) analyses. The PPK analyses suggest that dose adjustments are not necessary based on measures of renal function (creatinine clearance and estimated glomerular filtration rate). While assessment of hepatic impairment was not available for use in PPK modeling, bilirubin (a component of the Child-Pugh scale for assessing hepatic impairment) was not a covariate on inebilizumab clearance. Hepatic impairment is not expected to affect inebilizumab elimination. Though weight is a covariate on inebilizumab PK, the efficacy data from Study 1155 provides support for the flat dosing regimen (300 mg every 2 weeks, followed by 300 mg every 6 months; 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 inebilizumab is a biologic administered by IV infusion, a food-drug interaction is not applicable.

The primary elimination pathway for inebilizumab is clearance by the reticuloendothelial system that is likely similar to endogenous IgG clearance. Therefore, the potential risk of PK interactions between inebilizumab and other drugs is low.

Treatment with inebilizumab led to reduced peripheral CD20+ B-cell counts below the lower limit of normal (which the Applicant defines as 74.4 CD20+ B-cells/ μ L). As with other B-cell depleting drugs, concomitant usage of inebilizumab and other immunosuppressant drugs may result in an increased risk of infection. Interactions may occur with other biologic immunosuppressants.

4 Appendices

4.1 Summary of Bioanalytical Method Validation and Performance

For the determination of plasma inebilizumab 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. The assay has no apparent hook effect at concentrations up to 262,736.64 ng/mL of inebilizumab. The method is specific to inebilizumab and accurately quantifies inebilizumab at levels ≥ 170.08 ng/mL in the presence of 50 ng/mL anti-drug antibody or $\geq 1,420.51$ ng/mL in the presence of 500 ng/mL anti-drug antibody. Serum samples may undergo five freeze-thaw cycles, be stored for up to 14 days at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$, for up to 20 hours at room temperature, for up to 28 days at $-80^{\circ}\text{C} \pm 10^{\circ}\text{C}$, or for up to 28 days at $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$ when undiluted.

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

Bioanalytical method validation	Report No.: CTVR-0062
LLOQ (ng/mL)	100.05

Validation assay range (ng/mL)	100.05 to 4105.26
Inter-day accuracy (% RE)	-2.9% to -18.9%
Inter-day precision (%CV)	5.5% to 7.0%
Intra-day accuracy (% RE)	-23.0% to 0.4%
Intra-day precision (%CV)	2.8% to 7.2%

4.2 Population Pharmacokinetic Analyses

The Applicant developed a population PK model to characterize the pharmacokinetics of inebilizumab in systemic sclerosis (SSc) patients, multiple sclerosis (MS) patients, and NMOSD patients. An additional objective was to assess the potential impact of potential covariates on inebilizumab PK.

4.2.1 Population Summary of PK Data

There were 1617 measurable observations of inebilizumab from n=213 subjects.

Table 6: Summary of Studies Included in Population Pharmacokinetic Analyses

Study ID	Design	Dosing	Subjects	PK Sampling
CP200	Phase 1, randomized, double-masked, placebo-controlled study to assess safety and tolerability in SSc patients	Single IV doses (0.1, 0.3, 1.0, 3.0, and 10.0 mg/kg or placebo)	A total of 28 subjects were enrolled into the study, with 5 cohorts of subjects receiving 1 of 5 single IV doses of inebilizumab (0.1, 0.3, 1.0, 3.0, or 10.0 mg/kg) or placebo	PK at predose, 30 minutes after the end of the infusion on Day 1, and on Days 3, 8, 15, 29, 57, and 85 ADA on Days 1, 29, 57, 85.
1102	Phase 1, randomized, masked, placebo-controlled dose-escalation study to assess safety and tolerability in RRMS patients	Two IV infusions on Days 1 and 15 of inebilizumab (30, 100 or 600 mg or placebo) Single SC administration of inebilizumab (60 or 300 mg) or placebo	A total of 28 subjects were enrolled in the study. Among them 21 received inebilizumab (15 IV and 6 SC) and 7 received placebo	PK at predose and 15 minutes after the end of infusion on Day 1 and Day 15, and on Days 8, 29, 57, 85, 113, 141 and 169 of the RCP ADA on Days 1 (predose), 29, 85, and 169, and at 3, 6, 9, 12, 15, and 18 months during the LTFU period
1155	Phase 2/3, randomized, double-masked, placebo-controlled study to assess efficacy, safety and tolerability in	Two IV infusions on Days 1 and 15 of inebilizumab (300 mg) or placebo during the RCP	A total of 230 subjects with NMOSD was enrolled and randomized in a 3:1 ratio to receive inebilizumab or placebo for a period of 197 days (RCP)	PK at predose and 15 minutes after the end of infusion on Day 1 and Day 15, and on Days 8, 29, 57, 85, 113, 155 and 197 of RCP ADA on Days 1 (predose), 29, 85, and 197 of RCP, and at Weeks 0,

	NMOSD patients			13, 26, 39 and 52 during the OLP then every 3 months for one year post last dose in SFP

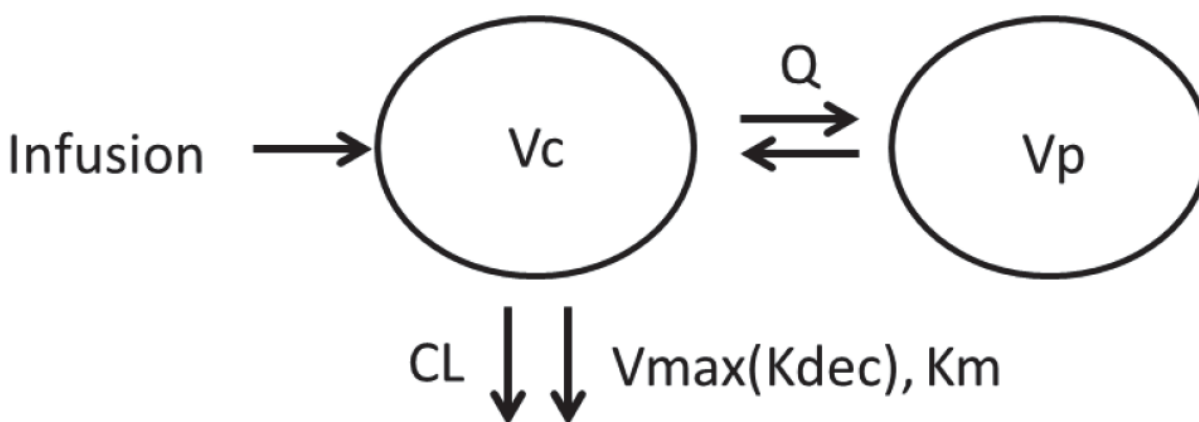
ADA = anti-drug antibody; IV = intravenous; LTFU = long-term follow-up; NMOSD = neuromyelitis optica spectrum disorders; No. = number; OLP = open-label period; PK = pharmacokinetic; RCP = randomized-control period; SC = subcutaneous; SFP = safety follow-up period; SSc = systemic sclerosis; RRMS = relapsing-remitting multiple sclerosis.

Source: sequence 0001, module 5335, inebi-ppk-report-10may2019-final.pdf, page 15 of 131

4.2.2 Population PK Model

The structural model includes two compartments, a zero-order input term to represent IV infusion, a linear elimination term and a non-linear elimination term. The non-linear elimination pathway is described using a modified Michaelis-Menten model. The modified Michaelis-Menten model includes a term describing the decrease in V_{max} over time using a mono-exponential decay term. A schematic description of the model is presented in **Figure 5**.

Figure 5: Schematic Representation of the Final PPK model



CL = clearance; V_c = volume of distribution in the central compartment; Q = inter-compartmental clearance; V_p = volume of distribution in the peripheral compartment; V_{max} = maximum velocity of Michaelis-Menten model; K_{dec} = first-order rate constant, describing the decrease of V_{max} over time; K_m = concentration to achieve half of V_{max} .

Source: sequence 0001, module 5335, inebi-ppk-report-10may2019-final.pdf, page 37 of 131

Allometric scaling: CL, V_c , Q , and V_p were scaled with body weight (normalized to the median body weight in the dataset, 66.2 kg) according to a power model. The power model exponent was estimated for each of the four PK parameters.

Inter-Individual Variability: exponential

Residual Variability: proportional

Covariates: Participation in Study CP200 was a covariate on V_{max} .

The Applicant determined that the available PK data do *not* support inclusion of the following variables as CL covariates in the PPK final model:

- a. measures of renal function (creatinine clearance nor estimated glomerular filtration rate)
- b. serum bilirubin (one of the components of the Child-Pugh hepatic impairment score)
- c. time-varying anti-drug-antibody (ADA) status
- d. concomitant paracetamol (also known as acetaminophen),
- e. concomitant methylprednisolone,
- f. concomitant diphenhydramine,
- g. concomitant prednisolone

Parameter estimates for the final model are presented in the table below.

Table 7: PK Parameter Estimates for the Final PPK Model (Run ^{(b) (4)} in NMOSD Patients

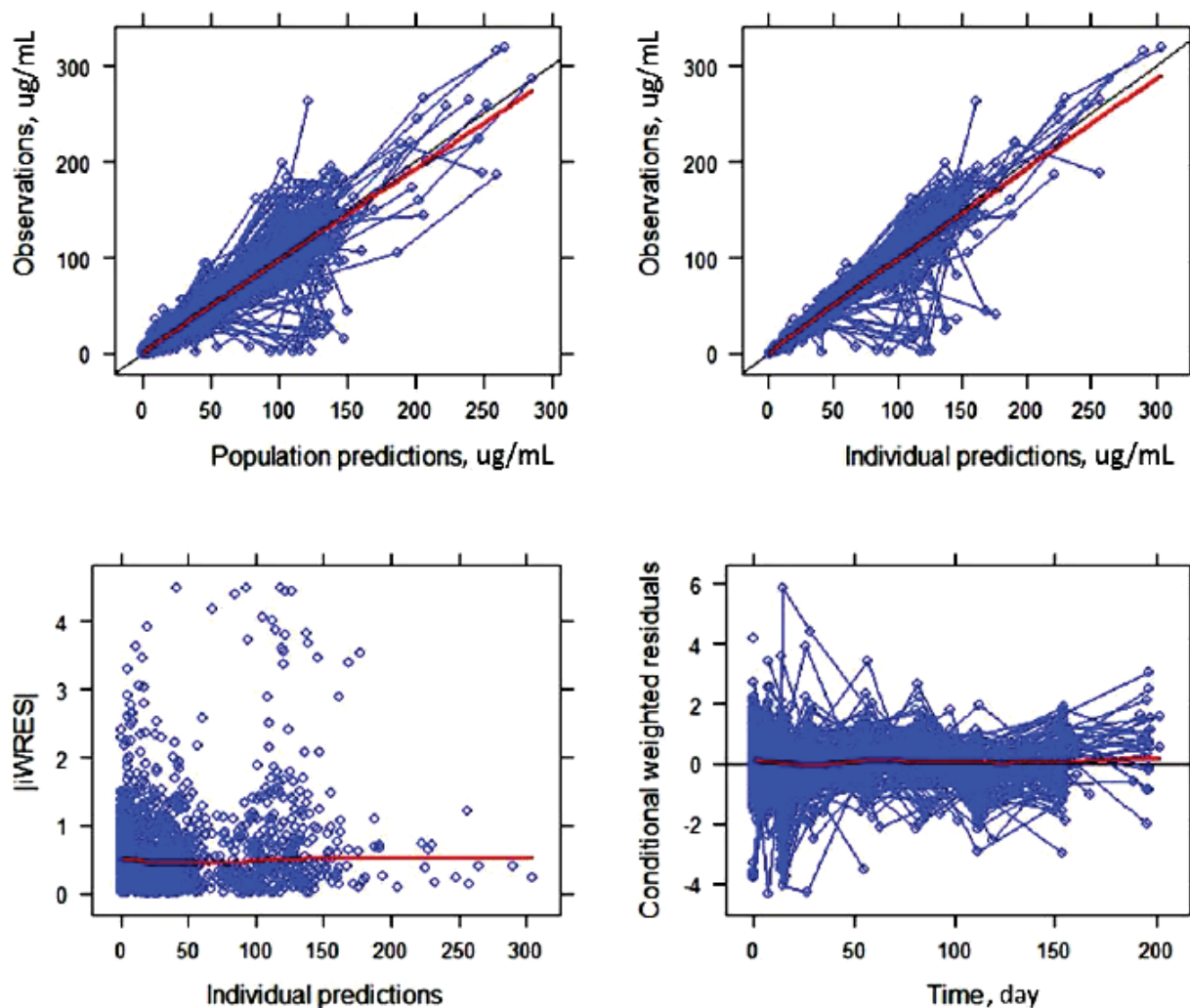
Parameter, unit	Estimates	RSE (%)	IIV (CV%)	RSE (%)	Shrinkage (%)
CL (mL/day)	188.22	2.2	27	25	8.2
Weight on CL	0.57	15.8	na	na	na
V _c (mL)	2946.39	1.4	17	30	27.4
Weight on V _c	0.39	22.4	na	na	na
Q (mL/day)	363.23	6.0	na	na	na
Weight on Q	0.84	21.1	na	na	na
V _p (mL)	2569.43	2.8	16	45	38.8
Weight on V _p	0.40	27.9	na	na	na
V _{max} (ug/day)	832.50	5.3	30	61	61.2
Study CP200 on V _{max} (%)	209.91	19.5	na	na	na
K _{dec} (1/day)	0.00294	55.1	na	na	na
K _m (ug/mL)	5.89	25.5	na	na	na
Proportional ERR (%CV)	21.78	4.6	na	na	12.1

CI = confidence interval; CL = clearance; CV = coefficient of variation; IIV = interindividual variability; K_{ee} = first-order rate constant for decrease in V_{max}; Km = concentration to achieve half of V_{max}; na = not available; Q = inter-compartmental clearance; RSE = relative standard error in percent; V_c = volume of distribution in the central compartment; V_{max} = maximum velocity of the non-linear clearance process; V_p = volume of distribution in the peripheral compartment

Source: sequence 0001, module 5335, inebi-ppk-report-10may2019-final.pdf, page 37 of 131

Model diagnostics are presented in the figures below.

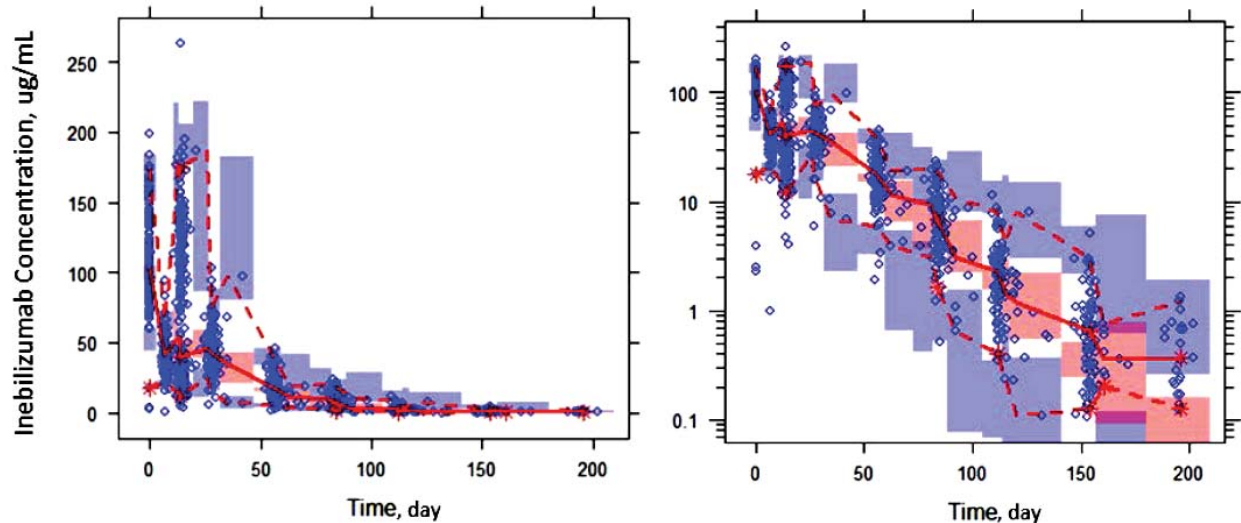
Figure 6: Goodness-of-Fit Plots for Final PPK Model (Run (b) (4))



IV = intravenous; $|iWRES|$ = absolute individual weighted residuals. “Observations” are the observed inebilizumab concentration measurements. “Population predictions” are the concentrations predicted based on typical (population) values of the pharmacokinetic parameters, whereas “Individual predictions” are the concentrations predicted based on individual values of pharmacokinetic parameters. All the concentrations are in $\mu\text{g/mL}$ unit. The circles are the pairs of observations and predictions or weighted residuals. The red solid lines are LOESS smoothing lines.

Source: sequence 0001, module 5335, inebi-ppk-report-10may2019-final.pdf, page 39 of 131

Figure 7: Prediction-Corrected Visual Predictive Check of Study 1155 in NMOSD Patients



The blue circle represents the observed concentration. The solid and dashed lines represent the median and 2.5th and 97.5th percentiles of the observations. The shaded red and blue areas represent the 95% confidence interval of the median and 2.5th and 97.5th percentiles predicted by the model, respectively.

Source: sequence 0001, module 5335, inebi-ppk-report-10may2019-final.pdf, page 41 of 131

[Reviewer comment: The diagnostic plots of weighted residuals (not shown in review) do not indicate the presence of bias with respect to the magnitude of population prediction nor throughout the time of the trial (see Figure 10 on page 40 of 131 of inebi-ppk-report-10may2019-final.pdf).

The prediction-corrected visual predictive check (pc-VPC) of the PK data from the Phase 3 Study 1155 suggests that at most timepoints ≥ 50 days, the model appears to capture central tendency and variability in inebilizumab concentration. However, the scale used to present the pc-VPC in **Figure 7** makes it difficult to assess performance for time periods at times < 50 days. To investigate the model performance at times < 50 days, the Reviewer inspected the Applicant's plots of individual-predicted IV PK profiles overlaid with population-predicted IV PK profiles and individual observed IV PK profiles. These figures, which are not shown in this review, suggest that the model is able to adequately represent the PK profile during times < 50 days (a time period which includes the two infusions). Please refer to inebi-ppk-report-10may2019-final.pdf, Figures 24 through 37 on pages 88 to page 101, for details.

In Study 1155, prior to receiving investigational product on Day 1 and Day 15, subjects were pretreated with IV methylprednisolone (80-125 mg or equivalent glucocorticoid such as prednisolone), oral diphenhydramine (25-50 mg or equivalent antihistamine), and oral paracetamol (also known as acetaminophen; 500-650 mg) prophylactically to reduce the risk of infusion-related reactions. Overall, paracetamol, methylprednisolone, diphenhydramine, and prednisolone were used by 97%, 90%, 82%, and 9% of patients in Study 1155, respectively. The breakdown of concomitant medication use is presented in the table below.

Table 8: Number of Subjects Receiving Each Co-medication in Study 1155

<i>Co-medication</i>	<i>Taken</i>	<i>Not Taken</i>
<i>Paracetamol</i>	<i>169 (97%)</i>	<i>5 (3%)</i>
<i>Methylprednisolone</i>	<i>157 (90%)</i>	<i>17 (10%)</i>
<i>Diphenhydramine</i>	<i>143 (82%)</i>	<i>31 (18%)</i>
<i>Prednisolone</i>	<i>16 (9%)</i>	<i>158 (91%)</i>

Source: sequence 0001, module 5335, inebi-ppk-report-10may2019-final.pdf, page 45 of 131

In the PPK analyses the Applicant assessed the effect of these 4 concomitant medications on inebilizumab PK. The Applicant provides a plot, not shown in this review, showing a comparison inebilizumab CL in patients taking a concomitant medication versus not taking the respective concomitant medication (inebi-ppk-report-10may2019-final.pdf, Figures 15 on page 46). The boxplot on page 46 appears to support the Applicant's conclusion that similar inebilizumab exposure was observed regardless of the co-administration with paracetamol, diphenhydramine, prednisolone, and methylprednisolone. Mechanistically, these medications are not expected to affect inebilizumab clearance.

While there is no apparent effect of these four concomitant medications on inebilizumab clearance, it should be noted the parameter estimates for these concomitant effects are not available. Considering the large proportion of subjects that took a drug paracetamol and methylprednisolone and large proportion of subject that didn't take prednisolone, it is not clear how reliable the drug interaction estimates are.

Overall, the IV PPK model (Run ^{(b) (4)}) is acceptable.

(b) (4)

4.2.3 Label Statements Based on Population PK Modeling

The Applicant proposes the following label statements based on PPK-modeling results.

Distribution:

“Based on population pharmacokinetic analysis, the estimated typical central and peripheral volume of distribution of UPLIZNA was 2.95 L and 2.57 L, respectively.”

[Reviewer comment: The proposed sentence for the “Distribution” section of the label is supported by the PPK analyses.]

Elimination:

“(b) (4) population pharmacokinetic analysis, the estimated UPLIZNA systemic clearance of the first-order elimination pathway was 0.19 L/day. At low (b) (4) levels, UPLIZNA was subject to the receptor (CD19)-mediated clearance, which decreased with time presumably due to the depletion of B cells by UPLIZNA treatment.”

[Reviewer comment: The population PK estimate of CL is 188.22 mL/day or 0.18822 L/day and is reasonably approximated by 0.19 L/day. The final PPK model includes a term that describes a time-dependent reduction in the non-linear elimination clearance pathway. As such, both sentences from the “Elimination” section of the label referenced above are supported by the PPK analyses.]

Specific Populations:

Geriatric Use

“Based on population pharmacokinetic analysis, age did not affect UPLIZNA clearance.”

[Reviewer comment: The proposed sentence regarding the effect of age on UPLINZA clearance is supported by the PPK analyses.]

Gender, Race

“A population pharmacokinetic analysis indicated that there was no significant effect of gender and race on UPLIZNA clearance.”

[Reviewer comment: The proposed sentence regarding the effect of gender and race on UPLINZA clearance is supported by the PK analyses.]

Renal Impairment

(b) (4)

[Reviewer comment: The proposed sentence regarding the effect of renal impairment on UPLINZA clearance is supported by the PK analyses.]

Hepatic impairment

(b) (4)

[Reviewer comment: The PK analyses indicate that bilirubin measurements are not a covariate on UPLINZA clearance. However, bilirubin levels alone are not likely to be predictive of hepatic impairment. Generally, information on encephalopathy grade, ascites, serum albumin, and prolongation of prothrombin time need to be integrated with serum bilirubin measurements in order to reliably assess hepatic impairment. As such, the PPK data do not support the proposed label statement regarding the effect of hepatic impairment on UPLINZA clearance.

OCP recommends modifying the label statement regarding the effect of hepatic impairment on UPLINZA PK in manner such that there is no such inconsistency with the available PK data.

Assuming UPLINZA is approved, the final label language will reflect ongoing negotiations between the Applicant and FDA.]

Drug Interaction Studies

(b) (4)

[Reviewer comment: The Phase 3 Study 1155 protocol included pretreatment with IV methylprednisolone (80-125 mg or equivalent glucocorticoid such as prednisolone), oral diphenhydramine (25-50 mg or equivalent antihistamine), and oral paracetamol (acetaminophen; 500-650 mg) prior to any administration of investigational product to prophylactically reduce the risk of infusion-related reactions. Paracetamol, methylprednisolone, diphenhydramine, and prednisolone were used by 97%, 90%, 82%, and 9% of patients in Study 1155, respectively. Mechanistically, these medications are not expected to affect inebilizumab clearance.

While there is no apparent effect of these four concomitant medications on inebilizumab clearance, it should be noted the parameter estimates for these concomitant effects are not available. Considering the large proportion of subjects that took a drug paracetamol and methylprednisolone and large proportion of subject that didn't take prednisolone, it is not clear how reliable the drug interaction estimates are.

OCP recommends modifying the label statement regarding the effect of concomitant medications on UPLINZA PK in manner to that is more reflective of the conclusions from the PPK-based drug interaction analyses.

Assuming UPLINZA is approved, the final label language will reflect ongoing negotiations between the Applicant and FDA.]

4.3 Exposure-Response Analyses

The Applicant developed an exposure-response model to characterize the relationship between inebilizumab exposure and the risk of an NMOSD attack (the primary endpoint from Study 1155) in NMOSD patients. Secondary objectives of described in this modeling report include constructing exposure-response models for a subset of secondary efficacy endpoints.

The Applicant did not conduct exposure-response analyses for safety. The key safety concerns are infections, a potentially clinically-relevant reduction in immunoglobulin levels, and one case of progressive multifocal leukoencephalopathy. At the time this review was archived, the main safety concerns are not likely to preclude approval. OCP will not pursue exposure-response analysis for safety at this time. Please refer to the clinical review by Dr. Lawrence Rodichok, M.D. for additional details regarding safety.

4.3.1 Summary of PK and Efficacy Data

The PK and efficacy data used in these analyses came from Study 1155. There were n=230 subjects included in the exposure-response analyses (n=174 on inebilizumab, n=56 on placebo). In Study 1155, n=25 subjects tested positive for ADA at baseline or in the RCP (n=17 in inebilizumab arm; n=8 in placebo arm). In the inebilizumab arm, PK data are available for the n=17 ADA positive subjects and n=157 ADA negative subjects.

PK Data: Details regarding Study 1155, including PK sampling, can be found in section “4.2.1 Population Summary of PK Data”.

The PPK model was utilized to obtain individual PK parameter estimates. Individual PK parameter estimates were utilized to simulate AUC values. The Applicant utilized three metrics of inebilizumab exposure for use in the current exposure-response analyses;

- a) **AUC_{0-14d}**: area under the concentration-time curve from time 0 to 14 days post-dose 1,
- b) **AUC_{cumulative}**: cumulative area under the concentration-time curve from time 0 of dose 1 to the last measurable concentration in RCP), and
- c) **CL**: individual estimate of linear CL process (which is proportional to the reciprocal of AUC_{0-∞} following a single administration of 300 mg). The Applicant’s rationale for using the only the linear CL pathway is that, at the therapeutic dose level, the nonlinear elimination pathway is expected to be saturated.

Efficacy Data: The primary endpoint and four secondary endpoints from Study 1155 were utilized as efficacy measures in the exposure-response analyses. The primary endpoint is the time from Day 1 until the time of an adjudication committee (AC)-confirmed NMOSD attack on or before the end of the RCP (Day 197/discontinuation visit). Secondary endpoints included in the analyses are 1) reduction of EDSS worsening, 2) change from baselines low contrast visual acuity score, 3) cumulative active MRI lesion count (new gadolinium-enhanced or new/enlarging T2 lesions), and 4) reduction in NMOSD-related in-patient hospitalizations.

4.3.2 Exposure-Response Models

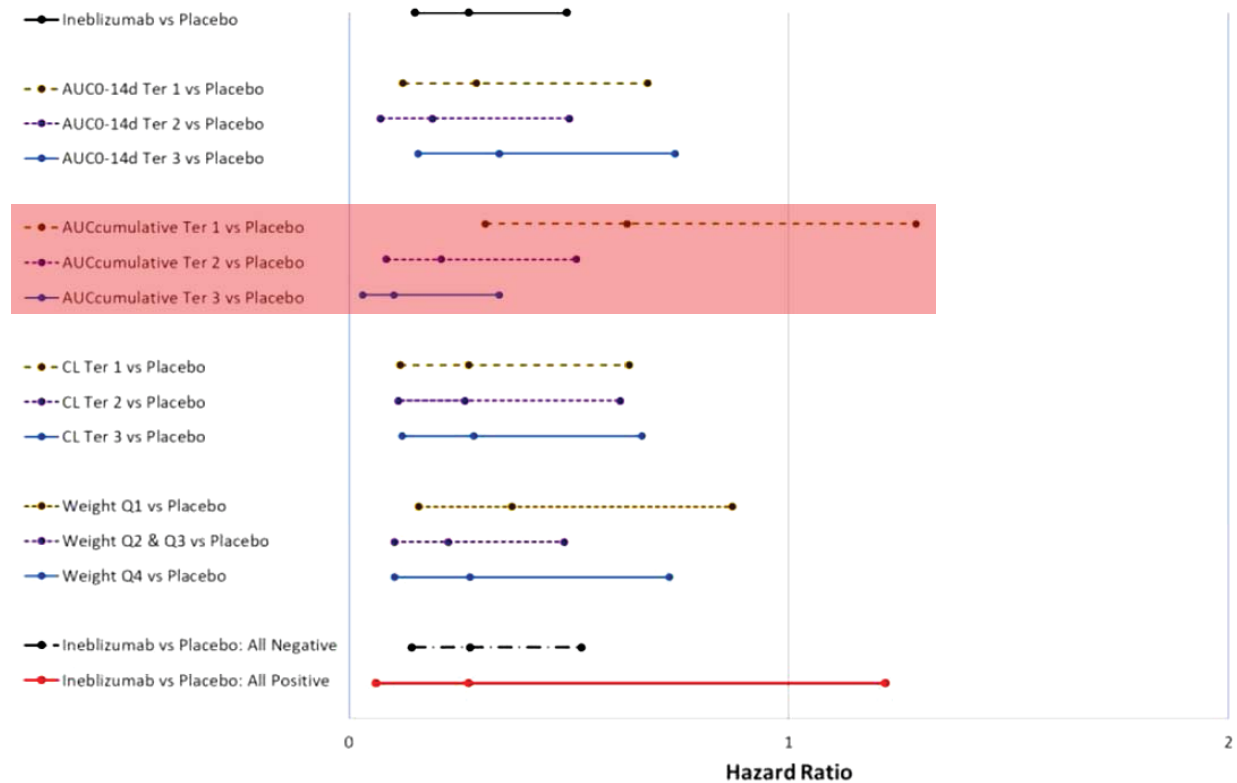
The E-R analysis focused on the empirical comparison of efficacy outcomes in patients receiving placebo or inebilizumab. The Applicant split the PK data from the inebilizumab arm into terciles based on exposure. Applicant assessed the potential impact of PK covariates (such as body weight and ADA) on inebilizumab efficacy by comparing primary and certain secondary efficacy outcomes across weight groups and immunogenicity status.

Primary Endpoint: A Cox proportional hazards model was used to characterize the relationship between inebilizumab exposure group (zero exposure for placebo or the tercile of inebilizumab exposure) and time until NMOSD attack. Subjects that did not experience an attack in the RCP (either by completing Day 197 visit without an attack or discontinued the study before Day 197 for reasons other than an NMOSD attack) were censored at their final visit.

The results of the exposure-response analyses for the primary efficacy endpoint are summarized in the forest plot below (see **Figure 8**). For this figure, the Applicant points out an apparent relationship between $AUC_{cumulative}$ and time until NMOSD attack. Please refer to section **4.3.3**

Applicant's Conclusions from Exposure-Response Analyses for discussion regarding this observation.

Figure 8: Forest Plot of Hazard Ratio for Time to AC-Determined NMOSD Attack During the RCP



ADA = anti-drug antibody;

AUC_{0-14d} = area under the concentration-time curve from time 0 to 14 days postdose;

AUC_{0-14d} Ter 1 = inebilizumab-treated subjects with low AUC_{0-14d} ;

AUC_{0-14d} Ter 2 = inebilizumab-treated subjects with medium AUC_{0-14d} ;

AUC_{0-14d} Ter3 = inebilizumab-treated subjects with high AUC_{0-14d} ;

$AUC_{cumulative}$ = cumulative area under the concentration-time curve from time 0 of Dose 1 to the last measurable concentration in RCP;

$AUC_{cumulative}$ Ter 1 = inebilizumab-treated subjects with low $AUC_{cumulative}$;

$AUC_{cumulative}$ Ter 2 = inebilizumab-treated subjects with medium $AUC_{cumulative}$;

$AUC_{cumulative}$ Ter 3 = inebilizumab-treated subjects with high $AUC_{cumulative}$;

CL = systemic clearance;

CL Ter 1 = inebilizumab-treated subjects with low CL;

CL Ter 2 = inebilizumab-treated subjects with medium CL;

CL Ter 3 = inebilizumab-treated subjects with high CL;

Weight Q1 = inebilizumab treated subjects with lowest quartile body weight;

Weight Q2 & Q3 = inebilizumab-treated subjects with interquartile range (2nd and 3rd Quartile) of body weight;

Weight Q4 = inebilizumab-treated subjects with large quartile of body weight.

All Negative = subjects who always tested ADA negative;

All Positive = subjects who provided at least one ADA positive test result.

Hazard ratio and 95% CI < 1 suggest inebilizumab perform better than placebo.

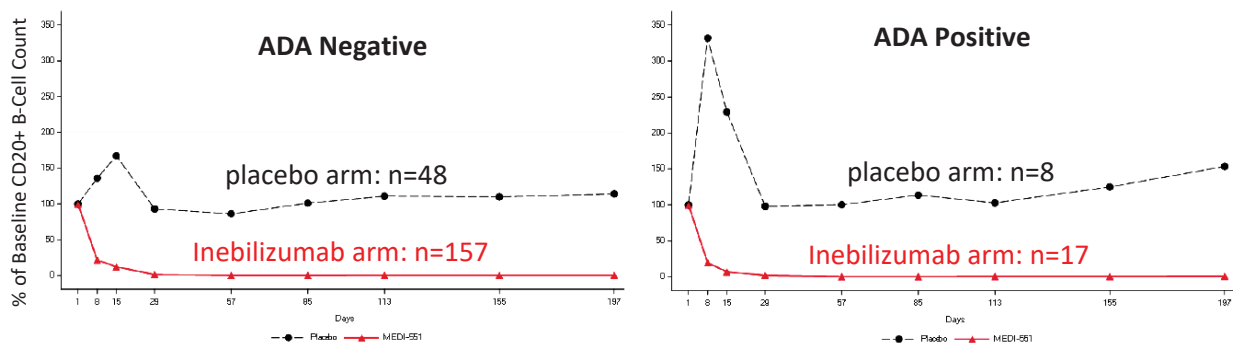
Source: sequence 0001, module 5342, inebi-ere-report-24may2019-final.pdf, page 28 of 62

[Reviewer comment: Please refer to section 4.3.3 **Applicant's Conclusions from Exposure-Response Analyses** for discussion regarding the apparent relationship of $AUC_{cumulative}$ and time until NMOSD attack shown in **Figure 8** above (denoted by the shaded box).]

The Applicant generated Kaplan-Meier plots (not shown in this review) which graphically illustrate the time profile for NMOSD attack onset in the Study 1155 patient population. If interested, the reader should refer to pages 17 through 24 inebi-ere-report-24may2019-final.pdf for the Kaplan-Meier plots that accompany the Cox-proportional hazard analysis results in **Figure 8**.

Potential Impact of ADA on CD20+ B-cell Counts: The Applicant conducted a graphical analysis of the ADA-status effect on CD20+ B-cell count as part of their exposure-response analyses. The PD effect of inebilizumab on B cells is assayed by measuring CD20+ B-cell counts, as inebilizumab interferes with CD19-based detection methods. The following plot shows the comparison of CD20+ B-cell count (expressed as % of baseline value) over time for subjects who were ADA negative versus subjects with at least one ADA positive test result at any time (including baseline) by arm in Study 1155.

Figure 9: CD20+ B Cell Count – Time Profiles in Subjects Who Tested Positive or Negative for ADA During the RCP in Study 1155



A subject is considered ADA-positive if the subject's ADA level is positive at any time points including baseline during Randomized-Controlled Period

Source: sequence 0001, module 5342, inebi-ere-report-24may2019-final.pdf, page 26 of 62

The Applicant states that there is no evidence of apparent effect of ADA on B-cell response.

[Reviewer comment: Within the inebilizumab arm in **Figure 9** (solid red curve with triangular points) the change from baseline B-cell profile appears to be unaffected by the ADA status.

The differing profile in the placebo arm (dashed black curve with circular points) for ADA negative versus ADA positive in **Figure 9** is unexpected. While the reasons for this phenomenon are not clear, it may be due, in part, to the small sample size of ADA positive subjects in the placebo arm.]

Secondary endpoints: The relationship between inebilizumab exposure group (zero exposure for placebo or the tercile of inebilizumab exposure) and secondary efficacy endpoints was characterized as follows:

- i. EDSS worsening was assessed using a logistic regression model
- ii. low-contrast visual acuity change was analyzed using an analysis of covariance model
- iii. cumulative number of active MRI lesions was modelled using negative binomial regression
- iv. number of NMOSD-related in-patient hospitalizations was modelled using negative binomial regression

Overall, no exposure-response relationship was apparent for any secondary endpoint. The plots of the exposure-response analysis results for the secondary efficacy endpoints are not shown in this review (see inebi-ere-report-24may2019-final.pdf, pages 31 to 38 of 62 for details).

4.3.3 Applicant's Conclusions from Exposure-Response Analyses

In Study 1155, the inebilizumab was superior to placebo in terms of the primary endpoint and secondary endpoints of EDSS, cumulative number of active MRI lesions, and NMOSD-related hospitalizations. The secondary endpoint of low-contrast visual acuity was comparable between the inebilizumab arm and placebo arm. The Applicant assessed the relationship between various metrics of inebilizumab exposure and these measures of efficacy such as AUC_{0-14d} , $AUC_{cumulative}$, and individual CL estimates.

Applicant mentions that there is an apparent exposure-response relationship between $AUC_{cumulative}$ and time until NMOSD attack (see the $AUC_{cumulative}$ section in **Figure 8**). However, as the Study 1155 protocol required subjects who experienced an NMOSD attack to exit the randomized controlled trial, the Applicant concludes that the apparent relationship between $AUC_{cumulative}$ and time until NMOSD attack is likely an artifact. Subjects who experienced an NMOSD exited the RCP earlier, which causes lower $AUC_{cumulative}$ values than in subjects who did not experience an NMOSD attack and completed the RCP on Day 197.

The following list provides a summary of the key conclusion points that the Applicant provides in their exposure-response analysis report:

- No apparent relationship between AUC_{0-14d} primary or secondary endpoints.
- No apparent relationship of CI (e.g. slow, medium, fast) with primary or secondary endpoints.
- Weight had no apparent impact on primary endpoint or secondary endpoints
- In some lower body weight subjects, exposure was higher, but efficacy was reduced
- ADA has no apparent effect on efficacy, though sample size was small.
- ADA has no apparent effect on B-cell depletion, though sample size was small.
- The 300 mg dose produces inebilizumab exposures that reside on the efficacy plateau which minimizes the impact of PK variability on efficacy outcome. Dose adjustment by body weight is not warranted and the 300 mg fixed dose of inebilizumab is the optimal dosage.

*[Reviewer comment: The reviewer agrees with the Applicant that the apparent relationship between $AUC_{cumulative}$ and time until NMOSD attack (shaded box in **Figure 8**) is likely an artifact. In addition, the Reviewer agrees with the Applicant that the $AUC_{cumulative}$ measure is not an*

appropriate exposure metric for exposure-response analyses. As such, $AUC_{cumulative}$ will not be further discussed in this review.

The exposure-response analyses for the primary endpoint (**Figure 8**) indicates a benefit of inebilizumab over placebo in Study 1155 but no clear exposure-response relationship among the inebilizumab exposure terciles. As the primary efficacy endpoint in Study 1155 was met, improvement was observed for these three secondary endpoints in the inebilizumab arm compared to placebo, and there is no apparent relationship of exposure to primary or secondary endpoints, it is possible that the inebilizumab exposures achieved in Trial 1155 are on the so-called “efficacy plateau” (an exposure level on a hypothetical exposure-response curve from which further increases in exposure are not expected to result in a clinically-relevant efficacy improvement).

Due to the flat E-R relationship for any of the efficacy measures included in these analyses, PK variability attributed to weight is unlikely to produce a clinically-relevant effect on efficacy. Thus, though body weight is a covariate on inebilizumab PK, a dose adjustment by body mass does not appear warranted. In addition, Study 1155 appears to support safety and efficacy of the “flat” dosing regimen of 300 mg Day 1, Day 14, and at 6 months.

The Applicant provided analyses of the effect of ADA status on pharmacodynamics and clinical measures. Based on the Applicant’s graphical analyses, the development of ADA does not appear to affect reduction in CD20+ B-cell count (**Figure 9**). However, the relationship of CD20+ B-cell count with efficacy is not established. In the exposure-response analyses for the primary endpoint, the confidence interval for ADA-positive subjects receiving inebilizumab is wider than any other factor tested (see **Figure 8**). Similarly, for each of the four secondary endpoints, the confidence interval for ADA-positive status is also wider than for all other factors tested (see *inebi-ere-report-24may2019-final.pdf*, pages 31 to 38 of 62 for details). The wide confidence intervals is likely due to the small sample size of ADA-positive subjects in the inebilizumab arm ($n=17$) compared to ADA-negative subjects in either the placebo arm or the inebilizumab arm.

While the Applicant assessed the time-varying ADA status effect on PK, the Applicant’s assessments of ADA status on pharmacodynamics and clinical measures do not address the time-variations in ADA status.

Due to the high level of uncertainty in the parameter estimates for ADA status effect on efficacy measures, as well as the complex profile of ADA status over time (i.e. instances of ADA test results alternating between positive and negative over time), the reviewer conducted independent analyses to explore the effect of time-varying ADA status on various clinical and pharmacodynamic measures (see section **4.3.4 Reviewer’s Assessment of ADA Development**).]

4.3.4 Reviewer's Assessment of ADA Development

The Applicant's exposure-response analyses included comparisons various endpoints and CD20+ B-cell counts in ADA-positive subjects (subjects who produced at least one ADA-positive test result) versus ADA-negative subjects (subjects that presented only ADA-negative test results; see 4.3.2 **Exposure-Response Models**). However, the Applicant's exposure-response analyses do not address the time-varying ADA status within or among patients.

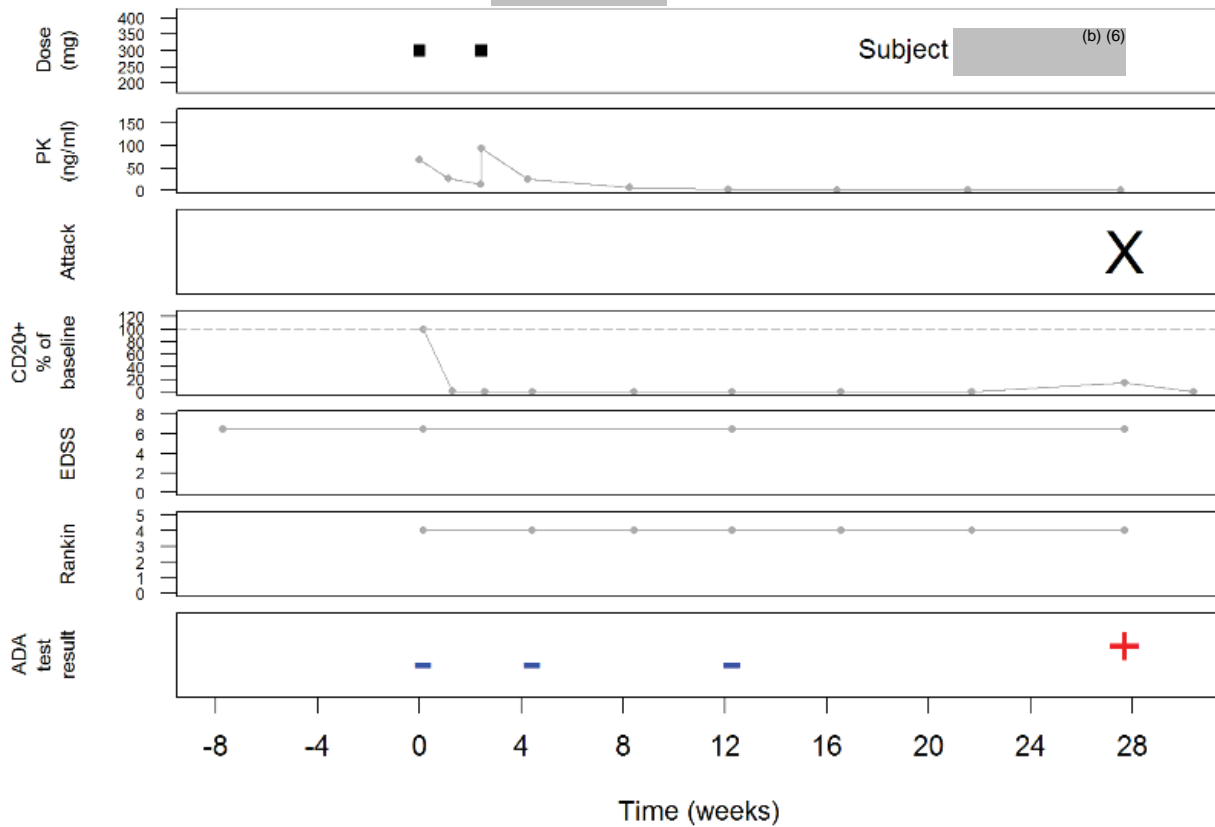
The reviewer conducted an independent assessment of the effect of time-varying ADA measurement on clinical measures and pharmacodynamic measures. In subjects that provided at least one positive ADA test result in the inebilizumab arm in Study 1155 (n=17), the time course of ADA test results is graphically compared alongside the dosing profile, PK profile, CD20+ B-cell profile, EDSS score profile, and Rankin score profile.

Neither the EDSS score, Rankin score, nor CD20+ B-cell count value appeared to be associated with the onset or offset of ADA-positive test results. In addition, there no apparent relationship between ADA test result and NMOSD attack during the RCP in Study 1155. The reviewer illustrates this concept with 3 general scenarios regarding ADA-status time profiles that are apparent from the graphical analysis of the data:

- 1) NMOSD attack occurring within a month of ADA-positive onset,
- 2) NMOSD attack occurring months after sustained ADA-positive test results, and
- 3) ADA-positive test results reverting to ADA-negative status, and an NMOSD attack occurs after months of sustained ADA-negative test results

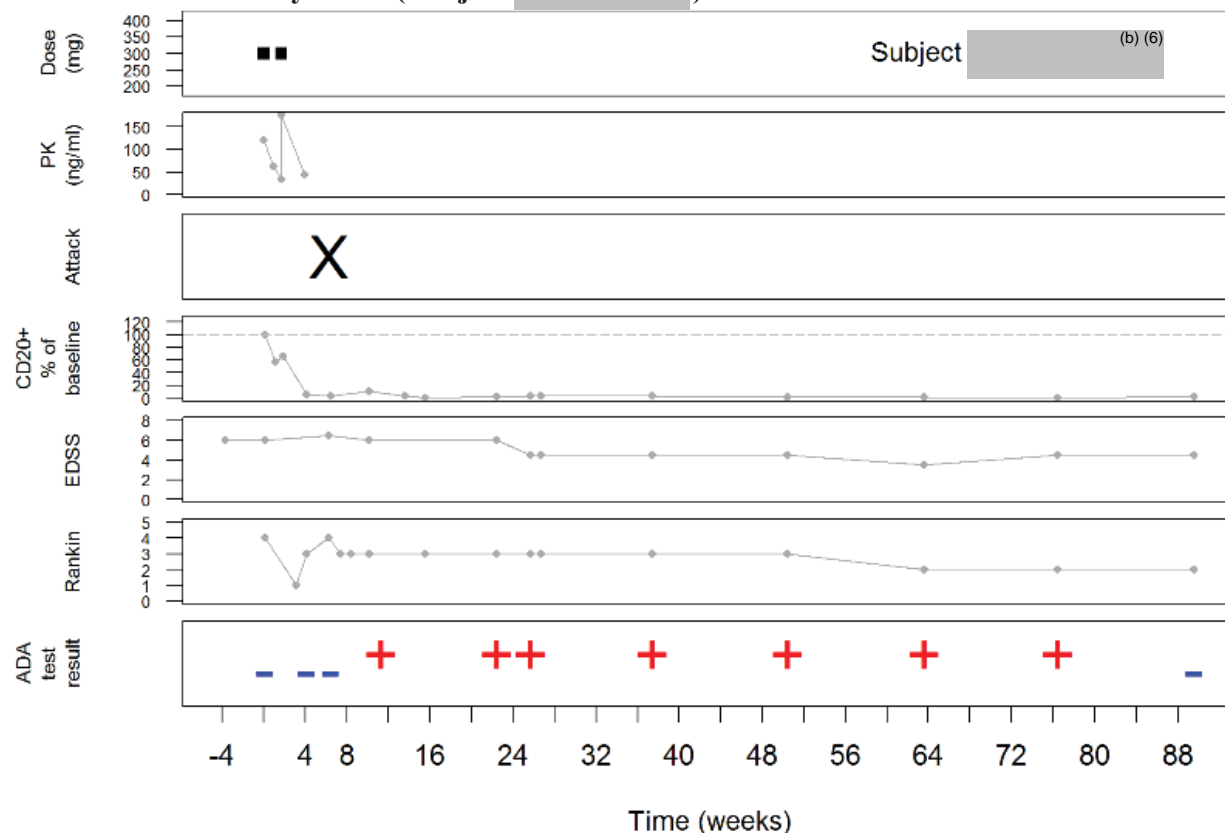
Figure 10 and **Figure 11** displays two subjects in whom NMOSD attacks occurred within a month of the first occurrence of an ADA positive test result (i.e. Subject (b) (6) and Subject (b) (6)).

Figure 10: Example of NMOSD Attack Occurring Within a Month of the First ADA-Positive Test in Study 1155 (Subject (b) (6))



The black squares depict the timing of inebilizumab administration. The black “X” depicts the timing of an NMOSD attack during the RCP. The “-” sign and “+” sign appear at the times when an ADA test was performed and depict ADA-negative test results and ADA-positive test results throughout the course of the clinical trial. Inebilizumab PK, CD20+ B-cell count (expressed as % of baseline), EDSS, and Rankin scores over time are represented as grey circles connected by grey line segments. PK samples do not occur after an NMOSD attack as subjects are removed from the RCP of Study 1155 at the occurrence of an NMOSD attack. As some patients may be enrolled into the open-label extension phase after an NMOSD attack, some subjects have additional CD20+ B-cell counts, EDSS, Rankin score, and ADA test results after an NMOSD attack.

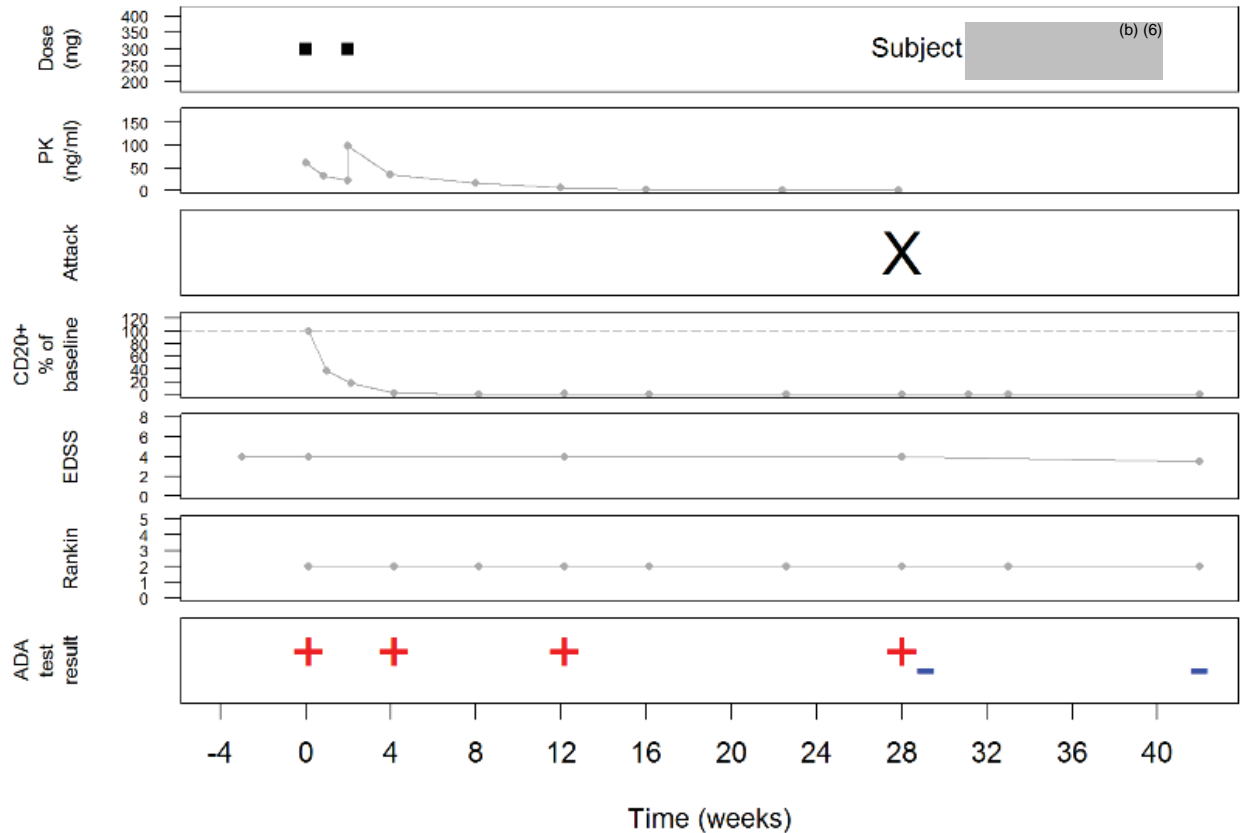
Figure 11: Example of NMOSD Attack Occurring Within a Month of the First ADA-Positive Test in Study 1155 (Subject (b) (6))



The black squares depict the timing of inebilizumab administration. The black “X” depicts the timing of an NMOSD attack during the RCP. The “-” sign and “+” sign appear at the times when an ADA test was performed and depict ADA-negative test results and ADA-positive test results throughout the course of the clinical trial. Inebilizumab PK, CD20+ B-cell count (expressed as % of baseline), EDSS, and Rankin scores over time are represented as grey circles connected by grey line segments. PK samples do not occur after an NMOSD attack as subjects are removed from the RCP of Study 1155 at the occurrence of an NMOSD attack. As some patients may be enrolled into the open-label extension phase after an NMOSD attack, some subjects have additional CD20+ B-cell counts, EDSS, Rankin score, and ADA test results after an NMOSD attack.

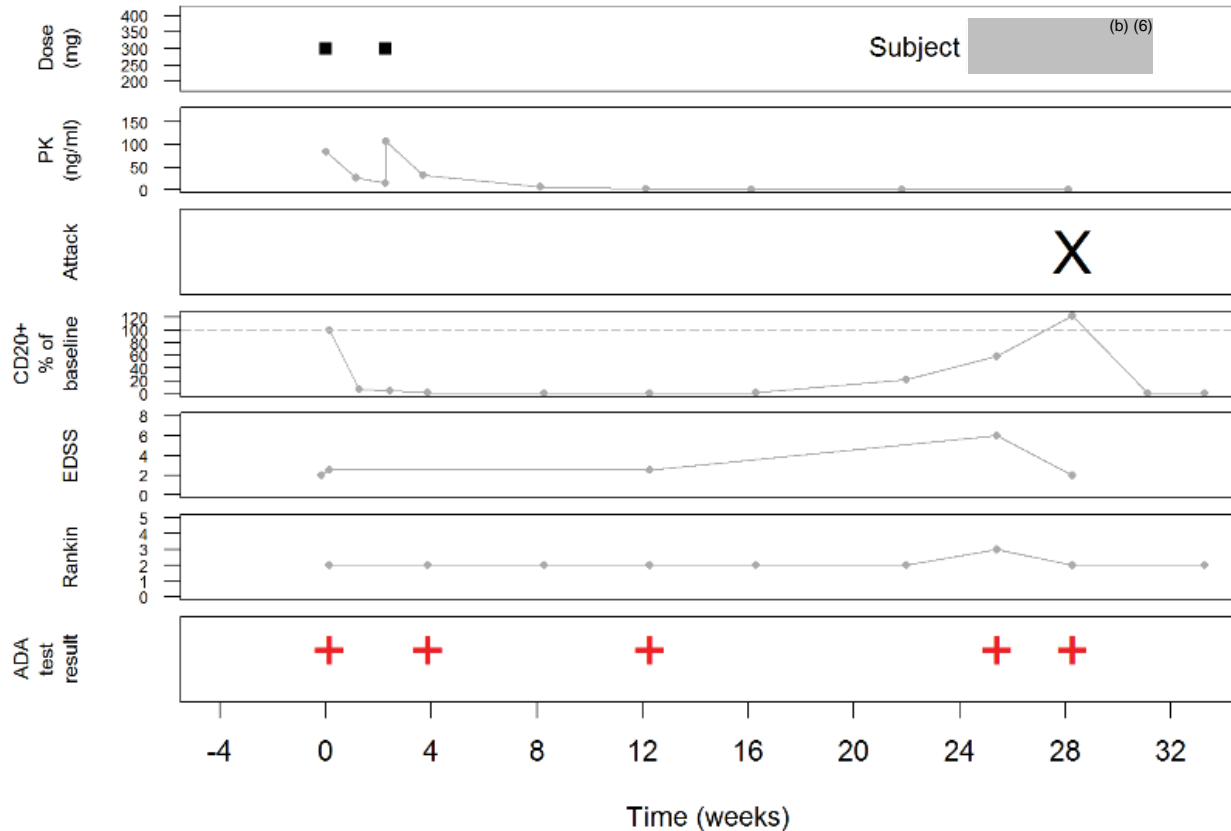
However, of the n=17 subjects in the inebilizumab arm of Study 1155 that provided at least one positive ADA test result, some subjects demonstrated numerous positive ADA test results several months prior to an NMOSD attack. Some examples of subjects with months of ADA-positive test results prior to an NMOSD attack include subjects (b) (6). Two such subjects are presented below to briefly illustrate this concept (see **Figure 12** and **Figure 13**).

Figure 12: Example of NMOSD Attack Occurring After Months of ADA-Positive Test Results in Study 1155 (Subject (b) (6))



The black squares depict the timing of inebilizumab administration. The black “X” depicts the timing of an NMOSD attack during the RCP. The “-” sign and “+” sign appear at the times when an ADA test was performed and depict ADA-negative test results and ADA-positive test results throughout the course of the clinical trial. Inebilizumab PK, CD20+ B-cell count (expressed as % of baseline), EDSS, and Rankin scores over time are represented as grey circles connected by grey line segments. PK samples do not occur after an NMOSD attack as subjects are removed from the RCP of Study 1155 at the occurrence of an NMOSD attack. As some patients may be enrolled into the open-label extension phase after an NMOSD attack, some subjects have additional CD20+ B-cell counts, EDSS, Rankin score, and ADA test results after an NMOSD attack.

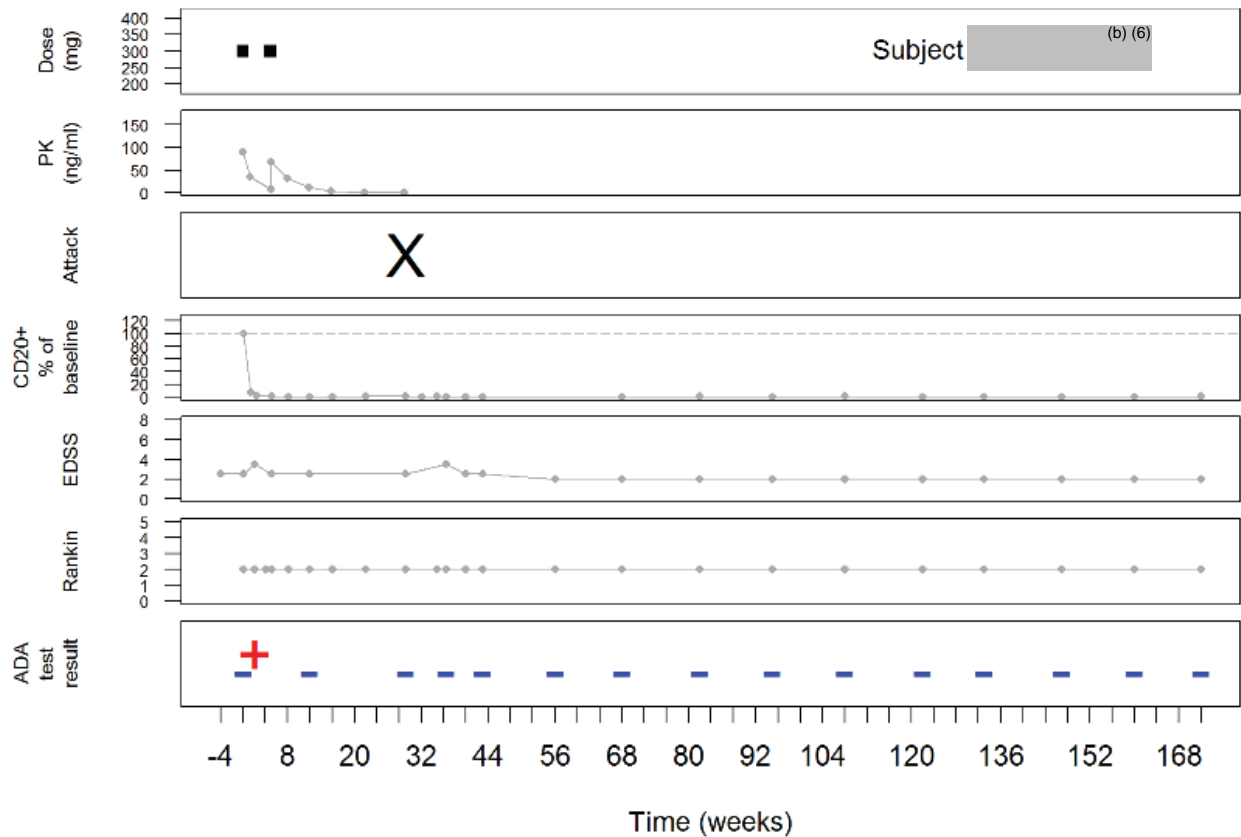
Figure 13: Example of NMOSD Attack Occurring After Months of ADA-Positive Test Results in Study 1155 (Subject (b) (6))



The black squares depict the timing of inebilizumab administration. The black “X” depicts the timing of an NMOSD attack during the RCP. The “-” sign and “+” sign appear at the times when an ADA test was performed and depict ADA-negative test results and ADA-positive test results throughout the course of the clinical trial. Inebilizumab PK, CD20+ B-cell count (expressed as % of baseline), EDSS, and Rankin scores over time are represented as grey circles connected by grey line segments. PK samples do not occur after an NMOSD attack as subjects are removed from the RCP of Study 1155 at the occurrence of an NMOSD attack. As some patients may be enrolled into the open-label extension phase after an NMOSD attack, some subjects have additional CD20+ B-cell counts, EDSS, Rankin score, and ADA test results after an NMOSD attack.

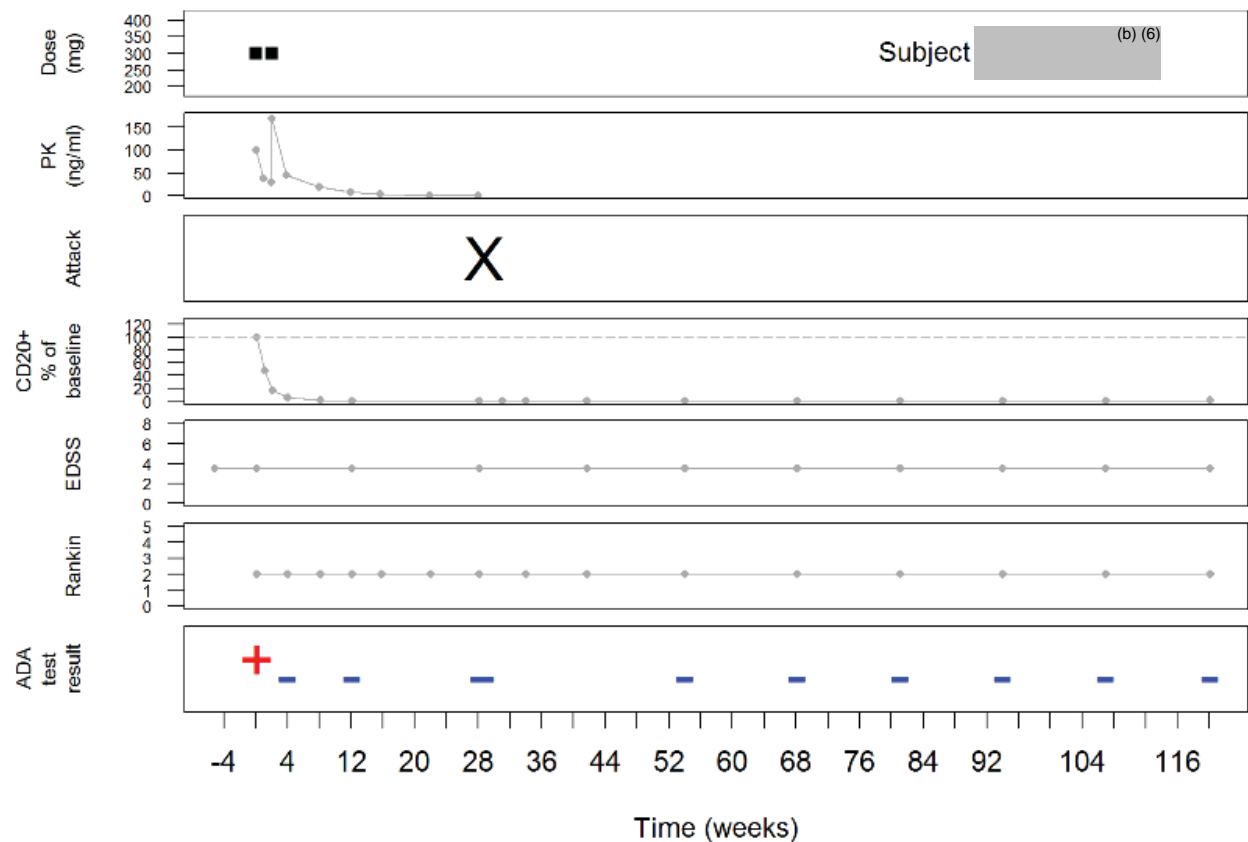
In addition, after an early ADA-positive test result, some subjects reverted to ADA-negative and remained negative up to the occurrence of an NMOSD attack (subjects (b) (6)). Two such subjects are presented below to illustrate this concept (see **Figure 14** and **Figure 15**).

Figure 14: Example of NMOSD Attack Occurring During ADA-Negative Test Result After Offset of ADA-Positive Test Result in Study 1155 (Subject (b) (6))



The black squares depict the timing of inebilizumab administration. The black “X” depicts the timing of an NMOSD attack during the RCP. The “-” sign and “+” sign appear at the times when an ADA test was performed and depict ADA-negative test results and ADA-positive test results throughout the course of the clinical trial. Inebilizumab PK, CD20+ B-cell count (expressed as % of baseline), EDSS, and Rankin scores over time are represented as grey circles connected by grey line segments. PK samples do not occur after an NMOSD attack as subjects are removed from the RCP of Study 1155 at the occurrence of an NMOSD attack. As some patients may be enrolled into the open-label extension phase after an NMOSD attack, some subjects have additional CD20+ B-cell counts, EDSS, Rankin score, and ADA test results after an NMOSD attack.

Figure 15: Example of NMOSD Attack Occurring During ADA-Negative Test Result After Offset of ADA-Positive Test Result in Study 1155 (Subject (b) (6))



The black squares depict the timing of inebilizumab administration. The black “X” depicts the timing of an NMOSD attack during the RCP. The “-” sign and “+” sign appear at the times when an ADA test was performed and depict ADA-negative test results and ADA-positive test results throughout the course of the clinical trial. Inebilizumab PK, CD20+ B-cell count (expressed as % of baseline), EDSS, and Rankin scores over time are represented as grey circles connected by grey line segments. PK samples do not occur after an NMOSD attack as subjects are removed from the RCP of Study 1155 at the occurrence of an NMOSD attack. As some patients may be enrolled into the open-label extension phase after an NMOSD attack, some subjects have additional CD20+ B-cell counts, EDSS, Rankin score, and ADA test results after an NMOSD attack.

As the occurrence of NMOSD attacks can occur months after ADA-positive status onset, within a month of the time of ADA-positive status onset, or after ADA-positive status reverts to ADA-negative, **then it is not clear whether NMOSD attack risk is related to ADA status.** These findings should be interpreted with caution as this graphical analysis is based on data subsets that are not the result of randomization (e.g. ADA-positive versus ADA-negative) and sample size is modest (n=17 subjects with at least one ADA-positive test result).

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/s/

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