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APPLICATION NUMBER:

210913Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology

Integrated Clinical Pharmacology Review

BLA Number	761119
Link to EDR	\\CDSESUB1\EVSPROD\BLA761119\761119.enx
Submission Date	2/21/2019
Submission Type	351(a), Standard Review
Brand Name	VYEPTI™
Generic Name	Eptinezumab (ALD403)
Dosage Form/Route of administration	100 mg/mL in single use vial/Intravenous infusion
Proposed Indication	Prevention of Migraine in Adults
Proposed Dose/regimen	100 mg administered by intravenous infusion every 3 months. Some patients may benefit from a dosage of 300 mg every 3 months.
Applicant	Alder BioPharmaceuticals, Inc.
Associated IND	114647
OCP Review Team	Gopichand Gottipati Ph.D., Atul Bhattaram, Ph.D., Sreedharan Sabarinath, Ph.D.
OCP Final Signatory	Mehul Mehta, Ph.D.

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1 Executive Summary

In this original Biologics License Application (BLA), Alder BioPharmaceuticals, Inc.is seeking approval for VYEPTI™ (Eptinezumab; ALD403) for the prevention of (b) (4) migraine in adults.

Eptinezumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody targeted against the calcitonin gene-related peptide (CGRP) ligand. It selectively binds to the CGRP ligand and blocks both α-and β-CGRP isoforms from binding to the CGRP receptor. Currently, three other monoclonal antibody products (erenumab, fremanezumab and galcanezumab) that target either CGRP ligand or CGRP receptor were approved by the agency for the same indication.

The applicant is proposing the following dosing options for VYEPTI™, to be administered as an intravenous infusion diluted in 100 ml of 0.9% Sodium Chloride Injection, USP, over 30 min:

- 100 mg every 3 months
- Some patients may benefit from a dosage of 300 mg every 3 months.

The applicant is relying on two pivotal randomized, double-blind, placebo-controlled, safety and efficacy studies, Study 006 in patients with episodic migraine (EM) and Study 011 in chronic migraine (CM). Study 006 in EM included three dose levels (30, 100 and 300 mg) while Study 011 in CM had two dose levels (100 and 300 mg). A single infusion, double-blind, placebo-controlled, phase 2 study in patients with chronic migraine (Study 005, 4 dose levels: 10, 30, 100 and 300 mg) provides supportive information. The applicant is seeking approval for the 100 and 300 mg doses. The reduction in baseline- and placebo-corrected monthly average number of migraine days during the 12 week treatment period was used as the primary efficacy endpoint in the pivotal studies in patients with CM and EM.

The primary focus of this review is to evaluate the acceptability of general dosing recommendations and dose optimization based on extrinsic and intrinsic factors.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the information submitted in BLA 761119 and recommends approval of 100 and 300 mg once every 3 months (quarterly) dosing regimens for the prevention of [redacted] (b) (4) migraine in adults.

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

Table 1-1 Summary of Review Issues and OCP Recommendations

Review Issues	Recommendations and Comments
Evidence of effectiveness	The primary evidence of effectiveness is from two pivotal randomized, double-blind, placebo-controlled studies (Phase 3: CLIN-011, CLIN-006), one each in patients with chronic migraine (CLIN-011) and episodic migraine (CLIN-006). An additional phase-2 randomized, double-blind, placebo-controlled study in patients with chronic migraine (CLIN-005) provided the supportive evidence.
General dosing instructions:	The recommended dosing regimens are 100 mg and 300 mg once every 3 months. They are administered intravenously in 100 ml bag of 0.9% Sodium Chloride Injection, USP, over 30 min.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose adjustments are needed based on age, race, sex, bodyweight, renal or hepatic impairment, food-intake or drug/transporter mediated interactions.

Review Issues	Recommendations and Comments
Bridge between the "to-be-marketed" and clinical trial formulations	There were major manufacturing changes for both drug substance and drug product, changes in manufacturing site and in the scale-up process between the commercial and clinical trial formulations. The applicant conducted a PK bridging study (CLIN-014) and Office of Study Integrity and Surveillance (OSIS) conducted inspection of the analytical site. OSIS noted that all reported drug concentrations obtained using dilution factors >100-fold in the study were not reliable and cannot be used to support regulatory decision. Specifically, those study samples did not meet the acceptance criteria for precision and accuracy. However, the CMC review team noted that the differences in the product quality attributes between clinical and commercial formulations were minor, and that the likelihood of these differences to impact the PK is low. Thus, study CLIN-014 was not considered pivotal to bridge between commercial and clinical trial formulations.

1.2 Post-marketing Requirements

None.

2 Summary of Clinical Pharmacology Assessment

2.1 The Pharmacology and Clinical Pharmacokinetics

Mechanism of Action:

Eptinezumab is a fully humanized monoclonal immunoglobulin G1 (IgG1) targeted against the calcitonin gene-related peptide (CGRP) ligand. CGRP is a 37-amino acid neuropeptide and is widely distributed throughout the central and peripheral nervous systems. The CGRP-mediated pathway has been widely reported in the pathophysiology of migraine. Eptinezumab is reported to bind selectively to the CGRP ligand and block both α-and β-CGRP isoforms from binding to the CGRP receptor.

Absorption

Since eptinezumab is administered intravenously, absorption is not relevant.

Distribution

The volume of distribution of eptinezumab is 3.6 liters (31% between-subject variability)

Metabolism and Excretion

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

The mean clearance of eptinezumab is 0.006 L/h and the mean terminal half-life was approximately 27 days.

Age, Race, Sex and Weight

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

Specific Populations

Patients with Renal or Hepatic Impairment

Generally, the IgG monoclonal antibodies undergo elimination via intracellular catabolism and therefore, hepatic impairment is not expected to significantly impact the disposition of eptinezumab. Furthermore, renal elimination of monoclonal antibodies is generally considered low. The applicant did not conduct any dedicated studies to evaluate the impact of renal or hepatic impairment on the PK of eptinezumab. The impact of renal/hepatic impairment is unlikely to be clinically relevant and therefore, no dose adjustments are recommended for eptinezumab based on renal or hepatic impairment.

Immunogenicity:

Overall, the final immunogenicity database consisted of 1993 subjects from 4 clinical studies in which ADA results were available. Of these patients, 316 showed (15.9%) treatment-emergent anti-eptinezumab antibody responses (i.e., ADA-positive status), while 124 (6.2%) developed neutralizing antibodies against eptinezumab. Overall, the impact of ADA status and ADA titer quartiles were generally consistent across dose levels and CM/EM populations – lower eptinezumab C_{trough} but were not associated with lower efficacy. Similar results were observed for NAb status. Please refer to section 4.2 and Office of Biotechnology Products for additional details on immunogenicity assessments.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended dosing regimens are 100 mg and 300 mg administered once every 3 months as intravenous infusion over 30 min in 100 ml of 0.9% Sodium Chloride Injection, USP. These two dose levels and dosing regimen were tested in efficacy/safety studies in patients with EM and CM.

2.2.2 Therapeutic individualization

No therapeutic individualization is necessary for extrinsic/intrinsic factors. Eptinezumab is administered by intravenous route, and therefore, food-drug interactions are not anticipated. In addition, its drug-drug interaction liability is considered low (See Section 3.3.4). No dedicated clinical studies were performed in subjects with renal or hepatic impairment, however, renal/hepatic impairment is not expected to impact the pharmacokinetics of eptinezumab. Therefore, no dose adjustment is warranted in patients with hepatic/renal impairment.

2.2.3 Outstanding Issues

None.

2.2.4 Summary of Labeling Recommendations

The applicant's labeling recommendations are generally acceptable.

3 Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

The drug product is supplied as a single-use vial containing 100 mg eptinezumab in a 1 mL sterile, (b) (4) solution for intravenous administration. The vial consists of a clear to slightly opalescent, colorless to brownish-yellow solution for dilution in a 100 mL bag of 0.9% Sodium Chloride Injection, USP, prior to intravenous infusion. The 300 mg dose is administered by injecting 1 mL each from 3 single-use vials into 100 mL bag of 0.9% sodium chloride injection, USP.

Currently, there are five FDA approved products for prevention of migraine. These include beta-adrenergic blocking agents, e.g., propranolol (tablets and liquid) and timolol (tablets); antiepileptic drugs, e.g., divalproex sodium (tablets) and topiramate (tablets); and onabotulinumtoxin A (injectable).

Eptinezumab is a humanized monoclonal antibody, which is reported to target α- and β- forms of calcitonin gene-related peptide (CGRP), preventing the activation of the CGRP receptors. Currently, there are three other monoclonal antibody products (erenumab, galcanezumab and fremanezumab) that were approved by the agency for the same indication, targeting either CGRP ligand or CGRP receptor.

The eptinezumab clinical program consisted of 10 studies in healthy subjects and patients with CM and EM: five phase 1 studies (four of them explored other routes of administration such as intramuscular, subcutaneous in addition to intravenous route), two phase 1b/2 randomized, double-blind, placebo-controlled, safety and efficacy studies and two phase 3 randomized, double-blind, placebo-controlled, safety and efficacy studies and one long-term safety study.

The key aspects of three safety and efficacy phase 3 studies are summarized in Table 2 below

Table 2 Summary of pivotal safety and efficacy studies

Clinical Studies (Population, Size)	CLIN-006* (Episodic Migraine N=888)	CLIN-011# (Chronic Migraine N=1072)
Primary efficacy endpoint	Change from baseline in frequency of monthly migraine days (weeks 1 – 12)	
Study Design	Randomized, Double-blind, Parallel group, Placebo-controlled, Safety and Efficacy Study	
Treatment(s)	Placebo, 30 mg, 100 mg, 300 mg once every 3 months (quarterly) [Total = 4 infusions]	Placebo, 100 mg, 300 mg, once every 3 months (quarterly) [Total = 2 infusions]
Study Duration	56 weeks	32 weeks

N = number of subjects treated (Full Analysis Population)

**CLIN-006: Patients with a history of migraine ≥ 12 months with: ≤ 14 headache days of which at least 4 had to be migraine days in each 28-day period in the 3 months prior to screening and during 28 days after the screening visit as recorded in eDiary*

#CLIN-011: Patients with a history of migraine ≥ 12 months with: ≥ 15 to ≤ 26 headache days, of which ≥ 8 days were assessed as migraine days during the 28-day screening period as recorded in eDiary

Source: Adapted based on Summary of Clinical Efficacy – Tables 1 & 2 on pages 13,14 and 16; and respective individual clinical study reports

3.2 General Pharmacological and Pharmacokinetic Characteristics

The eptinezumab was studied across various routes of administration (e.g., intramuscular, subcutaneous and intravenous) in the early phase 1 studies. A summary of eptinezumab PK characteristics from studies in healthy subjects and subjects with migraine.

Table 3-3 Summary of Pharmacological and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Eptinezumab is a humanized monoclonal antibody that binds to α- and β- forms of CGRP ligand. CGRP is a neuropeptide that modulates nociceptive signaling and a vasodilation effect that has been associated with migraine pathophysiology.
General Information	
Healthy volunteers vs. patients	No clinically relevant differences in PK were noted.
Dose proportionality	The systemic exposures increased in a dose proportional manner from 10 mg to 300 mg.
Accumulation	Mean accumulation ratio was 1.2 with once-quarterly regimen.
Immunogenicity	A total of 1993 patients have been tested for anti-drug antibody (ADA). Among those, 316 patients (15.9%) were identified to have treatment-emergent patients anti-eptinezumab antibody responses. 124 (6.2%) patients developed neutralizing antibodies against eptinezumab. Please refer to the review from Office of Biotechnology Products for additional details on immunogenicity assessments.
Absorption	
Tmax	At the end of infusion (~ 30 min)
Distribution	
Volume of Distribution	3.6 L

Elimination	
Terminal Elimination Half-life	Approximately 27 days
Metabolism / Excretion	Monoclonal antibodies are not known to be metabolized by the cytochrome P450 system or affected by drug transporters. As a humanized IgG4 monoclonal antibody, eptinezumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

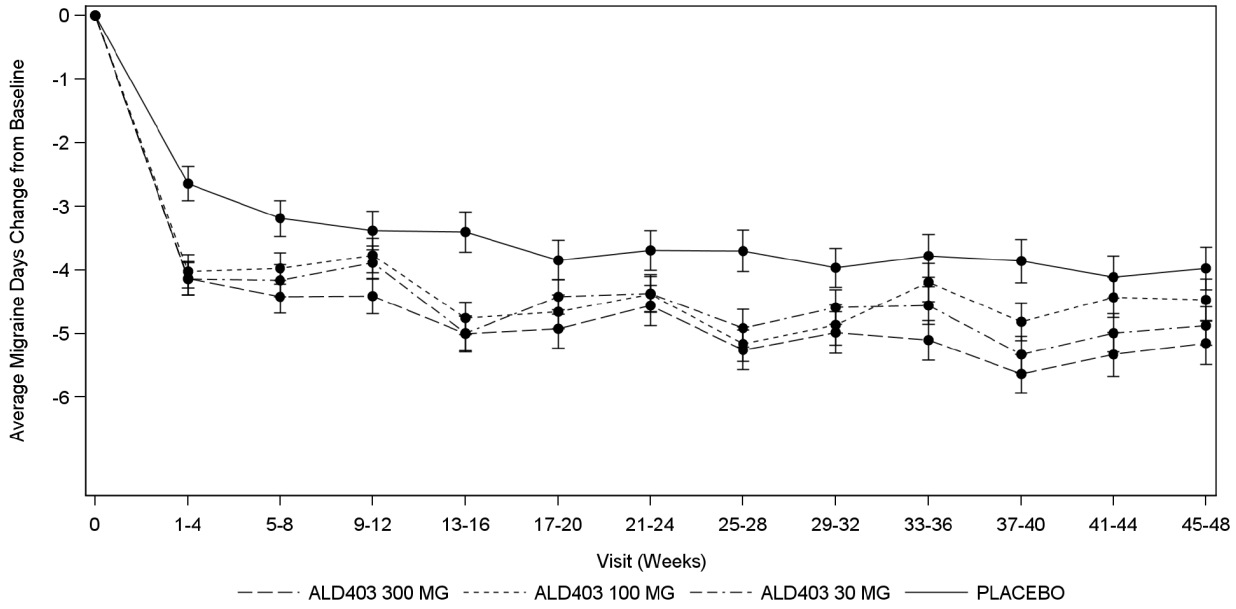
3.3 Clinical Pharmacology Questions

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

The evidence of effectiveness of eptinezumab in the prevention of (b) (4) migraine is based on two placebo-controlled, randomized, double-blind, efficacy and safety phase 3 studies, one each in patients with episodic migraine (CLIN-006) and chronic migraine (CLIN-011). Additional supportive evidence is from one placebo-controlled, randomized, double-blind, efficacy and safety phase 2 study (CLIN-005). The mean baseline- and placebo-corrected reduction in monthly average number of migraine days favored eptinezumab in patients with episodic migraine in CLIN-006 and patients with chronic migraine in CLIN-011 respectively.

Study CLIN-006 in patients with episodic migraine, consisted of a 4-week screening period, followed by 24-week double-blind treatment period during which quarterly doses of 30 mg, 100 mg or 300 mg were administered as intravenous infusion. The patients enrolled in the study were defined as those who had received diagnosis of migraine at ≤ 50 years of age, had a history of migraine ≥ 1 year experiencing 4 – 14 headache days with ≥ 4 migraine days during (a) each of three 28-day period in the 3 months prior to screening, and (b) 28 days after screening visit as documented in eDiary. While the 100 mg and 300 mg quarterly dosing regimens met the pre-specified statistical criteria for baseline- and placebo-corrected mean reduction in the mean monthly migraine days (weeks 1 – 12), the primary efficacy endpoint, the 30 mg quarterly dosing regimen did not [Figure 1 and Table 4]. (Please refer to statistical review by Dr. Steve Bai and Dr. Kun Jin, DARRTS 11/7/2019 for further details).

Figure 1 Least squares mean change from baseline in mean monthly number of migraine days by month and treatment group for study CLIN-006 in patients with episodic migraine (full analysis dataset)

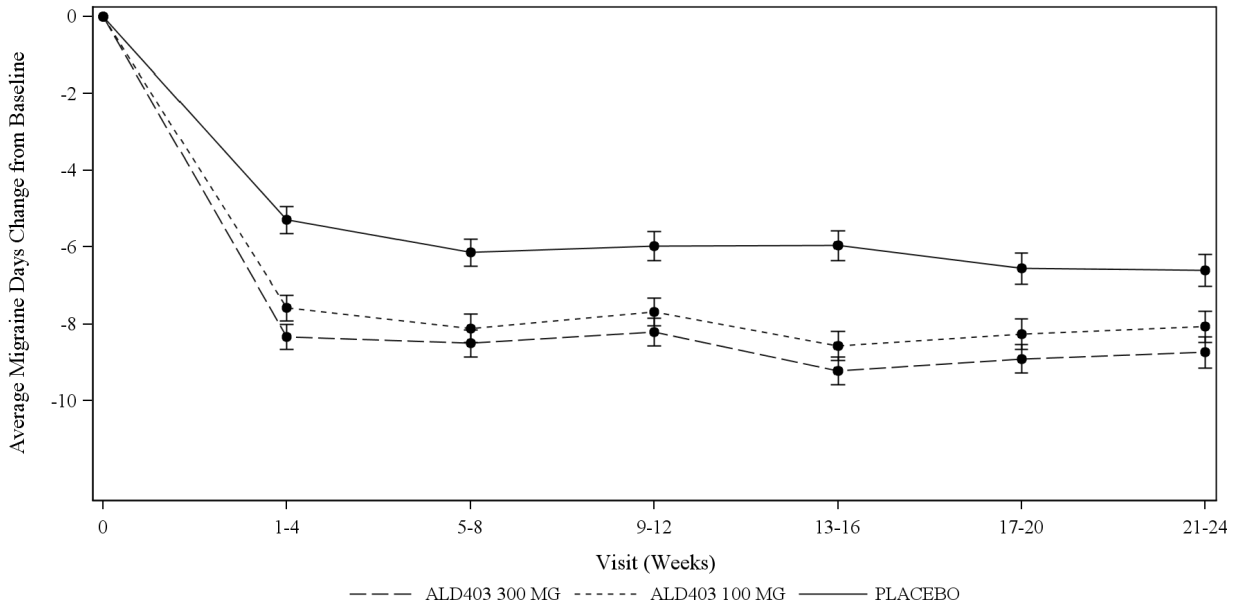


Source: Clinical study report of CLIN-006, Figure 6 on page 106

Study CLIN-011 in patients with chronic migraine, consisted of a 4-week screening period, followed by 12-week double-blind treatment period during which either quarterly doses of 100 mg or 300 mg were administered as intravenous infusion. The patients enrolled in the study were defined as those who had received a diagnosis of migraine at ≤ 50 years of age, have a history of chronic migraine ≥ 1 year prior to screening, and experiencing ≥ 15 and ≤ 26 headache days with ≥ 8 migraine days during the 28-day screening period as documented in eDiary. Both the dosing

regimens met the pre-specified statistical criteria for baseline- and placebo-corrected mean reduction in the mean monthly migraine days (weeks 1 – 12), the primary efficacy endpoint [Figure 2 and Table 4]. (Please refer to statistical review by Dr. Steve Bai and Dr. Kun Jin, DARRTS 11/7/2019 for further details).

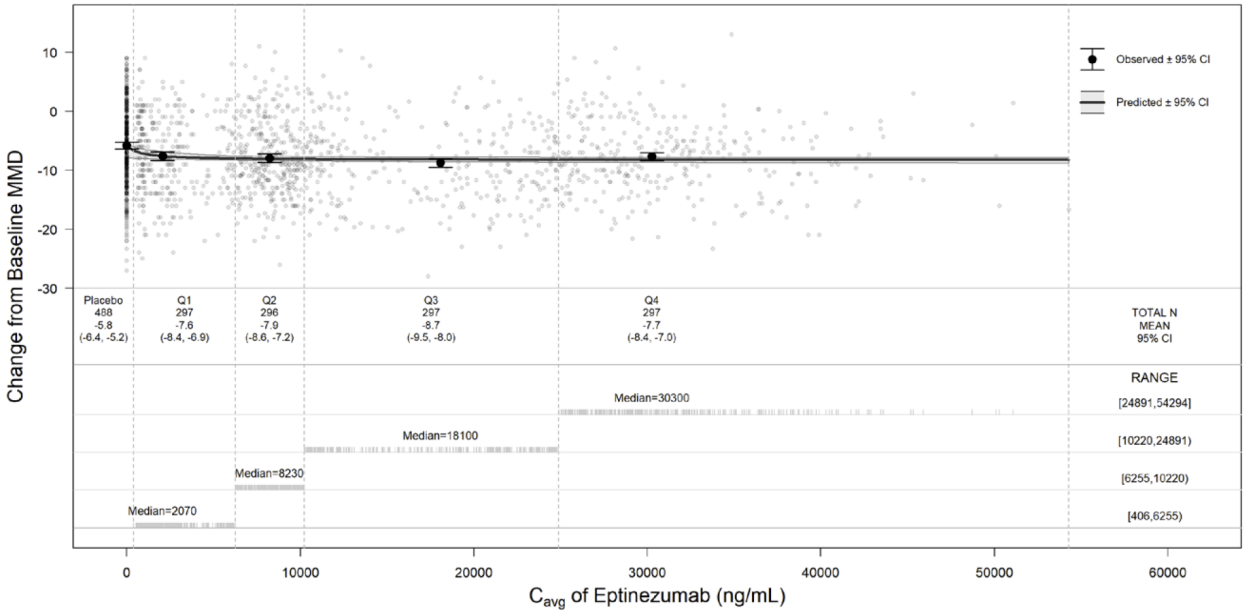
Figure 2 Least squares mean change from baseline in mean monthly number of migraine days by month and treatment group for study CLIN-011 in patients with chronic migraine (full analysis dataset)



Source: Clinical study report of CLIN-011, Figure 14.5.2.1 on page 651

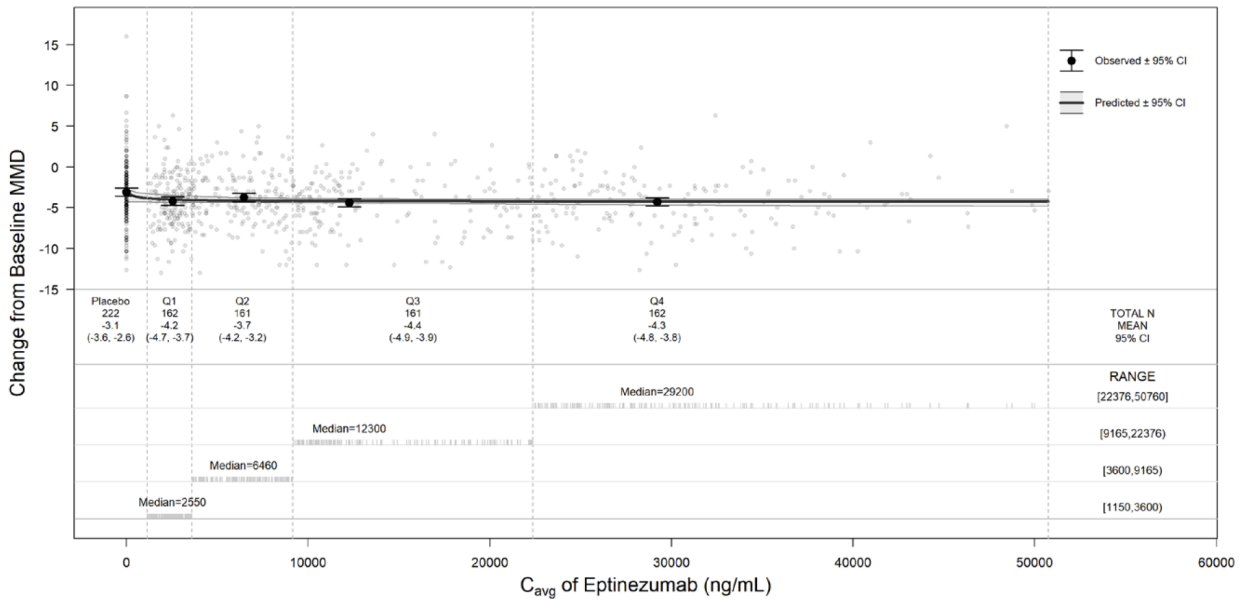
Exposure-response (E-R) analyses were conducted with exposure metrics such as $C_{max,}$ $AUC_{0\text{-}12w}$, C_{trough} and the average plasma concentrations of eptinezumab over the dosing interval (C_{av}) over the dosing interval and primary efficacy endpoint. The E-R analyses using C_{av} is shown in Figure 3 and Figure 4 in chronic and episodic migraine respectively for representative purposes.

Figure 3: Inhibitory Emax – exposure-response model predicted change from baseline in mean monthly migraine days versus eptinezumab Cav in chronic migraine



Source: Response to clinical pharmacology information request (10/13/19), figure 3 on page 13.

Figure 4 Inhibitory Emax – exposure-response model predicted change from baseline in mean monthly migraine days versus eptinezumab Cav in episodic migraine



Source: Response to clinical pharmacology information request (10/13/19), figure 4 on page 14. Please note that the black line and shaded area represent the model-predicted fit and associated 95% confidence intervals and the closed circles with standard bars represent the observed mean and 95% confidence interval.

Table 4 Summary of efficacy results from phase 3 studies

Study CLIN-006 (PROMISE 1) [Episodic Migraine]				
	Placebo (N=222)	30 mg Q3M* (N=221)	100 mg Q3M* (N=222)	300 mg Q3M* (N=223)
Mean change from baseline monthly average number of migraine days from weeks 1-12	-3.2	-4.0	-3.9	-4.0
Placebo-corrected, Mean (95% CI)		-0.82[#] (-1.39, -0.25)	-0.69 (-1.25, -0.12)	-1.11 (-1.68, -0.59)

Study CLIN-011 (PROMISE 2) [Chronic Migraine]			
	Placebo (N=366)	100 mg Q3M* (N=356)	300 mg Q3M* (N=350)
Mean change from baseline monthly average number of migraine days from weeks 1-12	-5.6	-7.7	-8.2
Placebo-corrected, Mean (95% CI)		-2.0 (-2.88, -1.18)	-2.6 (-3.45, -1.74)

*Note: *Q3M: Every 3 months (Quarterly regimen); [#]Not adjusted for multiplicity;*

Clinical study reports from respective studies (full analysis populations): CLIN-006: Table 16 on Page 94; CLIN-011: Table 16 on Page 97;

Please refer to statistical review by Dr. Steve Bai and Dr. Kun Jin for additional details, DARRTS 11/7/2019

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

The applicant is seeking approval for two dosing options for the prevention of (b) (4) migraine:

- 100 mg every 3 months
- Some patients may benefit from a dosage of 300 mg every 3 months.

Both these doses were evaluated in phase 2/3 studies in both CM and EM populations. Based on the efficacy results presented above, both these regimens were shown to be effective and well-tolerated. Though the 30 mg Q3M dosing regimen seem to show comparable treatment effect, but, was not statistically significant, and it was evaluated only in the phase 3 study in EM population. Additionally, the phase 2 study in CM populations showed similar trends, but it was evaluated as secondary endpoint and the analysis was conducted in a modified analysis population (by excluding subjects [N=28] from one clinical study site that was terminated early due and reported to IRB and the agency for potential research misconduct).

Overall, no major safety concerns were observed for both dose levels. The most commonly reported AEs include nasopharyngitis and upper respiratory tract infections. Please refer the clinical review by Dr. Emily R. Freilich and Dr. Heather Fitter for more details.

In conclusion, eptinezumab 100 mg and 300 mg once every 3 months dosing regimens are approvable from a clinical pharmacology perspective.

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

No. Dose adjustment is not necessary based on intrinsic factors such as race, age, sex, bodyweight, BMI, renal or hepatic impairment. No dedicated renal or hepatic impairment studies were conducted. Population pharmacokinetic analysis was conducted on data from 2123 subjects to evaluate the impact of intrinsic and extrinsic factors.

Bodyweight

Bodyweight was reported as significant covariate on both clearance and volume of distribution. Overall, bodyweight in entire PK data ranged between 39 – 190 kg. The steady-state exposures ($AUC_{0\text{-}Tau}$) for these subjects showed 51% higher (39 kg) and 51% lower (190 kg) relative to a 70 kg typical subject based on final population PK model. However, for majority of patients (25^{th} percentile – 75^{th} percentile: 63 – 88 kg respectively), the impact of bodyweight was minimal < ~8-15% change in steady-state exposures ($AUC_{0\text{-}Tau}$) and therefore it is unlikely to be clinically relevant, given the observed dose- and exposure-response relationship for efficacy. Additionally,

it is worth noting that only fixed doses of eptinezumab were administered in all the clinical studies. Therefore, no dose adjustment is warranted based on bodyweight.

Sex

Sex was reported as a significant covariate on volume of distribution. However, based on the magnitude of the impact (males showed 10% higher volume of distribution than females), sex is unlikely to be clinically relevant covariate. Therefore, no dose adjustment is needed based on sex.

Renal impairment[1]

Based on population PK analysis, creatinine clearance (estimated using Cockcroft-Gault equation and capped at 150 ml/min) was reported as a significant covariate on clearance. In subject with 45 ml/min (lowest in the PK population), steady-state exposures ($AUC_{0\text{-}Tau}$) was 18% highest than typical subject with creatinine clearance of 118 ml/min. In general, renal elimination of monoclonal antibodies is considered low and given the minimal impact on exposures, no dose adjustment is recommended based on renal impairment.

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

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

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

The applicant conducted a randomized, double-blind, parallel-group, placebo-controlled study in healthy subjects to assess the drug-drug interaction potential with co-administration of sumatriptan (ALD403-CLIN-001 – Part B). In this study, a single dose of 300 mg intravenous infusion of eptinezumab was co-administered with a single subcutaneous dose of 6 mg sumatriptan. There was no clinically relevant impact on sumatriptan or eptinezumab PK.

[1] The criteria for renal function classification was based on FDA guidance

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

The applicant is seeking approval for 100 mg/ml single-dose vial. They conducted a pivotal PK bridging study (CLIN-014) and demonstrated bioequivalence between the formulation used in phase 3 studies and the commercial to-marketed formulation at 300 mg dose level. There were major manufacturing changes for both drug substance and drug product, changes in manufacturing site and scale-up process between the commercial and clinical trial formulations.

A consult request (DARRTS dated 4/26/2019) was submitted to Office of Study Integrity and Surveillance (OSIS) for inspection of both clinical and analytical sites for pivotal PK study bridging between clinical trial formulation and the to-be-marketed commercial formulation. OSIS conducted inspection for one of the clinical sites and found the data are reliable to support a regulatory decision (DARRTS 08/15/2019) and determined that an inspection is not required at the other clinical sites (DARRTS 5/16/2019). OSIS also conducted inspection of the analytical site and found that portion of data from study CLIN-014 is not reliable to support a regulatory decision. Form 483 was issued at the close-out and Voluntary Action Indicated (VAI) was issued (DARRTS 12/18/2019).

Specifically, dilution linearity was assessed using 40-, 160- and 320-fold dilutions (two replicates of each dilution) and 4 out of 6 dilution samples met the acceptance criteria (± 20% nominal concentration), only one of the two samples were assessed at both 160- and 320-fold dilution and accurate based on the criteria. Consequently, OSIS report indicated that all the reported drug concentrations obtained using dilution factors >100-fold, which include end of infusion (15 min), 1, 2, 4, 6, 8 hours, Day 2 and Day 7 timepoints from all subjects are not reliable.

The firm (i.e., analytical site) proposed to amend the method validation protocol (00997069) and conduct additional dilutional integrity and dilutional linearity experiments and submit the results in an amendment to the method validation report to the applicant by October 31, 2019. In the end, OSIS noted that in the absence of additional validation data demonstrating the precision and accuracy of the dilution factors above 100-fold, the reliability of study sample concentrations cannot be assured.

It is worth noting that the analytical method used for measuring free eptinezumab concentrations from samples collected from the rest of the studies was validated by a different method ((b) (4) – 997005\\cdsesub1\evsprod\bla761119\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met (b) (4)-997005 (b) (4)-997005.pdf). The validation of this study indicated that dilution linearity for 6 out of 6 dilution samples (included two each at 160- and 320-fold dilutions) met the acceptance criteria for both accuracy and precision.

During the discussions at the wrap-up meeting, the CMC review team noted that the differences in the product quality attributes between the clinical the commercial formulations were minor,

and that the likelihood of these differences to impact the PK is low. Thus, study CLIN-014 was not considered pivotal for bridging the formulations.

4 APPENDICES

4.1 Summary of Bioanalytical Method Validation

For the determination of plasma eptinezumab concentrations, the applicant used a ligand-binding Enzyme-Linked Immunosorbent Assay (ELISA) method. Briefly, in this method, eptinezumab in human plasma is bound to α-CGRP coated on 96-well microtiter plate wells, followed by detection using a horseradish peroxidase (HRP)-labeled mouse anti-human IgG antibody. This method was developed and validated by (b) (4)
The ELISA method was validated in compliance with the standards set forth in the FDA Bioanalytical Method Validation guidance. Summary of the validation parameters in presented in the table below:

Bioanalytical method validation report	Study report (b) (4) 997005 (the same procedure was used for both the pivotal phase 3 studies)
Method description	Validation of an ELISA Procedure for the Quantification of Free ALD403 in Human K2 EDTA Plasma
Validation assay range	50 – 1600 ng/ml
Inter-day precision (%CV)	10.02% – 13.19%
Inter-day accuracy (% RE)	-10.59% - 5.22%
Intra-day precision (%CV)	0.99% - 17.30%
Intra-day accuracy (% RE)	-30.56% - 18.87%
Reference standard	ALD403, LOT #14&095
Specificity	No interference in the blank matrix was seen
Freeze/thaw stability	6 cycles: Precision (%CV): 2.78% – 7.74%; Accuracy (%RE): -0.94% – 8.89%

4.2 Evaluation of Effect of Immunogenicity on PK/Efficacy/Safety of Eptinezumab

Applicant's analyses:

The clinical immunogenicity database for eptinezumab includes results from five clinical studies in which total of 2076 subjects (ADA results available from 2074 subjects) with CM or EM. An overview of the clinical study design features is shown in Table 5 below. Out of the 5 studies shown, 4 were randomized, double-blind, placebo-controlled trials (ALD403-CLIN-002, -005, -006 and -011) and the other was an open label study (ALD403-CLIN-013). It should be noted that data from study CLIN-002 were omitted in the calculation of the final numbers for labeling purposes because different assay methods were used in that study. The scheduled duration of ADA monitoring extended to 56 weeks for 3 studies, and to 104 weeks for subjects enrolled in CLIN-013, with provision for follow-up monitoring for up to 6 months in subjects with confirmed ADA positive result at the end-of-study visit. The schedule of assessment for each study is summarized in Table 6.

Table 5 Overview of clinical studies contributing to immunogenicity evaluation for eptinezumab

Study	Phase & Blinding	Migraine Type	Dose Levels Number of Doses	Dose level	Number of subjects with ADA results
-002	Phase 1b Double Blind	EM	1000 mg, Placebo Single dose – Day 0	1000 mg	81
-005	Phase 2 Double Blind	CM	10, 30, 100, 300 mg, Placebo Single dose- Day 0	300 mg 100 mg 30 mg 10 mg	120 122 122 129
-006	Phase 3 Double blind	EM	30, 100, 300 mg, Placebo Four doses – Day 0, Weeks 12, 24, 36	300 mg 100 mg 30 mg	224 223 219
-011	Phase 3 Double blind	CM	100, 300 mg, Placebo Two doses – Day 0, Week 12	300 mg 100 mg	350 356
-013 Part 1	Phase 3 Open Label	CM	300 mg Four doses – Day 0, Weeks 12, 24, 36	300 mg	128
Total number of subjects treated with eptinezumab with ADA results					2074

Abbreviations: ADA = anti-drug antibody; CM = Chronic Migraine; EM = Episodic Migraine

Source: Integrated summary of immunogenicity report – table 58 on page 120

Table 6 Schedule of dosing, PK, efficacy, safety assessments in clinical studies contributing immunogenicity evaluation for eptinezumab

Assessment	Screen	Treatment (Day 0)	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48/49	Wk 56
ALD403-CLIN-002 (FEM)							PC	PC	EOS							
ALD403/Placebo dosing		X														
Adverse Event Review	X	X	X	X	X	X	X	X	X							
Migraine Data (eDiary)				X												
Serum Anti-ALD403 Antibody		X	X		X	X			X							
Plasma ALD403 (PK)		X	X	X	X	X			X							
ALD403-CLIN-005 (CM)							PC	PC		PC	PC		PC	PC	EOS	
ALD403/Placebo dosing		X														
Adverse Event Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Migraine Data (eDiary)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum Anti-ALD403 Antibody		X		X	X	X			X			X			X	
Plasma ALD403 (PK)		X		X	X	X			X			X			X	
ALD403-CLIN-006 (FEM)			N/A								N/A		N/A	N/A		EOS
ALD403/Placebo dosing		X				X			X			X				
Adverse Event Review	X	X		X	X	X	X	X	X	X		X			X	X
Migraine Data (eDiary)							X									
Serum Anti-ALD403 Antibody		X		X	X	X	X	X	X			X			X	X
Plasma ALD403 (PK)		X		X	X	X	X	X	X			X			X	X
ALD403-CLIN-011 (CM)										N/A	EOS					
ALD403/Placebo dosing		X				X										
Adverse Event Review	X	X	X	X	X	X	X	X	X		X					
Migraine Data (eDiary)				X												
Serum Anti-ALD403 Antibody		X	X	X	X	X			X		X					
Plasma ALD403 (PK)		X	X	X	X	X			X		X					
ALD403-CLIN-013 (CM)[a]							N/A	N/A		N/A	N/A		N/A	N/A		
ALD403 dosing		X				X			X			X				
Adverse Event Review	X	X	X	X	X	X			X			X			X	X
Serum Anti-ALD403 Antibody		X	X	X	X	X			X			X			X	X
Plasma ALD403 (PK)		X	X	X	X	X			X			X			X	X

[a] ALD403-CLIN-013 includes two treatment phases. In the primary treatment phase, subjects receive 4 IV infusions of eptinezumab on Day 0, Weeks 12, 24, and 36. Subjects who receive all 4 infusions of eptinezumab in the primary treatment phase may enter the secondary treatment phase. In the secondary treatment phase, subjects receive up to 4 additional IV infusions of eptinezumab for a total of 8 infusions. Eptinezumab IV infusions occur on Weeks 48, 60, 72, and 84, which are not presented.

Note: Immunogenicity sampling for those subjects ADA positive at the last scheduled visit will be done every 3 months for up to 6 months following the last on study visit.

Abbreviations: CM = Chronic Migraine; EOS = End of Study; FEM = Frequent Episodic Migraine; N/A = Not Applicable (not a protocol specified study visit); PC = Telephone contact with subject; no in clinical visit scheduled; PK = pharmacokinetics; Wk = week

Source: Integrated summary of immunogenicity report – table 59, 60 on pages 121-122

The immune response dynamics relative to the time-course of the treatment based on the were characterized based on Anti-eptinezumab Antibody (ADA) - (1) positive vs. negative status, and (2) ADA titer. ADA positive refers to samples confirmed as positive in a confirmatory assay. ADA titer refers to the value within the screening assay through a series of dilutions beginning with the minimum required dilution of confirmed positive ADA samples.

ADA or neutralizing antibody (NAb) positive status corresponded to confirmed positive ADA/NAb signal at any signal visit (defined as "ever positive") and the impact of ADA/NAb were evaluated on PK/efficacy. However, for evaluating the impact on safety, in addition to "ever positive", "coincident positive" (confirmed ADA positive result in the sample taken just prior to dose associated with TEAE) ADA/NAb status was also considered.

Eptinezumab trough plasma concentrations (C_{trough}) were collected pre-dose, i.e., just prior to next dose administration for treatment visits and at each scheduled visit when available in PK population. The applicant noted that the eptinezumab C_{trough} values should be interpreted with caution because they can be potentially confounded by the ADA interference. Specifically, reduction of apparent C_{trough} could represent ADA interference rather than, or in addition to, enhanced clearance. The applicant attributes this to the nature of the ligand-binding assay in which there is competition between eptinezumab and anti-eptinezumab antibody for binding to the target antigen, α-CGRP. Furthermore, the applicant conducted a interference study (ALD403 free PK human assay ADA interference – EDMS – 01776) by pre-incubation of normal human plasma spiked with eptinezumab (specified concentrations) and anti-eptinezumab (positive control) antibody) at fixed concentrations of 100, 250 and 2500 ng/ml). The results are shown in Table 7 below.

Table 7 Impact of ADA – Results from ALD403 free human assay ADA interference study (EDMS-01776)

%RE = ((Test – Reference) / Reference) * 100			
Eptinezumab only, ng/mL	**Eptinezumab + 100 ng anti-eptinezumab antibody / mL (ADA Titer ~200)**	**Eptinezumab + 250 ng anti-eptinezumab antibody / mL (ADA Titer ~500)**	**Eptinezumab + 2,500 ng anti-eptinezumab antibody / mL (ADA Titer ~4500)**
95,300	-6.6	-4.2	-8.9
46,600	1.0	-6.2	-10.8
24,250	1.0	-3.1	-3.9
12,250	-4.1	-6.1	-19.5
5,930	-0.7	-8.3	-30.4
2,945	-1.9	-11.4	-70.8[a]
1,445	-0.3	-17.3	-96.5
770	-41.5	-31.6	-96.3[a]

[a] Estimate only - Sample concentration fell below LLOQ
Abbreviations: ADA = anti-drug antibody; LLOQ = lower limit of quantitation; RE = Relative Error
Source: EDMS-01776, ALD403 Free PK Human Assay ADA Interference Study

Lastly, the applicant also described a caveat that the interference study was based on a surrogate positive control antibody reagent that may not accurately reflect interreference by the ADA present in clinical samples.

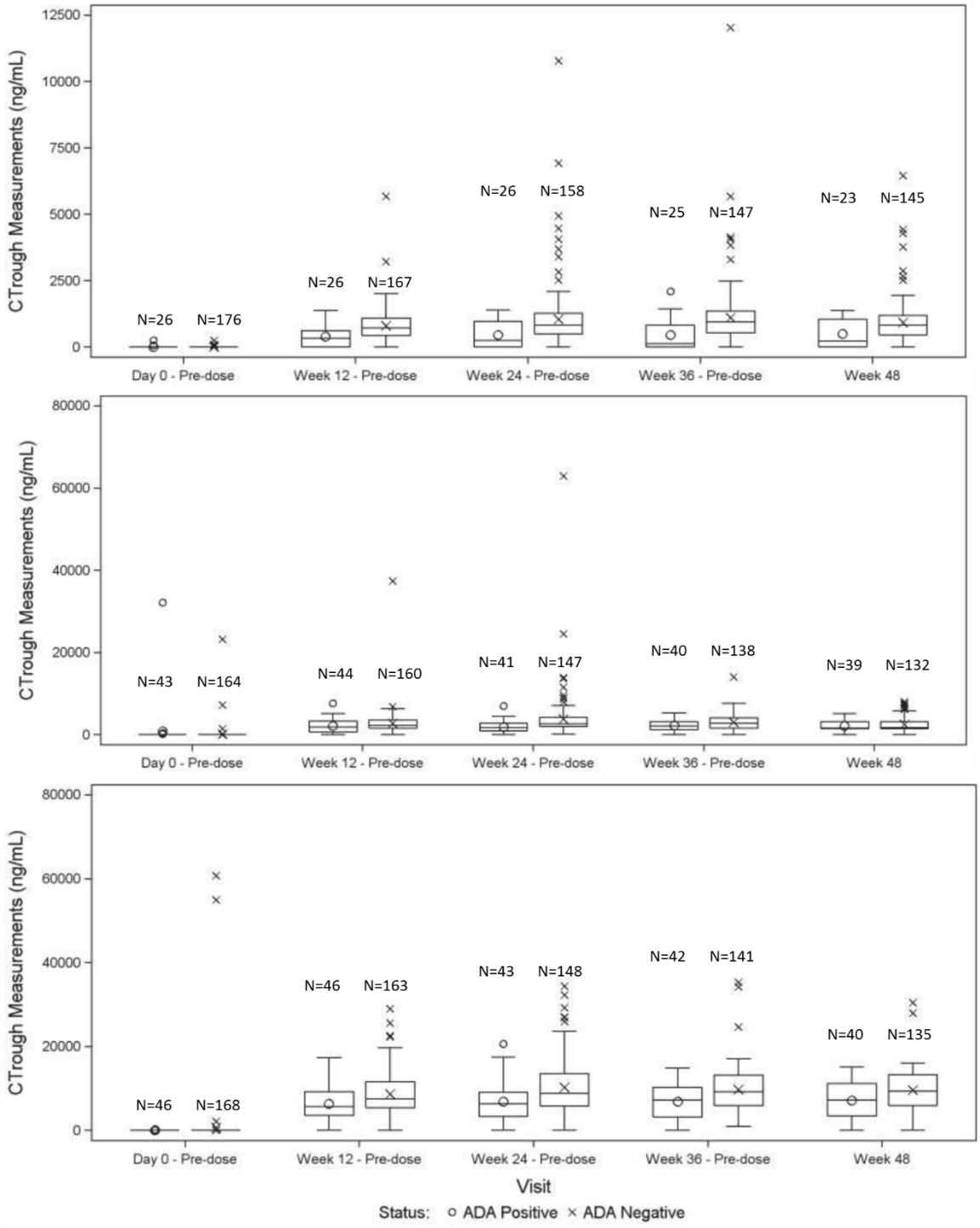
The impact of ADA status on eptinezumab C_{trough} for pivotal phase 3 studies: CLIN-006 in patients with EM and CLIN-011 in patients with CM are shown in Figure 5 and Table 8 respectively. The applicant noted that the mean C_{trough} for subjects with ADA positive status was in general 12-50% than subjects with ADA negative status (please refer to Table 9 and Table 10 for CLIN-006 in EM and CLIN-011 in CM respectively).

The time course of the evolution of ADA titer for pivotal studies: CLIN-006 in EM and CLIN-011 in CM are shown Figure 6 and Figure 7 respectively. The applicant noted that the ADA frequency and mean titer were maximal at week 24 followed by decline through week 32 in CLIN-011 or week 48 in CLIN-006 respectively and that there was no apparent difference in the distribution of ADA titer values relative to eptinezumab dose levels. Additionally, it was noted that the upper quartile of ADA titer was in general lower across all the dose levels and across EM/CM populations, likely because of the confounding effect of interference of ADA on eptinezumab C_{trough} concentrations.

The impact of NAb status on eptinezumab C_{trough} for pivotal studies: CLIN-006 in EM and CLIN-011 in CM are shown in Figure 8 and Figure 9 respectively. The applicant noted that the mean C_{trough} for subjects with NAb positive status were in general lower than in subjects with NAb negative status.

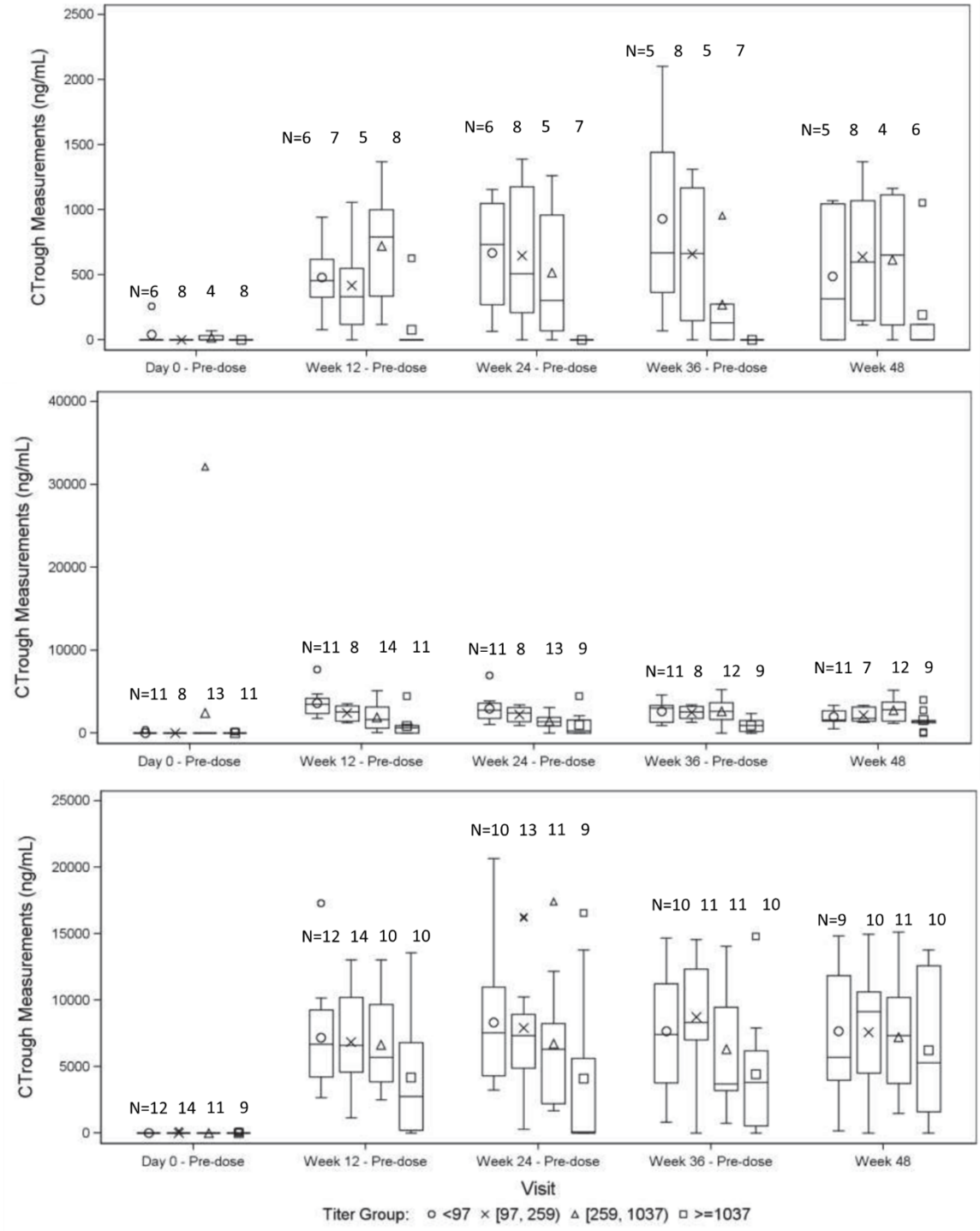
The impact of ADA status on eptinezumab efficacy for pivotal phase 3 studies: CLIN-006 in EM and CLIN-011 in CM are shown in Figure 10 and Figure 11 respectively. The applicant noted that lower C_{trough} in subjects with ADA (/NAb) positive status was not associated with lower efficacy. Similarly, no apparent relationship in efficacy was noted based on ADA titer across dose levels or across EM/CM populations as shown in Figure 12 and Figure 13 respectively.

Figure 5 Boxplot of eptinezumab Ctrough by ADA status, visit, and treatment (PK population) CLIN-006 – Phase 3 study in patients with EM for 30 mg (top panel) 100 mg (middle panel) and 300 mg (bottom panel) [Note: Y-axis unit scales vary by panel]



Source: Integrated summary of immunogenicity report – tlfs - Figures 14.3.2.2.6 pages 1146-1148

Figure 6 Boxplot of eptinezumab Ctrough by maximum ADA titer, visit, and treatment (PK population) CLIN-006 – Phase 3 study in patients with EM for 30 mg (top panel) 100 mg (middle panel) and 300 mg (bottom panel) [Note: Y-axis unit scales vary by panel]



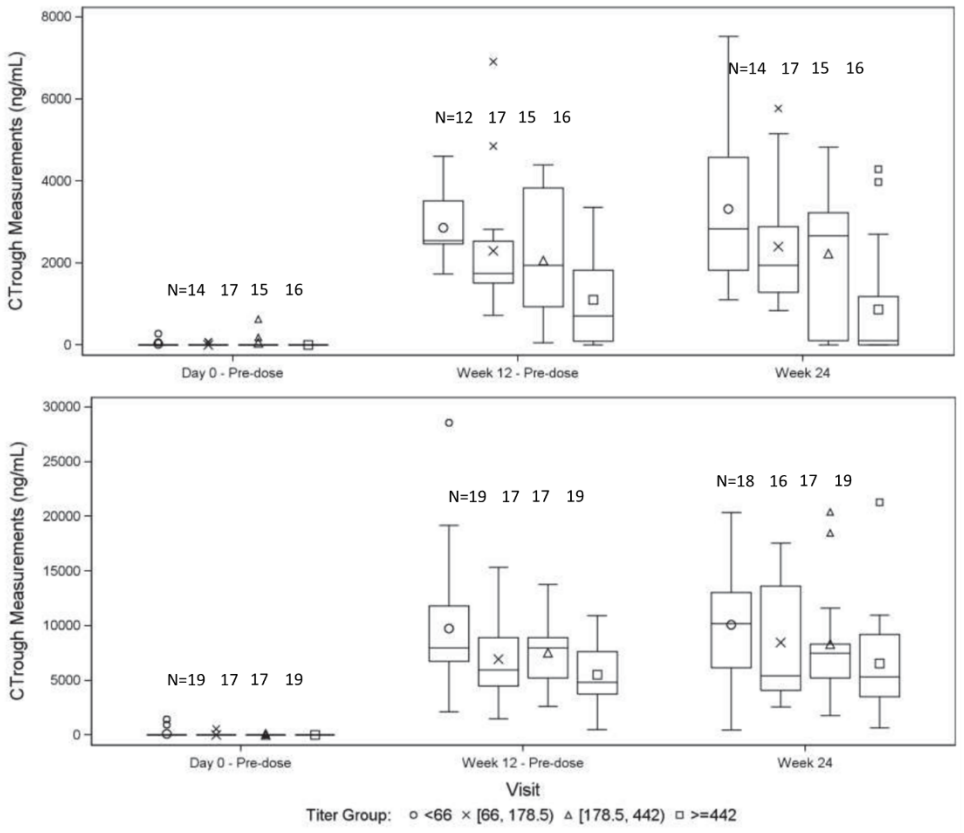
Source: Integrated summary of immunogenicity report – tIfs - Figures 14.3.1.6 page 1106-1108

Table 8 Summary of eptinezumab Ctrough by ADA status, visit and treatment CLIN-011 – Phase 3 study in patients with CM

	Epti 300 mg		Epti 100 mg	
Visit	ADA + N=69	ADA - N=280	ADA + N=60	ADA - N=294
Day 0 - Pre-dose				
n	69	278	60	294
Mean (SD)	48.992 (214.2144)	675.378 (6016.1200)	22.656 (92.1504)	1854.985 (24892.6176)
Median	0.000	0.000	0.000	0.000
Q1, Q3	0.000, 0.000	0.000, 0.000	0.000, 0.000	0.000, 0.000
Min, Max	0.00, 1436.00	0.00, 82940.00	0.00, 634.90	0.00, 422900.00
Week 12 - Pre-dose				
n	69	269	58	282
Mean (SD)	7336.235 (4494.9355)	9607.561 (4453.8882)	1993.839 (1419.8065)	2993.445 (1511.5645)
Median	6727.000	9021.000	1789.500	2759.000
Q1, Q3	4484.000, 9081.000	6559.000, 12140.000	966.600, 2680.000	1989.000, 3632.000
Min, Max	504.20, 28580.00	1285.00, 29230.00	0.00, 6908.00	55.55, 11750.00
Week 24				
n	68	256	60	262
Mean (SD)	8255.784 (5016.3746)	10178.387 (4561.8431)	2132.770 (1826.8610)	3469.278 (2123.1354)
Median	7252.000	9455.500	1892.500	3183.000
Q1, Q3	4432.000, 11040.000	6932.000, 12740.000	197.800, 3183.000	2057.000, 4172.000
Min, Max	446.20, 21320.00	1940.00, 25010.00	0.00, 7533.00	131.40, 13910.00

Source: Integrated summary of immunogenicity report – tlfs – Table 14.3.2.11 on page 85

Figure 7 Boxplot of eptinezumab Ctrough by maximum ADA titer, visit, and treatment (PK population) CLIN-011 – Phase 3 study in patients with CM for 100 mg (top panel) and 300 mg (bottom panel) [Note: Y-axis unit scales vary by panel]



Source: Integrated summary of immunogenicity report – tlfs - Figures 14.3.1.11 page 1109-1110

Table 9 Mean eptinezumab Ctrough by ADA status for subjects treated with 100 or 300 mg (PK population) - CLIN-006 – Phase 3 study in patients with EM

	30 mg Eptinezumab			100 mg Eptinezumab			300 mg Eptinezumab		
	Mean Ctrough (ng/ml) for ADA Negative, (N)	Mean Ctrough (ng/ml) for ADA Positive, (N)	Ctrough % for ADA Positive/ ADA negative	Mean Ctrough (ng/ml) for ADA Negative, (N)	Mean Ctrough (ng/ml) for ADA Positive, (N)	Ctrough % for ADA Positive/ ADA negative	Mean Ctrough (ng/ml) for ADA Negative, (N)	Mean Ctrough (ng/ml) for ADA Positive, (N)	Ctrough % for ADA Positive/ ADA negative
Week 12	802.8 (167)	386.8 (26)	48.2%	2828.0 (160)	2168.1 (44)	76.7%	8726.6 (163)	6320.5 (46)	72.4%
Week 24	1048.5 (158)	435.5 (26)	41.5%	3876.2 (147)	1900.1 (41)	49.0%	10292.3 (148)	6896.4 (43)	67.0%
Week 36	1114.3 (147)	451.2 (25)	40.5%	3064.0 (138)	2221.2 (40)	72.5%	9784.6 (141)	6825.5 (42)	69.8%
Week 48	935.2 (145)	486.3 (23)	52.0%	2453.3 (132)	2170.3 (39)	88.5%	9573.0 (135)	7154.4 (40)	74.7%

Source: Integrated summary of immunogenicity report – Table 71 on page 147

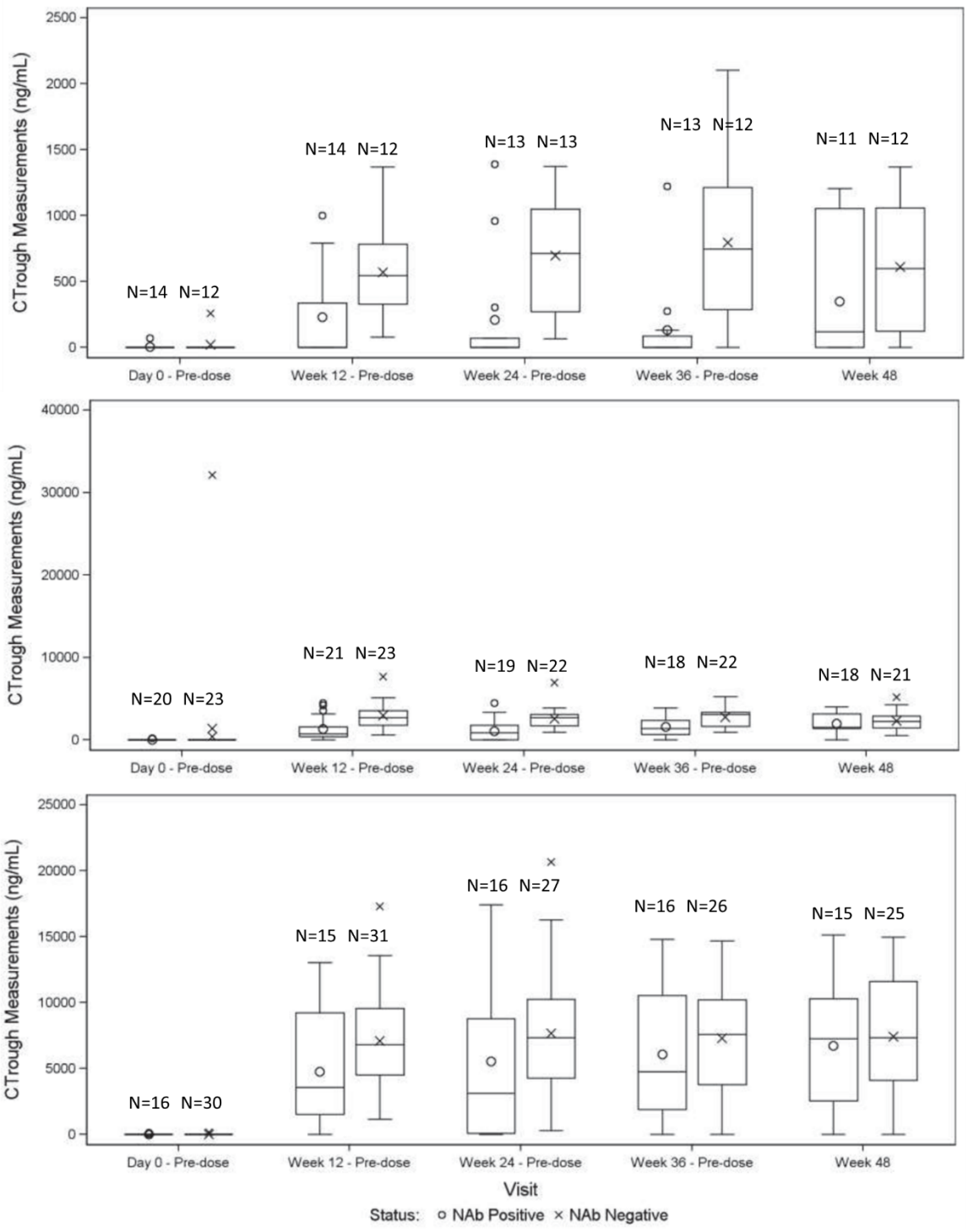
Table 10 Mean eptinezumab Ctrough by ADA status for subjects treated with 100 or 300 mg (PK population) - CLIN-011 – Phase 3 study in patients with CM

Sample time-point	300 mg eptinezumab			100 mg eptinezumab		
	Mean C_{trough} for ADA negative, ng/mL (n)	Mean C_{trough} for ADA positive, ng/mL (n)	C_{trough} as % for ADA positive / ADA negative	Mean C_{trough} for ADA negative, ng/mL (n)	Mean C_{trough} for ADA positive, ng/mL (n)	C_{trough} as % for ADA positive / ADA negative
Week 12	9607.6 (269)	7336.2 (69)	76.4%	2993.4 (282)	1993.8 (58)	66.6%
Week 24	10178.4 (256)	8255.8 (68)	81.1%	3469.3 (262)	2132.8 (60)	61.5%

Abbreviations: ADA = anti-drug antibody; C_{trough} = mean concentration of eptinezumab in plasma just prior to next administration; n = number of evaluable results

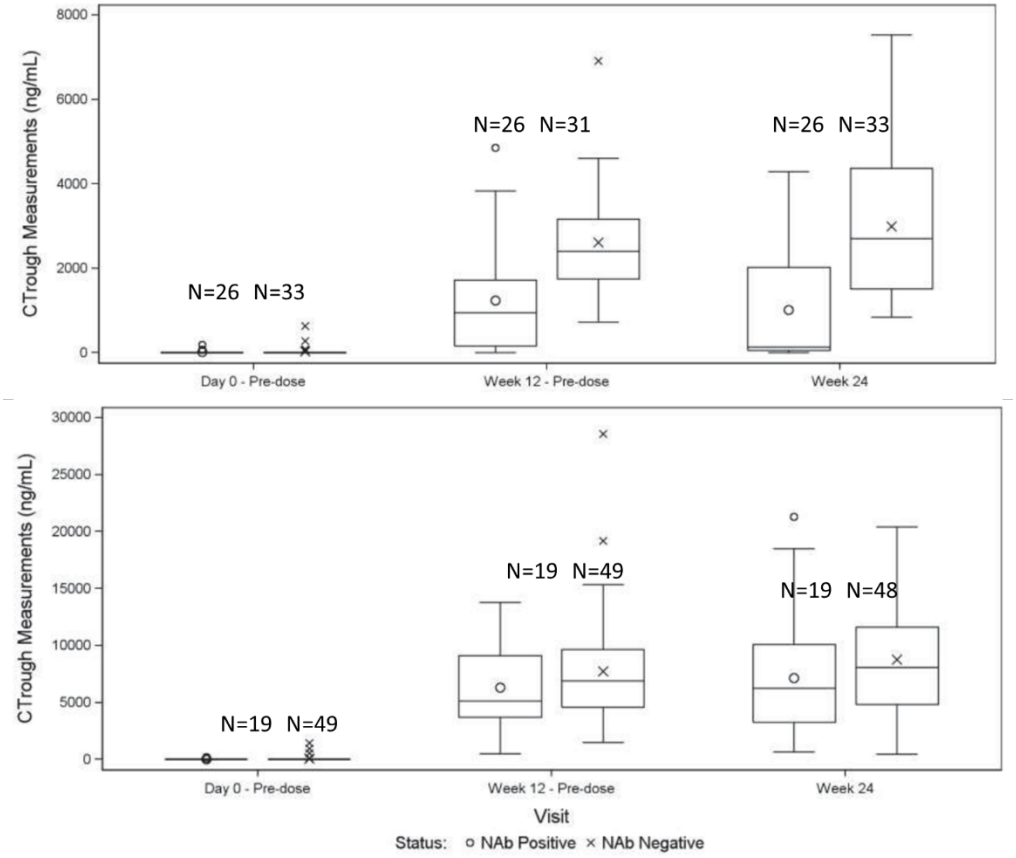
Source: Integrated summary of immunogenicity report – Table 85 on page 180

Figure 8 Boxplot of eptinezumab Ctrough by NAb status, visit, and treatment (PK population) CLIN-006 – Phase 3 study in patients with EM for 30 mg (top panel) 100 mg (middle panel) and 300 mg (bottom panel) [Note: Y-axis unit scales vary by panel]



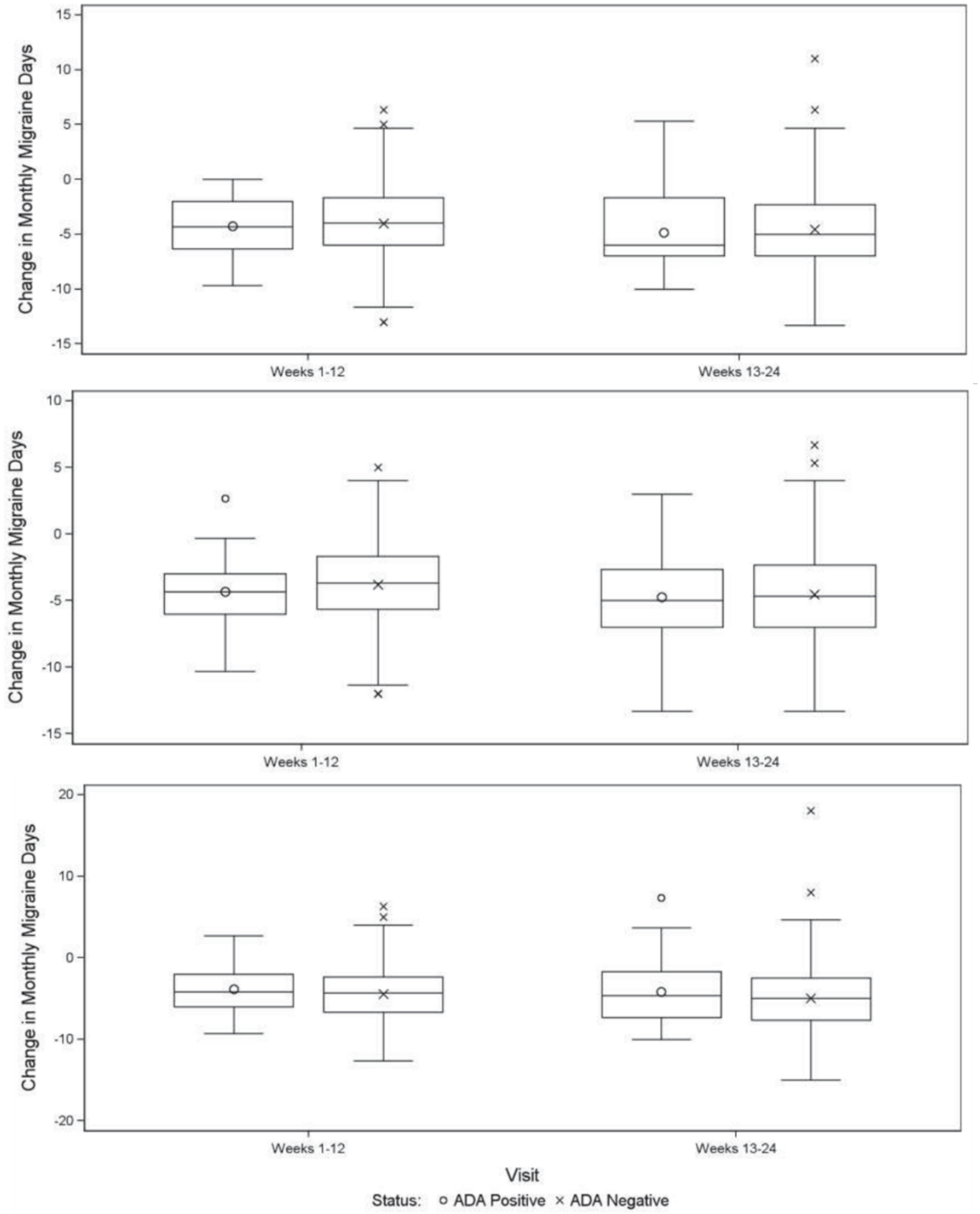
Source: Integrated summary of immunogenicity report – tIfs - Figure 14.3.3.2.6 pages 1186-1188

Figure 9 Boxplot of eptinezumab Ctrough by NAb status, visit, and treatment (PK population) CLIN-011 – Phase 3 study in patients with CM for 100 mg (top panel) and 300 mg (bottom panel) [Note: Y-axis unit scales vary by panel]



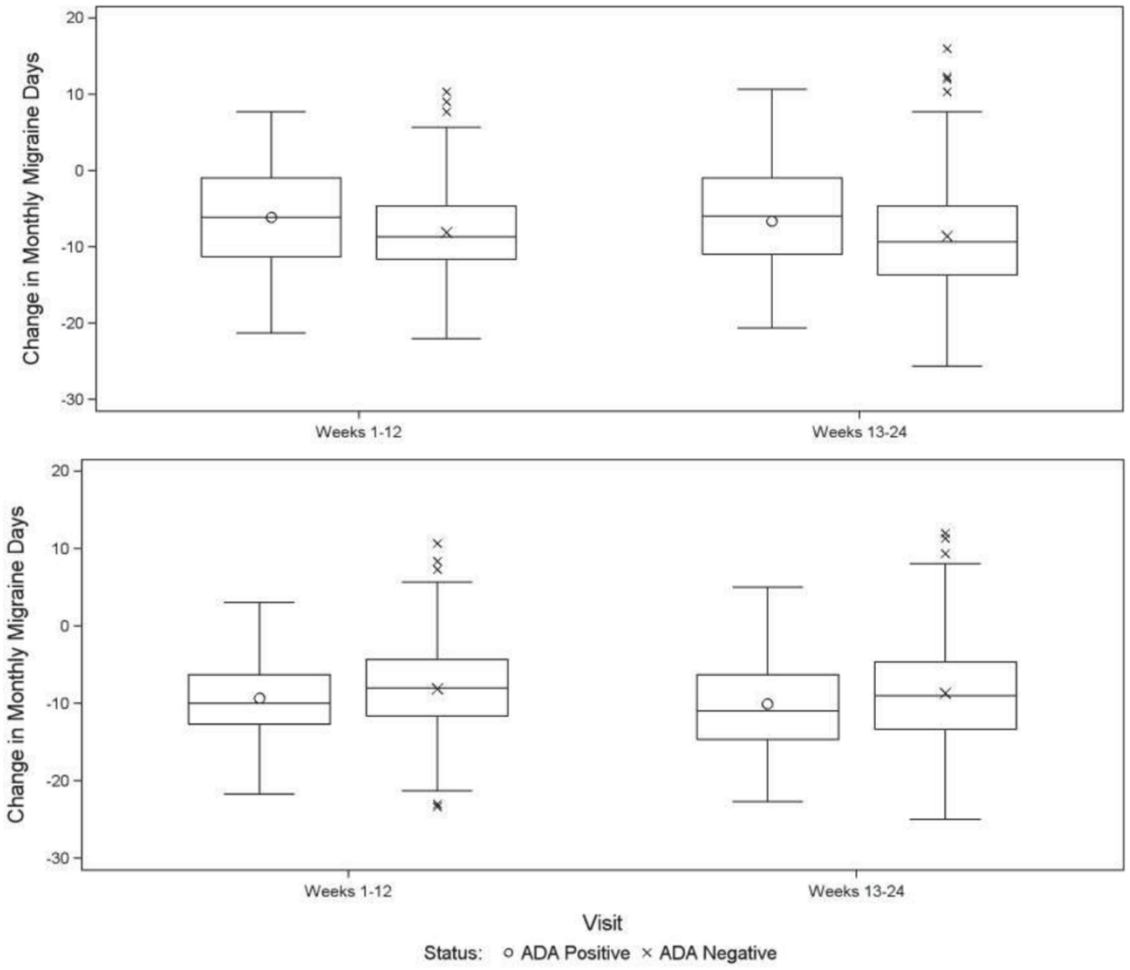
Source: Integrated summary of immunogenicity report – tIfs - Figure 14.3.3.2.11 pages 1189-1190

Figure 10 Boxplot of change in monthly migraine days by ADA status, visit, and treatment (full analysis population) CLIN-006 – Phase 3 study in patients with EM for 30 mg (top panel) 100 mg (middle panel) and 300 mg (bottom panel) [Note: Y-axis unit scales vary by panel]



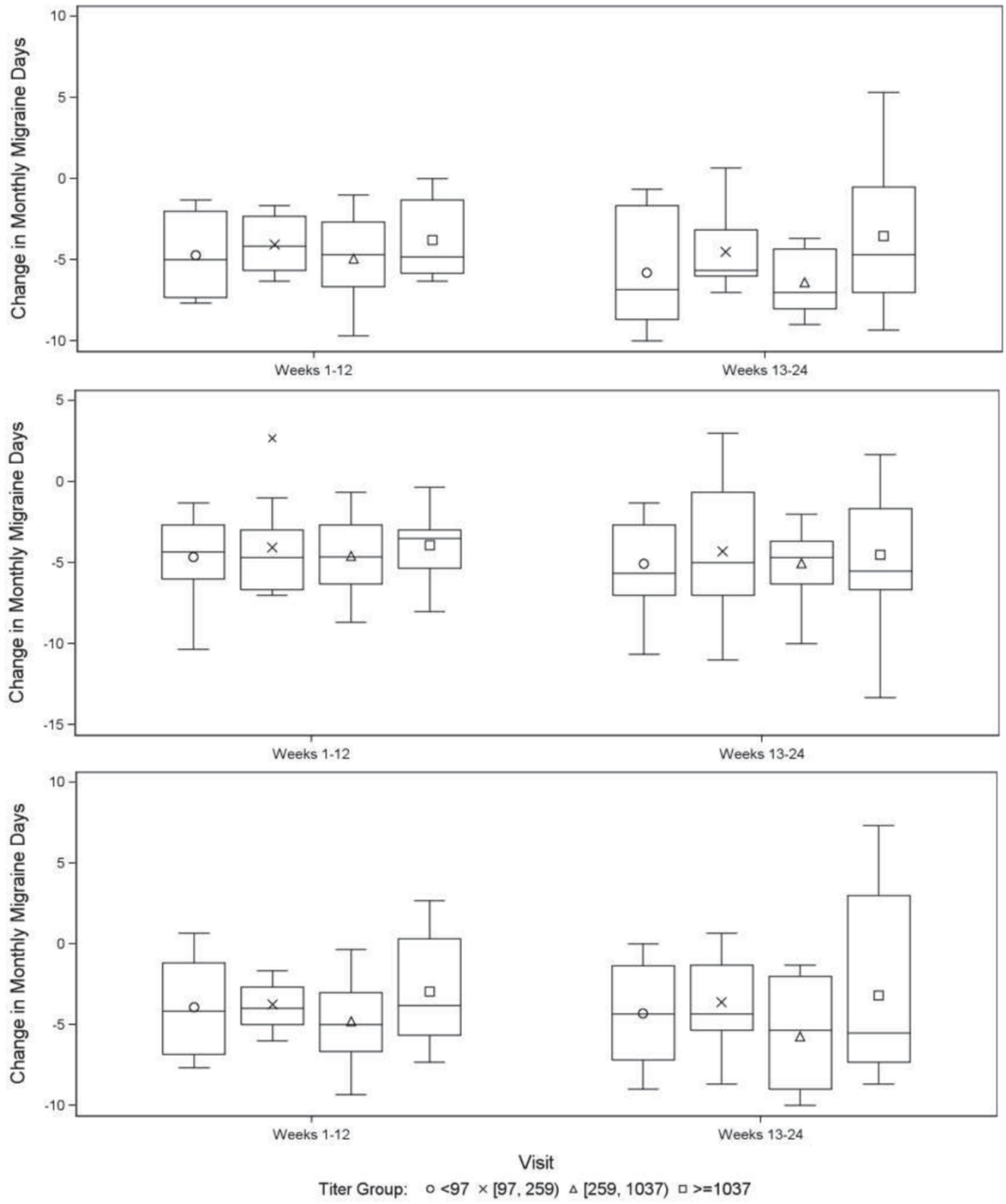
Source: Integrated summary of immunogenicity report – tIfs - Figure 14.4.2.6 pages 1205-1207

Figure 11 Boxplot of change in monthly migraine days by ADA status, visit, and treatment (full analysis population) CLIN-011 – Phase 3 study in patients with CM for 100 mg (top panel) and 300 mg (bottom panel)



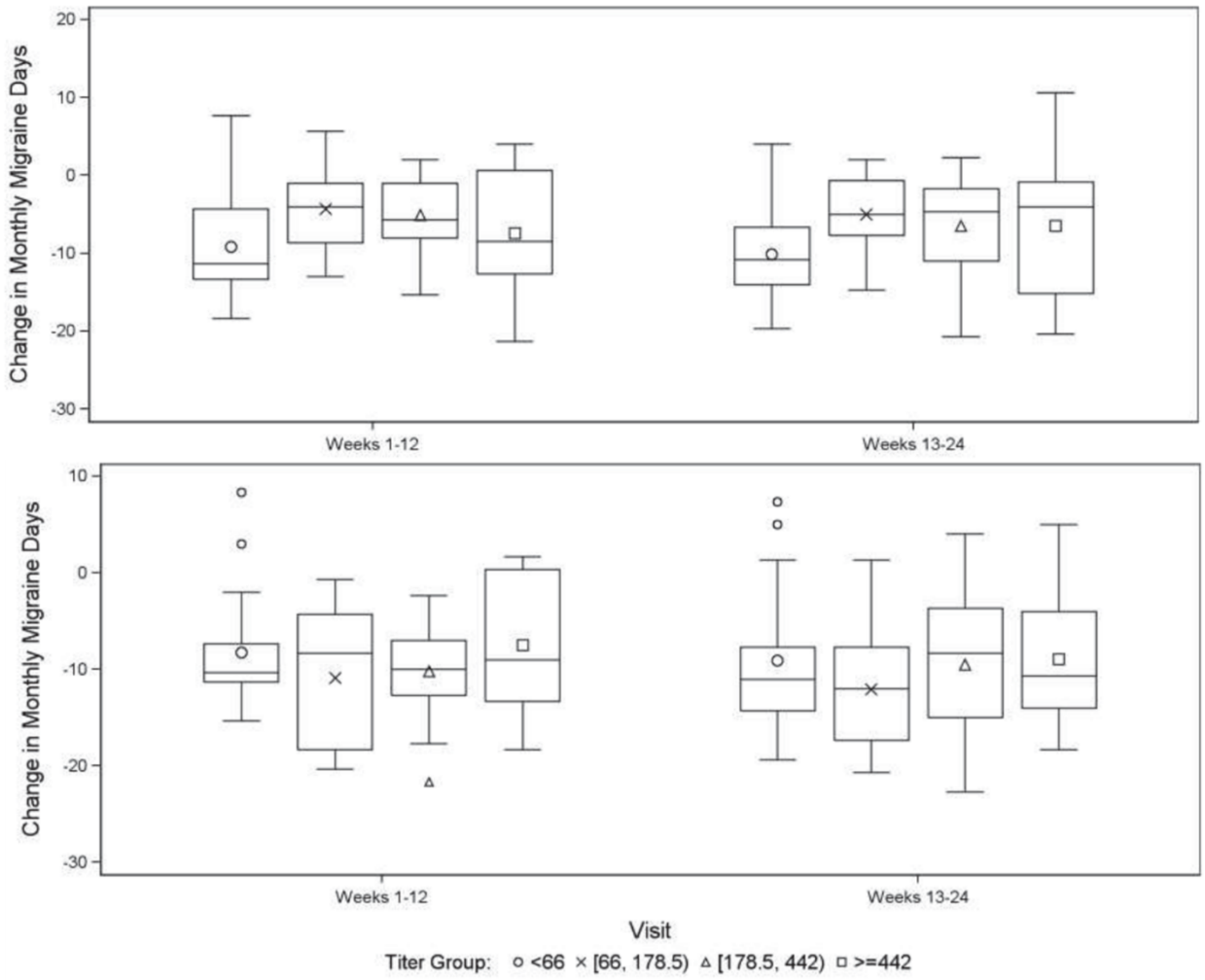
Source: Integrated summary of immunogenicity report – tIfs - Figure 14.4.2.11 pages 1208-1209

Figure 12 Boxplot of change in monthly migraine days by ADA titer, visit, and treatment (full analysis population) CLIN-006 – Phase 3 study in patients with EM for 30 mg (top panel) 100 mg (middle panel) and 300 mg (bottom panel) [Note: Y-axis unit scales vary by panel]



Source: Integrated summary of immunogenicity report – tIfs - Figure 14.4.1.6 pages 1196-1198

Figure 13 Boxplot of change in monthly migraine days by ADA titer, visit, and treatment (full analysis population) CLIN-011 – Phase 3 study in patients with CM for 100 mg (top panel) and 300 mg (bottom panel) [Note: Y-axis unit scales vary by panel]



Source: Integrated summary of immunogenicity report – tlfs - Figure 14.4.1.11 pages 1199-1200

Figure 14 Comparison of eptinezumab plasma trough concentrations (left y-axis) and ADA titer (right y-axis) across dose levels and across study visits for subjects who are consistently ADA positive across study visits listed: CLIN-006 – Phase 3 study in patients with EM

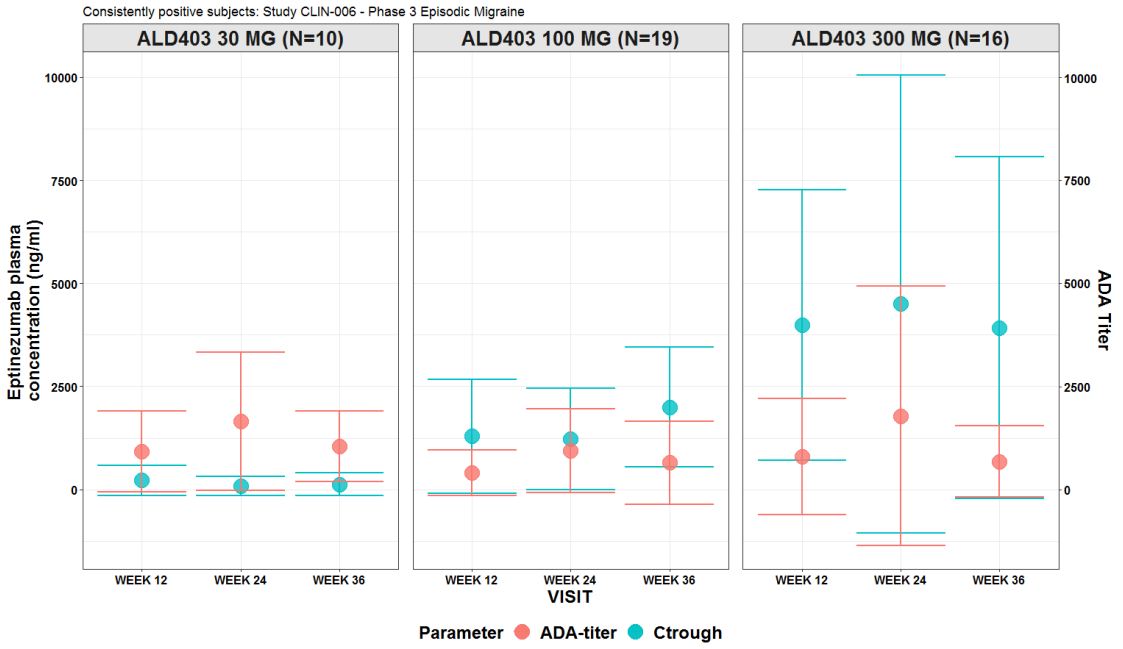
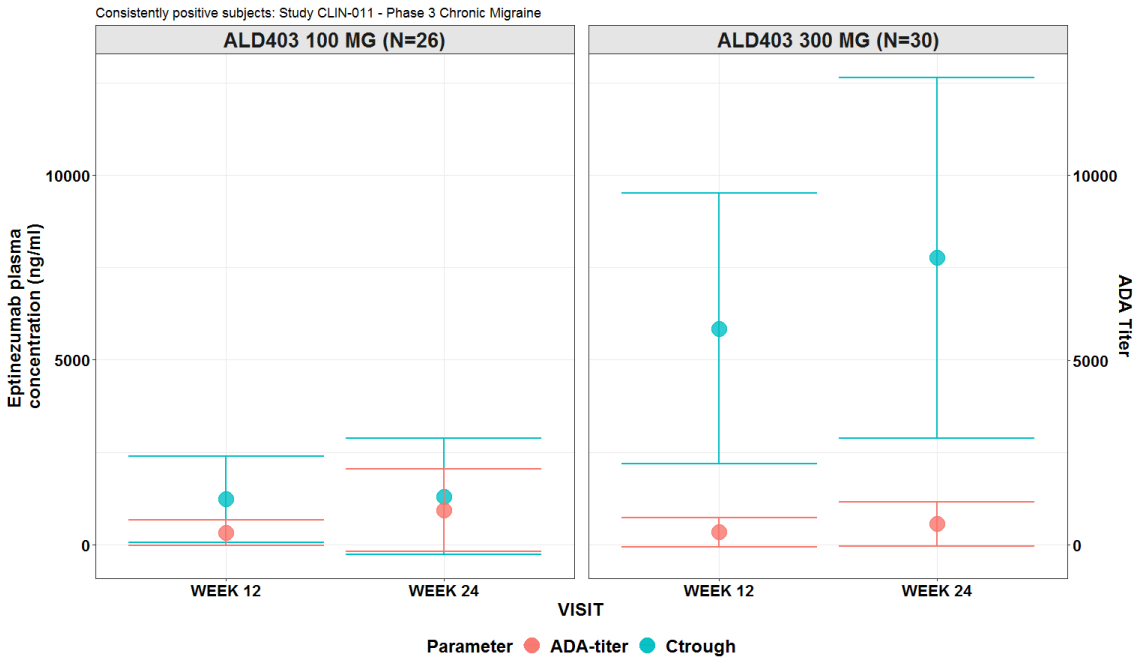


Figure 15 Comparison of eptinezumab plasma trough concentrations (left y-axis) and ADA titer (right y-axis) across dose levels and across study visits for subjects who are consistently ADA positive across study visits listed: CLIN-011 – Phase 3 study in patients with CM



Source: Reviewer's analyses: datasets include adpc.xpt and adlbim.xpt for phase 3 studies

Reviewer comments:

The applicant conducted comprehensive analyses and are considered acceptable. Overall, the impact of ADA status and ADA titer quartiles across dose levels and CM/EM populations were in general consistent – lower eptinezumab C_{trough} but were not associated with lower efficacy (it should be noted that the sub groups were not adjusted for imbalances at baseline while exploring the impact of immunogenicity on efficacy). Additionally, mean eptinezumab C_{trough} were in general lower in the higher quartiles of mean ADA titer, likely due to the confounding effect of ADA interference with eptinezumab C_{trough} measurement. Similar results were observed for NAb status.

4.3 Pharmacometrics Assessment: Population PK Analyses

4.3.1 Applicant's Population PK analysis:

Population PK (PopPK) analyses were conducted by the applicant to characterize the PK of eptinezumab in healthy subjects and subjects with episodic and chronic migraine (EM & CM respectively). Their key objectives were to: (1) evaluate the effects of intrinsic and extrinsic factors on the PK of eptinezumab that can potentially explain the interindividual differences in PK and inform relevant dose adjustment(s), if necessary; and (2) derive exposure metrics that can be used for subsequent exposure-response analyses of the efficacy and safety endpoints.

Data from 8 clinical studies were used in the population PK analyses and a brief description of these studies is given in Table 11.

Table 11 Summary of the characteristics of the studies used for PopPK analyses

Study ID	Subjects	Doses/Route	Description of data
CLIN-001	Phase 1: Healthy subjects [N=53]	A) Single IV dose: 1, 10, 30, 100, 300 and 1000 mg, B) Single IV dose 300 mg without combined Sumatriptan	Rich PK: Predose on day 1, 30, 60, 90, 120, 180, 240, 480 and 720 min post-dose on days 2, 3, 5, 12, 21, 28, 42, 54, 70 and 84.
CLIN-002	Phase 1b: Patients with episodic migraine [N = 81]	Single IV dose: 1000 mg	Sparse PK: Pre-dose (within 1 hour prior to dosing) and 4 hours post dose (± 30 min) on days 0, 14 ±1, 28 ±1, 56±2 and 84±2
CLIN-005	Phase 2: Patients with chronic migraine [N = 484]	Single IV dose: 10, 30, 100 and 300 mg	Sparse PK: Pre-dose (within 1 hour prior to dosing), immediately post-dose (within 15 min) and 4 hours post dose (± 30 min) on days 0, 28 ±3, 56±3, 84±3, 168±7, 252±7 and 343±7

Study ID	Subjects	Doses/Route	Description of data
CLIN-006	Phase 3: Patients with episodic migraine	IV dosing regimen: 30 mg Q4W*4 [N= 211], 100 mg Q4W*4 [N= 216], 300 mg Q4W*4 [N = 219]	Sparse PK: Pre-dose (within 1 hour prior to dosing), and on days 0, 28 ±3, 56±3, 84±3, 112±3, 140±3, 168±3, 252±3, 336±7 and 392±7
CLIN-010	Phase 1: Healthy overweight or obese subjects [N = 16]	Single IV dose: 100 mg	Sparse PK: Pre-dose, day 7, 28 ±3, 56±3 and 84±3
CLIN-011	Phase 3: Patients with chronic migraine	IV dosing regimens: 100 mg Q4W*2 [N = 354] 300 mg Q4W*2 [N = 349]	Sparse PK: Pre-dose (within 1 hour prior to dosing), post-dose (within 15 min) on days 0, 14±3, 28±3, 56±3, 84±3, 168±7 and 224±7
CLIN-012	Phase 1: Subjects with type 1 diabetes mellitus [N = 14]	Single IV dose: 100 mg	Sparse PK: Pre-dose (within 1 hour prior to dosing), on days 1, 7, 28±3, 56±3, 84±3 and 168±7
CLIN-013	Phase 3 (Open Label extension): Patients with chronic migraine [N = 126]	IV dose dosing regimen: 300 mg Q4W*4	Sparse PK: Pre-dose on days 0, 14±3, 28±3, 56±3, 84±3, 168±3, 252±3, 336(-7/+14), 504±7, 392 or 728 (±7)

Note: N: Number of subjects included in the popPK in the respective trials; IV = Intravenous
Source: Adapted from the ALD403-088-PK report: Table 1 on pages 33-35 and individual clinical study reports for each respective study

The final dataset for the PopPK analyses consists of a total of 15135 quantifiable eptinezumab plasma concentrations from a total of 2123 subjects, of whom 83 were healthy subjects, 1313 subjects were patients with chronic migraine and 727 were subjects with episodic migraine. In total, N=54 (0.4%) PK samples were excluded, of which, N=12 (0.1%) were below the limit of quantification, while rest were excluded mostly because the subjects received less than planned dose volume.

The popPK data of eptinezumab was modeled using usng Phoenix® NLME™ 8.0 (non-linear mixed effects modeling [NLME]. The structural model developed by the applicant consists of 2-compartmental model whose distribution was characterized by volume of distribution of central (Vc) and a peripheral compartment (Vp) and elimination was characterized by intercompartmental clearance between the two compartments (CLp) and linear elimination from the central compartment (CL). Lastly, additive and proportional error models were used to characterize the residual variability.

Covariate identification was explored graphically and then conducted in a stepwise manner (forward additive and backward elimination) and the list of covariates explored include bodyweight, race, sex, age, disease status (healthy subjects vs. patients), alanine transferase levels at baseline, renal function markers (creatinine clearance estimated by Cockcroft-Gault and Modification of Diet in Renal Disease [MDRD] methods) and respective renal function status at baseline, mean monthly migraine days at baseline, immunogenicity (anti-drug antibodies [ADA] and neutralizing antibodies [NAb] status) and concomitant prophylactic headache/migraine medication use (i.e., beta blockers, topiramate, valproate, and tricyclic antidepressants). Overall, the effect of ADA on the PK parameters of eptinezumab was not retained. The applicant noted that: "the interpretation of the eptinezumab plasma concentration values is potentially confounded by the presence of ADA, which may interfere with the drug concentration assay. A reduction in apparent eptinezumab plasma concentration could represent ADA interference rather than, or in addition to, enhanced clearance, and ADA may not be a random (independent) covariate on PK parameters".

The parameter estimates of the final PopPK model along with their precision are shown in Table 12. Furthermore, the qualification of the final popPK model was performed using goodness of fit diagnostics and visual predictive checks shown in Figure 16 and Figure 17 respectively.

Bodyweight, creatinine clearance, disease status (healthy, CM or EM patients) and baseline migraine days were reported as significant covariates for describing the variability of eptinezumb clearance. Bodyweight, disease status (healthy, CM or EM patients) and sex were significant covariates for describing variability in the volume of distribution of central compartment. Additionally, the applicant categorized the clinical relevance of the covariates in the final model using a forest plot on the impact of the steady-state exposures ($AUC_{0\text{-}Tau}$). These are summarized below:

- The impact of bodyweight in the forest plot was presented relative to a typical subject (70 kg) based on summary statistics of bodyweight in the popPK dataset: minimum (39 kg), 25th (63 kg), median (74 kg), 75th percentile (88 kg) and maximum (190 kg). Overall, subject with the lowest and the highest bodyweight showed the greatest impact: 51% higher and 51% lower steady-state $AUC_{0\text{-}Tau}$ respectively.
- Similar approach was followed for assessing the impact of creatinine clearance relative to typical subject with 118 ml/min. Overall, subject with 45 ml/min showed 18% higher and subject with 150 ml/min showed 4% lower $AUC_{0\text{-}Tau}$ respectively.
- The impact of number of migraine days (MMD) at baseline was minimal – 5% higher and 3% lower for subjects with MMD of 4 days and 28 days respectively relative to a subject with MMD of 13 days.
- The impact of disease status indicated that the subjects with EM and CM showed 32% and 27% higher $AUC_{0\text{-}Tau}$ respectively relative to a healthy subject.

Overall, the applicant noted that except for the impact of bodyweight, none of the covariates in the final popPK model are likely to be clinically relevant, given: (a) the small estimated effect sizes (less than 1.5-fold changes) in $AUC_{0\text{-}Tau}$ relative to typical patient and (b) absence of safety results suggesting limits of maximum exposure, and (c) relatively flat exposure-response at doses 100-300 mg. Therefore, the applicant does not recommend dose adjustment based on any covariates.

Table 12 Parameter estimates of the final PopPK model

Parameter	Estimate	RSE%	BSV%	RSE%	Shrinkage
CL (L/h)	0.00620	0.8	29.0	4.4	9.0%
× (WT/70)$^{\Theta}$	0.709	2.8			
× Θ if EM	-0.231	-2.6			
× Θ if CM	-0.272	-2.8	N/A		
× (MDBASE/13.0)$^{\Theta}$	0.044	2.3			
× (CL_{cr_cap}/118)$^{\Theta}$	0.162	3.5			
Vc (L)	3.636	1.1	31.0	2.3	20.2%
× (WT/70)$^{\Theta}$	0.544	3.7			
× Θ if EM	-0.311	-2.8			
× Θ if CM	-0.422	-3.0	N/A		
× Θ if Male	0.091	2.7			
CLp× (WT/70)$^{\Theta}$ (L/h)	0.039	2.2	111.3	5.7	56.8%
Vd× (WT/70)$^{\Theta}$ (L)	2.012	1.4	34.8	4.6	29.2%
Error Model					
Additive (ng/mL)	37.5	5.7			
Prop Error (%)	25.2				

For continuous covariates (weight, MDBASE, CL_{cr_cap}), a power model standardized by the median was used. For the categorical covariates (disease state, sex) an exponentiated factor relative to the reference category was used.

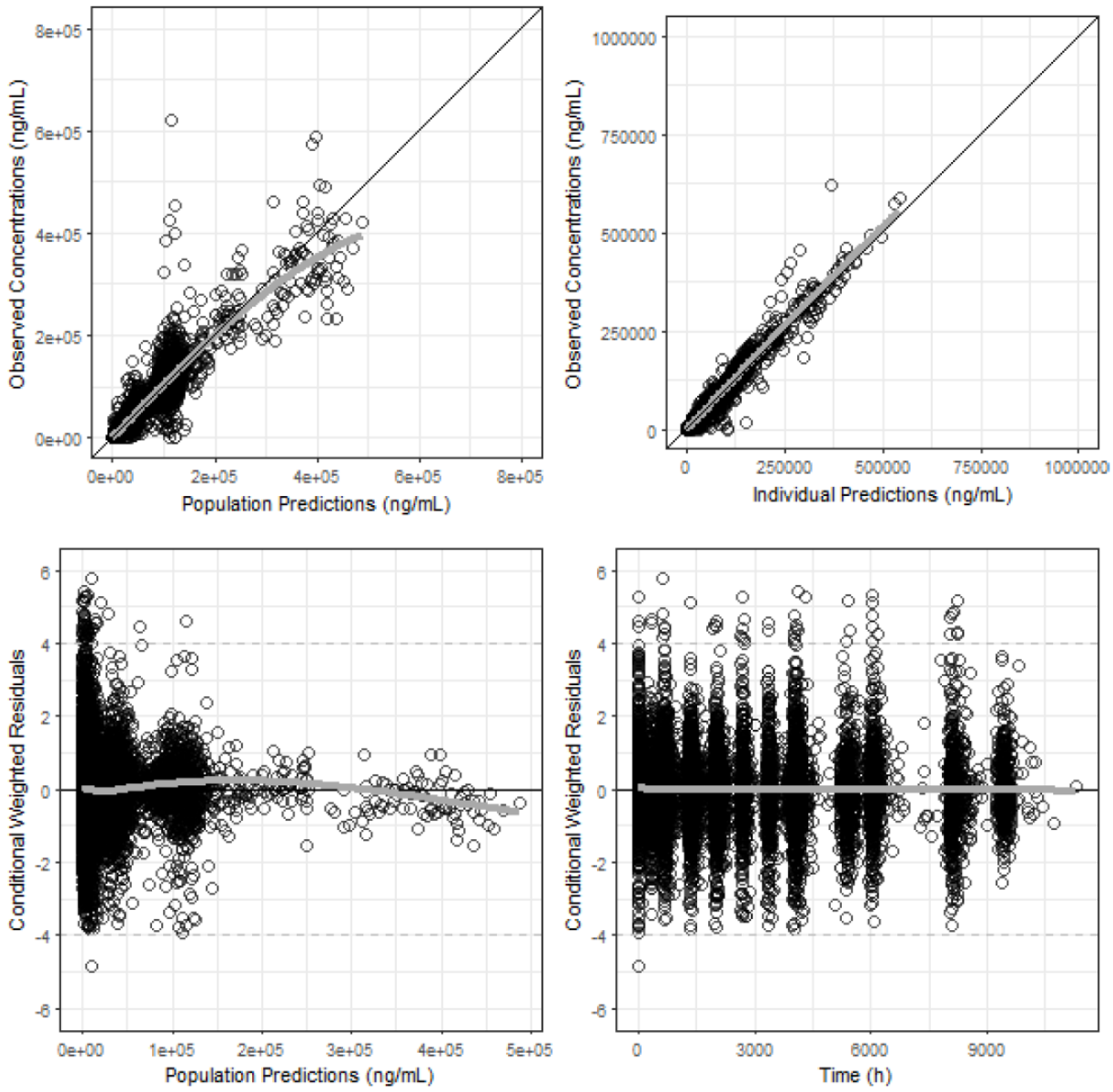
BSV= Between-subject variability; CL= systemic clearance; CM: chronic mirgraine; CLcr_cap: creatinine clearance capped at 150 mL/min; CV= coefficient of variation; CLp= inter-compartmental clearance; EM: episodic migraine; RSE= relative standard error; Vc= central volume of distribution; Vp= peripheral volume of distribution; WT= body weight (kg).

Note 1: CV% were calculated as $\sqrt{e^{omega} - 1}$.

Note 2: The full omega block for the final model is presented on the next page.

Source: Study report ALD403-088-PK – Table 7 on Pages 56

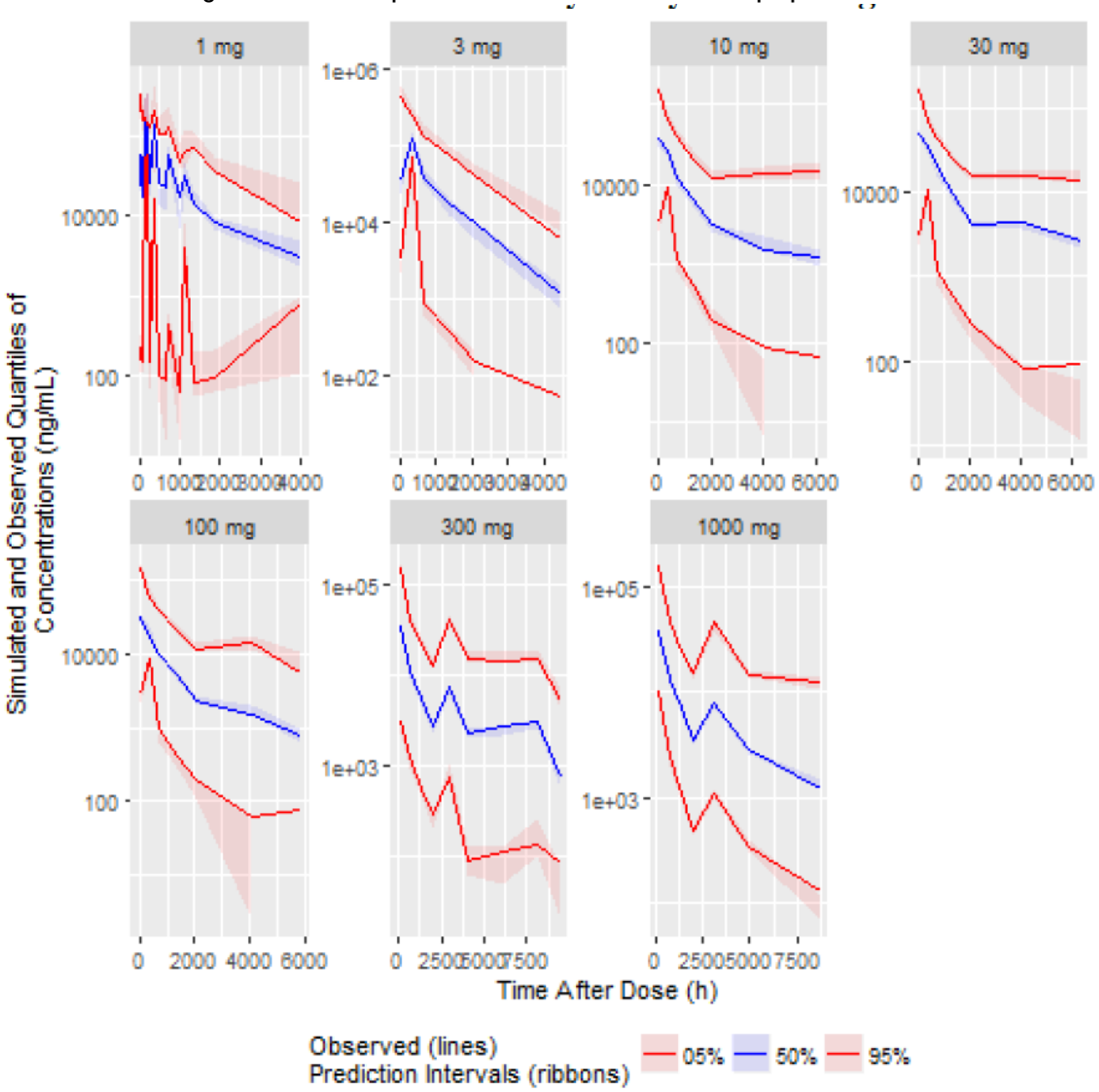
Figure 16 Goodness of fit plots for the final PopPK model



Note: The thick grey line represents the LOESS (Locally weighted scatter plot smoothing) and the solid black line represents the line of identity (upper panels) or line of reference (y=0, bottom panels)

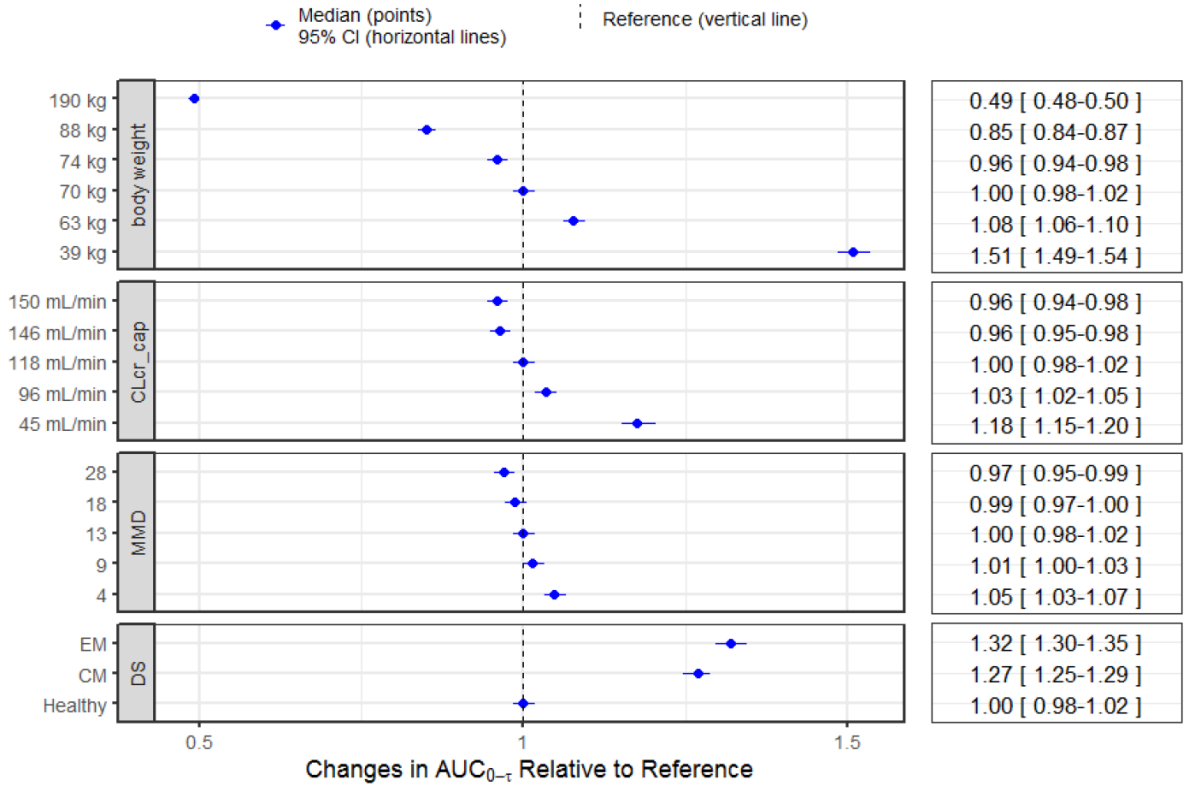
Source: Study report ALD403-088-PK – Figure 4 on Pages 59

Figure 17 Visual predictive check of the final popPK model



Source: Study report ALD403-088-PK – 1.10.2 on Pages 311

Figure 18 Forest plot: Geometric mean ratios and 90% CIs for the effect of covariates on eptinezumab steady-state exposures ($AUC_{0\text{-}Tau}$)



Note: Left panel: For the continuous covariates (baseline MMD [MDBASE], body weight and CLcr_cap) the minimum, 25th quantile, median, 75th quantile and maximum values of the population are presented on the y-axis. Right panel: The changes in exposure to eptinezumab are presented as median ratios and associated 95% confidence intervals. The dotted vertical line marks the $AUC_{0\text{-}\tau}$ for a typical patient (healthy female subject, weight=70kg; CL_{cr_cap}=118 mL/min, baseline MMD of 13 days). The effects of "test" covariates are presented relative to the aforementioned reference $AUC_{0\text{-}\tau}$.

Source: Study report ALD403-088-PK – Figure 3 on Pages 58

Reviewer's comments:

The applicant modeled the PK data of eptinezumab from studies listed in Table 11, which included both rich and sparse PK sampling designs in healthy subjects (N=83) and sparse PK sampling in subjects with episodic and chronic migraine. The final popPK model parameter estimates and associated uncertainty in the estimation reported in Table 12 seem reasonable for most of the parameters except for the intercompartmental clearance (which showed large between-subject variability and high shrinkage).

The covariate modeling results indicated that bodyweight, disease status, baseline migraine days, and creatinine clearance were significant covariates on eptinezumab systemic clearance. Additionally, bodyweight, disease status and sex were significant covariates on volume of distribution of the central compartment for eptinezumab. However, based on the magnitude of the impact of covariates and dosing regimens evaluated in the clinical studies, none of these are likely to be clinically relevant. Therefore, the applicant's proposal of lack of a need to adjust doses based on covariates is acceptable.

4.4 Exposure-Response for Efficacy Analyses

4.4.1 Applicant's Exposure-Response Analysis for Efficacy:

Exposure metrics, namely, average eptinezumab plasma concentrations over the dosing interval [C_{av}], area under the concentration-time curve over the dosing interval [$AUC_{0\text{-}12weeks}$], eptinezumab concentration at the end of the dosing interval [C_{trough}], or peak eptinezumab concentration [C_{max}], were obtained from the final popPK model. Subsequently, the relationships were explored for the change in frequency of monthly migraine days (primary efficacy endpoint) as a function of the eptinezumab exposures using linear regression with a placebo-anchored approach. Various structural models were explored ranging from simplistic statistical linear models with an intercept (placebo effect), a slope and an error term, to E_{max} and sigmoidal E_{max} models. Similar structural models were explored for both episodic and chronic migraine populations.

The final structural model was a saturable inhibitory E_{max} model for each of the exposure metrics described above. Briefly, it is described as follows:

$$\text{Reduction of migraine days} = E_0 + \text{Imax}^* \left[\text{Exposure}/(\text{Exposure}_{50} + \text{Exposure})\right.$$

where, E_0 represents the baseline effect, I_{max} is the maximum inhibitory effect, Exposure_{50} is the exposure achieving the half-maximum change in effect. The final model parameter estimates for the exposure metrics are summarized below in Table 13.

The applicant did not provide the exposure-response plots for the primary efficacy endpoint as a function of all the exposure metrics evaluated in study report ALD403-088-PK. Therefore, the review team sent an information request (10/08/2019) for these plots and the applicant response included them in the response (10/17/2019) [\\CDSESUB1\evsprod\BLA761119\0020\m1\us].

The plots for the inhibitory Emax models for each of the exposure metrics evaluated are shown in Figures below.

Table 13 Final exposure-response model: Inhibitory Emax model derived parameters

Eptinezumab Exposure Metric	Disease State	EC_{50} (CV%)	EC_{90}[a]	Mean (CV%) PK Parameters following a Single Dose[b]		
				30 mg	100 mg	300 mg
$AUC_{0\text{-}12wk}$ (hr*µg/mL)	CM	1480 (85.6)	13300	5770 (41.1)	17900(29.0)	54500(27.7)
	EM	1190 (225.7)	10700			
C_{max} (µg/mL)	CM	3.78 (84.0)	34.0	12.4 (38.6)	37.3 (28.1)	114 (27.7)
	EM	2.54 (228.4)	22.8			
C_{trough} (µg/mL)	CM	0.109 (105.6)	0.983	0.821 (55.4)	2.66 (46.1)	8.06 (42.4)
	EM	0.183 (187.7)	1.65			
C_{avg} (ng/mL)	CM	745 (85.7)	6710	2870 (41.2)	8950 (29.3)	27200(27.8)
	EM	585 (227.3)	5260			

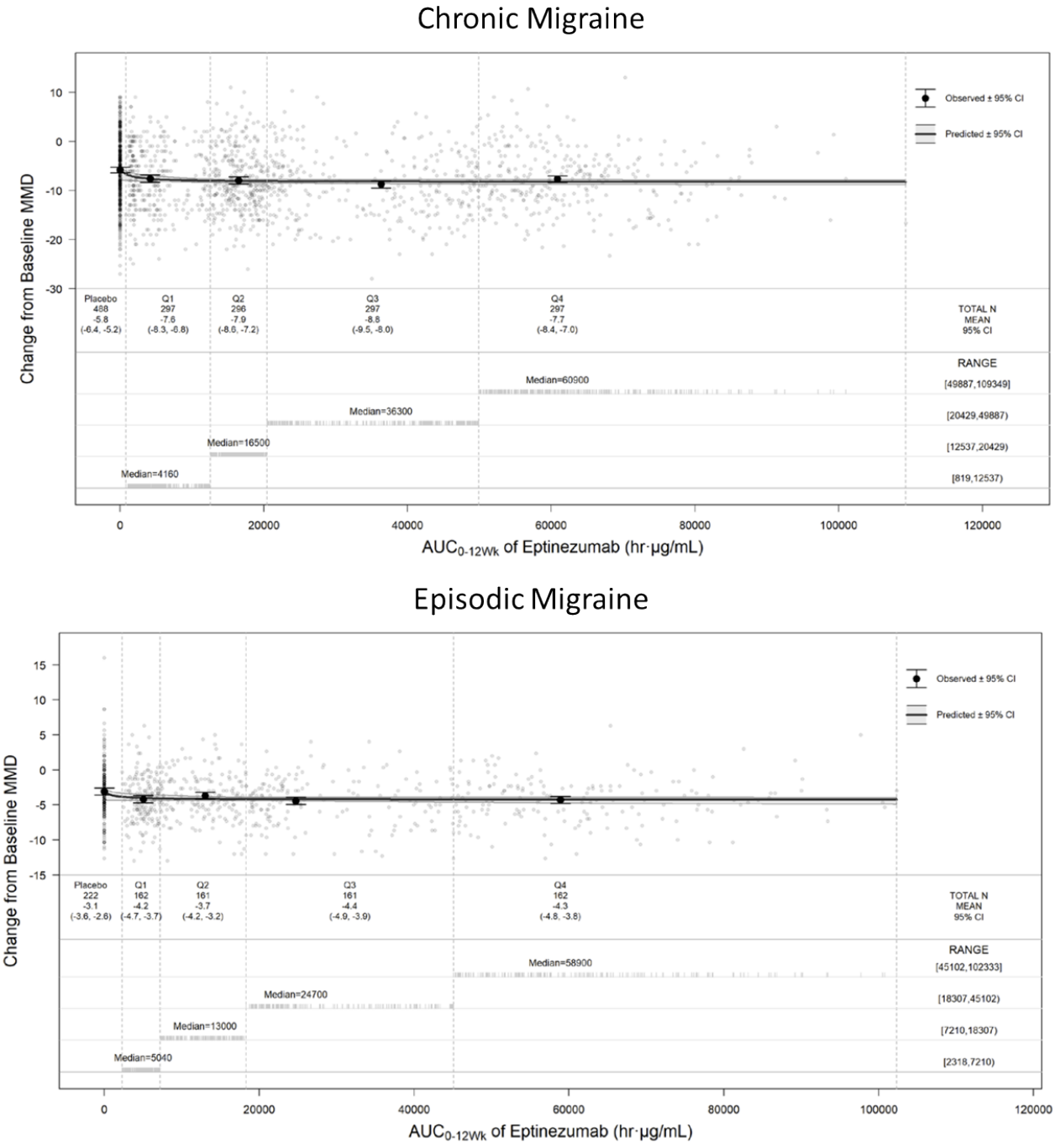
[a] Predicted from the EC_{50} fitted from the inhibitory E_{max} model. Same CV% as EC_{50}.

[b] Refer to Table 6 for the complete simulations by infusion duration.

Notes: CM=chronic migraine; EM=episodic migraine; EC_{50}= concentration (eptinezumab exposure metrics) achieving the half-maximal change in effect;EC_{90}= concentration (eptinezumab exposure metrics) achieving 90% of the maximum change in effect.

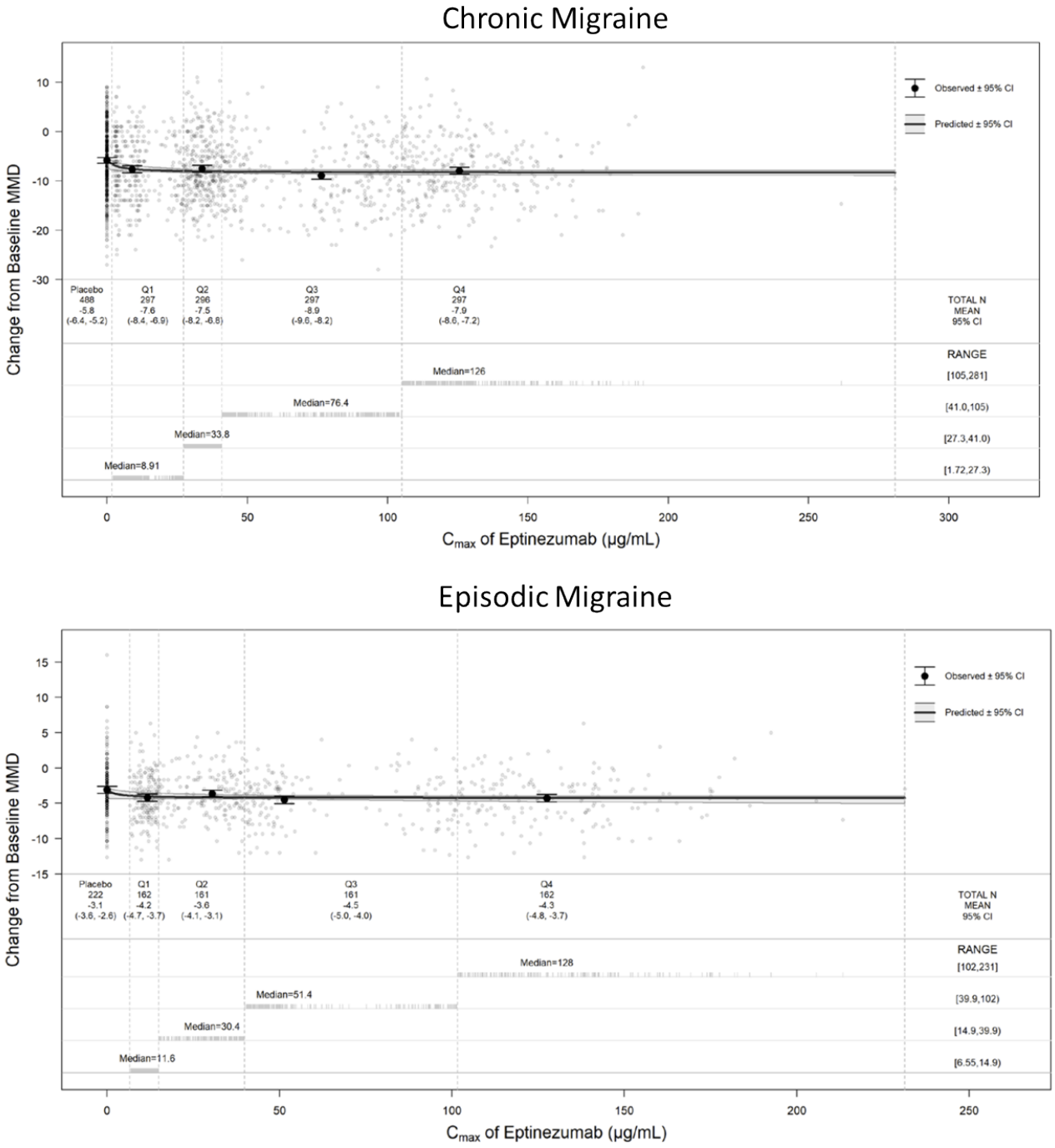
Source: Source: Study report ALD403-088-PK – Table 14 on Pages 71

Figure 19 Inhibitory Emax – exposure-response model predicted change from baseline in mean monthly migraine days versus eptinezumab $AUC_{0\text{-}12weeks}$



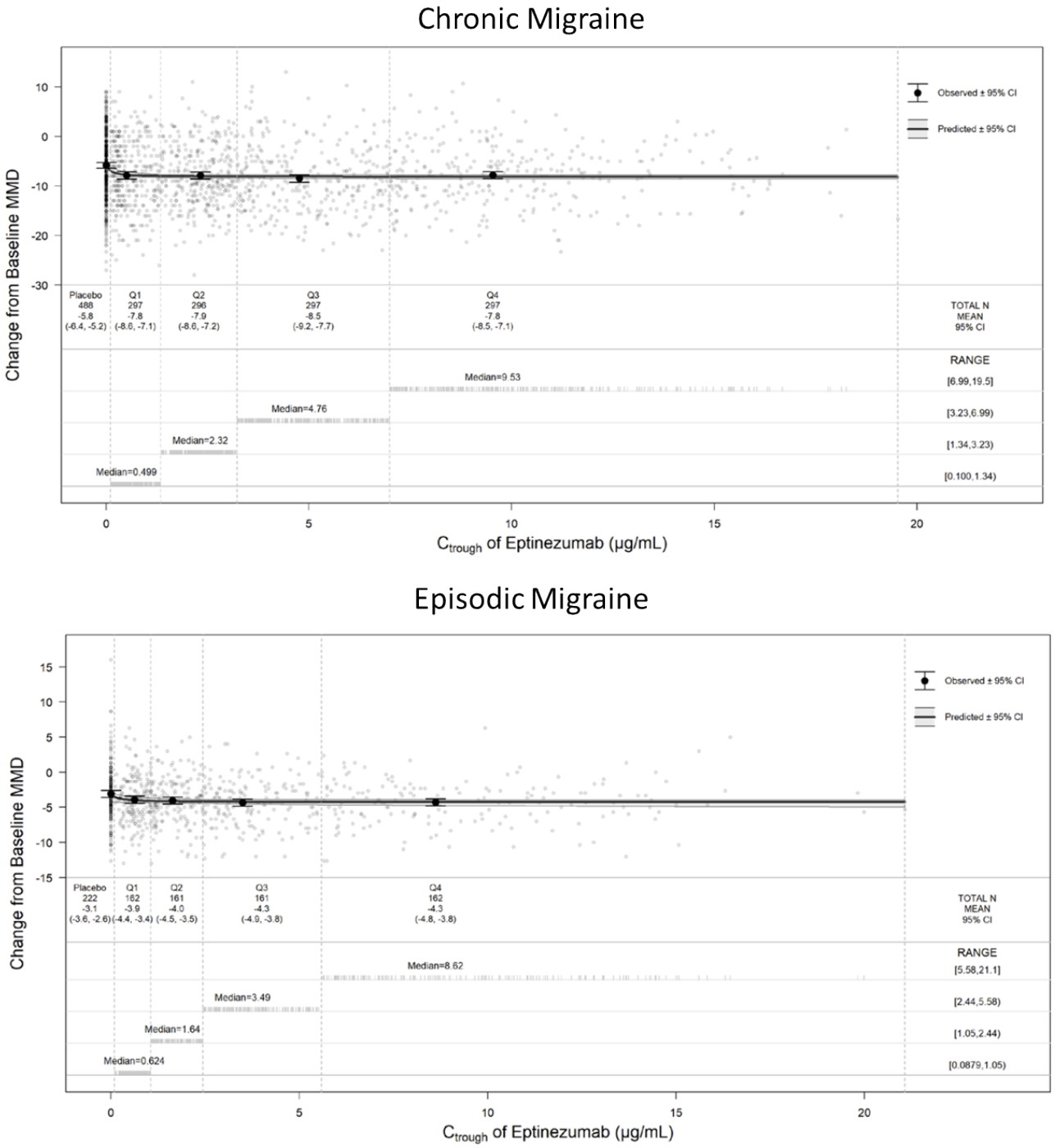
Source: Applicant's response to information request: Figure 1,2 on pages 11 and 12

Figure 20 Inhibitory Emax – exposure-response model predicted change from baseline in mean monthly migraine days versus eptinezumab C_{max}



Source: Applicant's response to information request: Figure 5, 6 on pages 14 and 15

Figure 21 Inhibitory Emax – exposure-response model predicted change from baseline in mean monthly migraine days versus eptinezumab C_{trough}



Source: Applicant's response to information request: Figure 7, 8 on pages 16 and 17

Reviewer's comments:

The applicant conducted exposure-response analyses from studies listed in Table 11, which included both rich and sparse PK sampling designs in healthy subjects (N=83) and sparse PK sampling in subjects with episodic and chronic migraine. The final exposure-response model parameter estimates reported in Table 12. Overall, the applicant's analyses are reasonable.

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/s/

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01/17/2020 12:32:53 PM

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