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APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology

Integrated Clinical Pharmacology Review

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Submission Date	17-May-2017
Submission Type	505b(1) Application (Standard Review)
Brand Name	AIMOVIG®
Generic Name	Erenumab (AMG-334)
Dosage Form (Strength)	Subcutaneous Injection (70 mg)
Proposed Indication	Migraine Prophylaxis
Applicant	Amgen, Inc.
Associated IND	IND-116098
OCP Review Team	Girish Bende, Ph.D., Gopichand Gottipati Ph.D., Kevin Krudys, Ph.D., Sreedharan Sabarinath, Ph.D.
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List of Abbreviations

AE	Adverse event
AI	Prefilled SureClick autoinjector for SC administration
AUC	Area under the concentration-time curve
AUClast	AUC from time 0 to last measurable concentration
BLA	Biologics License Application
CGRP	Calcitonin gene-related peptide receptor
Cmax	Maximum (peak) drug concentration
EC50	Serum concentration associated with the half maximal effect
FDA	Food and drug administration
LLOQ	Lower limit of quantification
MMD	Monthly Migraine Days
OSIS	Office of Study Integrity and Surveillance
PD	Pharmacodynamics
PK	Pharmacokinetics
SAE	Serious adverse event
SC	Subcutaneous administration
Tmax	Time of maximum (peak) drug concentration

1 Executive Summary

In this original Biologics License Application (BLA), Amgen, Inc is seeking approval for AIMOVIG® (Erenumab; AMG334) for the prevention of chronic and episodic migraine in adults.

Erenumab is a human immunoglobulin G2 (IgG2) monoclonal antibody targeted against calcitonin gene-related peptide (CGRP) receptor and is a first-in-class product for this indication. There are currently three other monoclonal antibody products in development that target CGRP ligand or CGRP receptor, two submitted to the agency (Fremanezumab and Galcanezumab), and the third in late-stage development (Eptinezumab) for the same indication.

The proposed dose of erenumab is 140 mg (as 70 mg × 2 injections) once monthly to be administered subcutaneously using single-use prefilled SureClick® autoinjector or single-use prefilled syringe. The applicant is relying on 3 randomized, double-blind, placebo-controlled safety and efficacy studies in patients with episodic migraine and one randomized, double-blind, placebo-controlled safety and efficacy study in patients with chronic migraine. The patients with chronic migraine were defined as those with history of migraine (with or without aura) who experienced ≥ 15 headache days per month, with ≥ 8 migraine days per month. Patients with episodic migraine were defined as those with history of migraine (with or without aura) for ≥ 12 months and who experienced ≥ 4 and < 15 migraine days per month with < 15 headache days per month on average across the 3 months prior to screening. Primary efficacy results from these studies showed that both 70 mg and 140 mg monthly doses are safe and effective in reducing the baseline- and placebo-corrected mean monthly migraine days (MMD).

The primary focus of this review is the evaluation of the proposed dosing regimen using dose- and exposure-response relationships for efficacy and safety in chronic and episodic migraine.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information submitted under BLA761077 and we recommend approval of 70 mg in addition to 140 mg dose of erenumab for the prevention of chronic and episodic 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 evidence of effectiveness of erenumab for the prevention of migraine is from four randomized, double-blind, placebo-controlled, phase 2/3, safety and efficacy studies in subjects with chronic migraine (Study 2012-0295) and episodic migraine (Studies 2012-0178, 2012-0296, and 2012-0297).
General dosing instructions:	The recommended dose is 70 mg or 140 once monthly, administered subcutaneously using either a prefilled autoinjector or a prefilled syringe.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose adjustments are recommended.

Review Issues	Recommendations and Comments
Bridge between the "to-be-marketed" and clinical trial formulations	The to-be-marketed 70 mg single-use prefilled syringe and 70 mg single-use prefilled SureClick autoinjector are bioequivalent.

1.2 Post-marketing Requirements

None.

2 Summary of Clinical Pharmacology Assessment

2.1 The Pharmacology and Clinical Pharmacokinetics

Mechanism of Action:

Erenumab is a human IgG2 monoclonal antibody that inhibits CGRP receptors. CGRP ligand is a neuropeptide that modulates nociceptive signaling and a vasodilation effect that has been associated with migraine pathophysiology. CGRP ligand levels are known to increase significantly during migraine attacks and the CGRP receptor is located at sites that are relevant to migraine pathophysiology. Peripheral release of CGRP from trigeminal nerve fibers within the dura and from the cell body of trigeminal ganglion neurons is likely to contribute to peripheral sensitization of trigeminal nociceptors. Similarly, the release of CGRP within the trigeminal nucleus caudalis can facilitate activation of nociceptive second order neurons and glial cells.

It is anticipated that erenumab selectively inhibits CGRP receptors in humans for prolonged periods, therefore preventing and/or reversing the activation of the trigeminal-vascular system, resulting in the prevention/relief of migraine headache.

Absorption:

Following a single subcutaneous dose of 140 mg erenumab administered to healthy adults, median peak serum concentrations were attained in 4 to 6 days. Based on population pharmacokinetic analyses, the estimated absolute bioavailability was 82%. The median time to reach Cmax (Tmax) ranged from 4 to 11 days within the dose range of 1 to 210 mg.

Distribution:

Following a single 140 mg intravenous dose, the mean (SD) steady state volume of distribution was estimated to be 3.9 (0.8) L.

Metabolism and Excretion:

Erenumab exhibits nonlinear pharmacokinetics but exposure is approximately dose proportional between 70 mg and 140 mg doses. Two elimination phases were observed for erenumab. At low concentrations, the elimination is predominantly through saturable binding to CGRP receptors, while at higher concentrations the elimination of erenumab is largely through a non-specific, non-saturable proteolytic pathway.

Special Populations:

No dedicated clinical studies were conducted to evaluate the effect of hepatic impairment or renal impairment on the PK of erenumab. Renal or hepatic impairment is not expected to affect pharmacokinetics of erenumab.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended dose is 70 mg once monthly, administered subcutaneously. Certain individuals may benefit from a 140 mg dose. Administer 140 mg once monthly as two consecutive 70 mg subcutaneous injections.

This recommendation is supported by the dose- and exposure-response relationships which indicated a shallow relationship between erenumab dose or its exposure and reduction in the baseline- and placebo-adjusted monthly migraine days.

2.2.2 Therapeutic individualization

No therapeutic individualization is necessary for extrinsic/intrinsic factors. Erenumab is to be administered by subcutaneous route and its drug-drug interaction potential is low (Section 3.3.4). No clinical studies were performed in subjects with renal or hepatic impairment. However, renal/hepatic impairment is not expected to affect pharmacokinetics of erenumab.

2.2.3 Outstanding Issues

None.

2.2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology has the following labeling concepts to be included in the final package insert.

- The recommended dose of Aimovig is 70 mg or 140 mg (as 70 mg × 2 injections) administered once monthly as subcutaneous injection(s) using either single-dose prefilled autoinjector or single-dose prefilled syringe.
- No dose adjustment is necessary for patients based on intrinsic or extrinsic factors

3 Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

There are FDA-approved products indicated for the prevention of migraine, namely, beta blockers (propranolol, timolol), antiepileptic drugs (divalproex sodium, topiramate), onabotulinumtoxin A and methysergide (no longer available in the US). Erenumab is a first-in-class product seeking approval for the prevention of chronic and episodic migraine.

In total, 13 clinical studies were performed during the clinical development of erenumab. It includes 7 phase 1 studies (2010-1267, 2010-1268, 2012-0130, 2012-0149, 2014-0255, 2015-0334, and 2014-0477); 4 placebo-controlled efficacy and safety studies in subjects with episodic

migraine (2012-0178, 2012-0296, 2012-0297) and chronic migraine (2012-0295) with ongoing open-label or active treatment extension phases; one phase 2 cardiovascular study (2014-0254); and one stand-alone open-label extension study that enrolled eligible subjects completing the chronic migraine placebo-controlled study. The key aspects of 4 safety and efficacy studies are summarized in the Table 3-1 below.

Table 3-1 Summary of Clinical Safety and Efficacy Studies

Clinical Studies (Population, n)	**2012-0295** (Chronic Migraine, n=667)	**2012-0178** (Episodic Migraine, n=483)	**2012-0297** (Episodic Migraine, n=955)	**2012-0296** (Episodic Migraine, n=577)
Objective(s)	MMD Reduction at month 3 (weeks 9 to 12)	MMD Reduction at month 3 (weeks 9 to 12)	MMD Reduction at month 3 (weeks 9 to 12)	MMD Reduction at month 6 (months 4, 5, and 6)
Study Design	Randomized, Double-blind, Placebo-controlled, Safety and Efficacy Study			
Treatment(s)	70, 140 mg Once monthly	7, 21, 70 mg Once monthly	70 mg Once monthly	70, 140 mg Once monthly
Study Extension	52-week open-label extension (Study 2013-0255)	256-week open-label extension	28-week open-label extension	28-week dose-blinded active treatment phase

n: number of subjects randomized in the study; chronic migraine: (≥ 15 headache days/month, at least 8 of which are migraine days); episodic migraine (4 to 14 migraine days/month, < 15 headache days/month); MMD: Monthly Migraine Days

3.2 General Pharmacological and Pharmacokinetic Characteristics

The pharmacokinetic properties of erenumab have been characterized in the phase 1 and 2 studies.

Table 3-2 Summary of Pharmacological and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Erenumab is a human IgG2 monoclonal antibody against CGRP receptors. CGRP ligand is a neuropeptide that modulates nociceptive signaling and a vasodilation effect that has been associated with migraine pathophysiology.
General Information	
Healthy volunteers vs. patients	There was no apparent difference in PK parameters between the healthy subjects and subjects with migraine following single and multiple (3 doses) subcutaneous administrations (Studies 2010-1267 and 2010-1268).
Dose proportionality	Erenumab exhibits nonlinear pharmacokinetics following single subcutaneous administration over the dose range of 1 to 210 mg, presumably due to target-mediated drug disposition. Erenumab exposure increases more than dose proportionally from 1 to 70 mg and approximately dose proportionally from 70 to 210 mg following a single

	subcutaneous administration (Study 2010-1267). The mean AUClast increased from 171 to 652 µg·day/mL (3.8-fold) and mean Cmax increased from 6.25 to 15.2 µg/mL (2.4-fold) following the 3-fold increase in dose from 70 to 210 mg.
Accumulation	Accumulation was approximately 1.8-fold from the first dose to the third dose, following 3 once monthly subcutaneous administrations (study 2010-1268).
Immunogenicity	Anti-drug antibodies were detected in about 7.2% of subjects across all studies in the development program (N=242/3361) and 2.6% subjects in the pivotal studies 2012-295 and 2012-296 (N=13/504). There was no evidence on the impact of anti-drug antibodies on the efficacy or safety of erenumab. Please refer to consult reviews from Division of Applied Regulatory Sciences in DARRTS dated 12/05/2017 and 2/15/2018 for details on anti-drug antibodies assays.
Absorption	
Bioavailability	Estimated bioavailability is approximately 82%.
Tmax	4 to 11 days within the dose range of 1 to 210 mg
Distribution	
Volume of Distribution	3.9 L
Elimination	
Mean Terminal Elimination Half-life	Approximately 21 days
Metabolism / Excretion	Monoclonal antibodies are not known to be metabolized by the cytochrome P450 system. Erenumab is not considered as a cytokine modulator. It is unlikely to influence drug metabolizing enzymes or transporters as a perpetrator.
Primary excretion pathways	At low concentrations, the elimination is predominantly through saturable binding to target (CGRP receptor), while at higher concentrations the elimination of erenumab is largely through a non-specific, non-saturable proteolytic pathway. Since erenumab is a human IgG2 immunoglobulin with large molecular size (~150kDa), excretion of intact antibody in the urine is expected to be minimal.

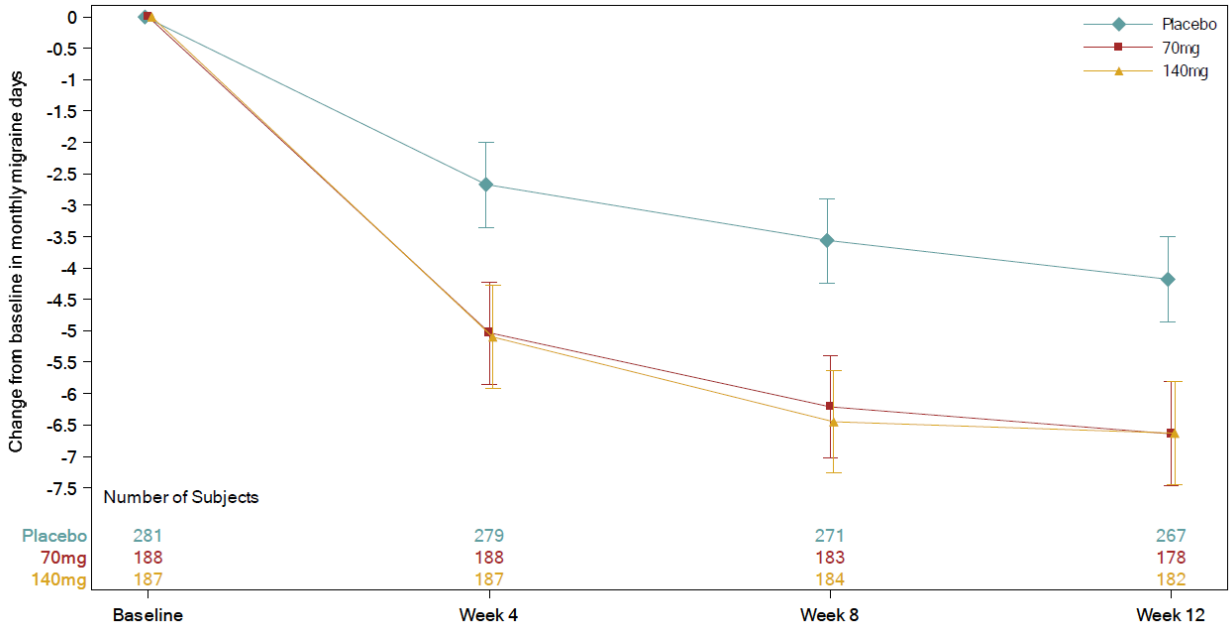
3.3 Clinical Pharmacology Questions

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

The evidence of effectiveness of erenumab in the prevention of chronic and episodic migraine is from four placebo-controlled, randomized, double-blind clinical studies. There was a reduction in mean monthly migraine days relative to baseline as compared to placebo in Study 2012-0295 in patients with chronic migraine for both 70 mg and 140 mg doses. Similarly, the mean reduction in monthly migraine days relative to baseline as compared to placebo favored erenumab in Studies 2012-0296, 2012-0178 and 2012-297 in patients with episodic migraine. The exposure-response relationships for efficacy in both chronic and episodic migraine were consistent with the observed dose-response relationship, providing additional supportive evidence.

Study 2012-0295 in patients with chronic migraine, consisted of a baseline period of 4 weeks followed by a 12-week double-blind treatment period during which 70 mg and 140 mg doses were administered on day 1 and at weeks 4 and 8. The study enrolled patients with history of migraine with or without aura who experienced ≥ 15 headache days per month, with ≥ 8 migraine days per month. Both 70 mg and 140 mg doses met the pre-specified statistical criteria for the reduction in the mean monthly migraine days at end of week 12 relative to baseline over placebo, and no dose-response was observed at the tested dose levels (Figure 3-1).

Figure 3-1 Least square mean changes from baseline in monthly migraine days by visit for pivotal study 2012-295 in chronic migraine (efficacy analysis set)

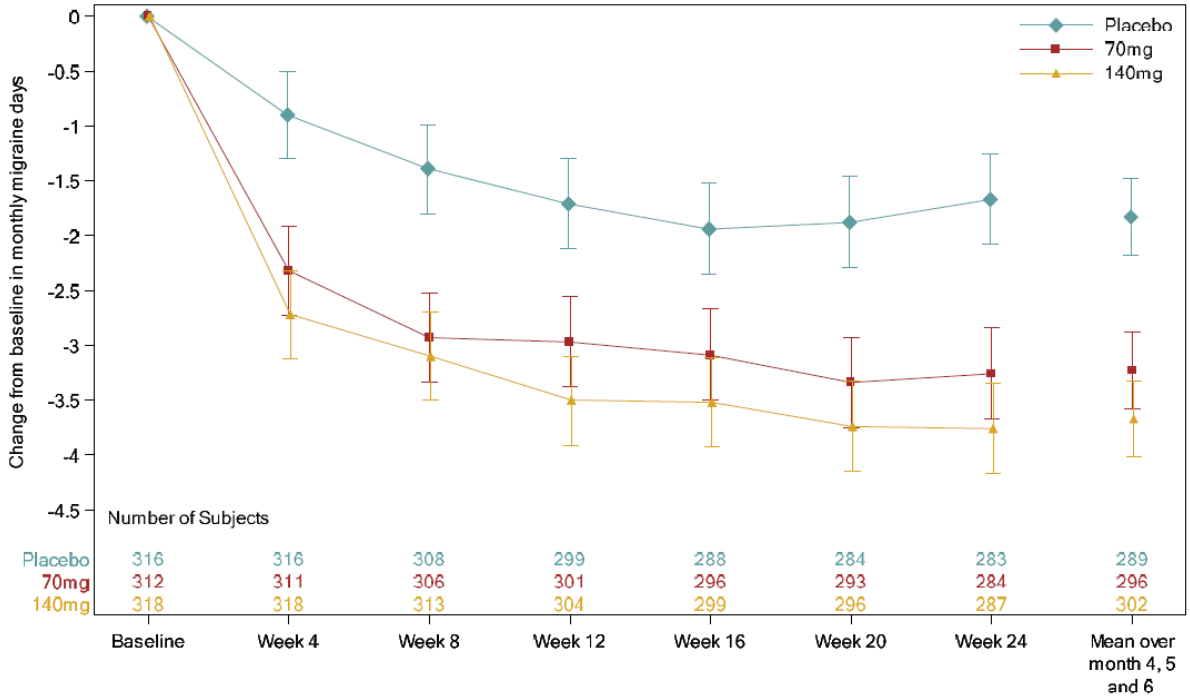


Source: Integrated Summary of Efficacy: Figure 18 on Page 257

Study 2012-0296 in patients with episodic migraine, consisted of a baseline period of 4 weeks followed by a 24-week double-blind treatment period during which 70 mg and 140 mg doses

were administered on day 1, at weeks 4, 8, 12, 16, and 20. The study enrolled patients with history of migraine with or without aura for ≥ 12 months and who experienced ≥ 4 and < 15 migraine days per month with <15 headache days per month on average across the 3 months prior to screening. Both 70 mg and 140 mg doses met the pre-specified statistical criteria for the mean reduction in the mean monthly migraine days over months 4-6. There seems to be a marginal numerical difference between the two doses, favoring the higher dose (Figure 3-2).

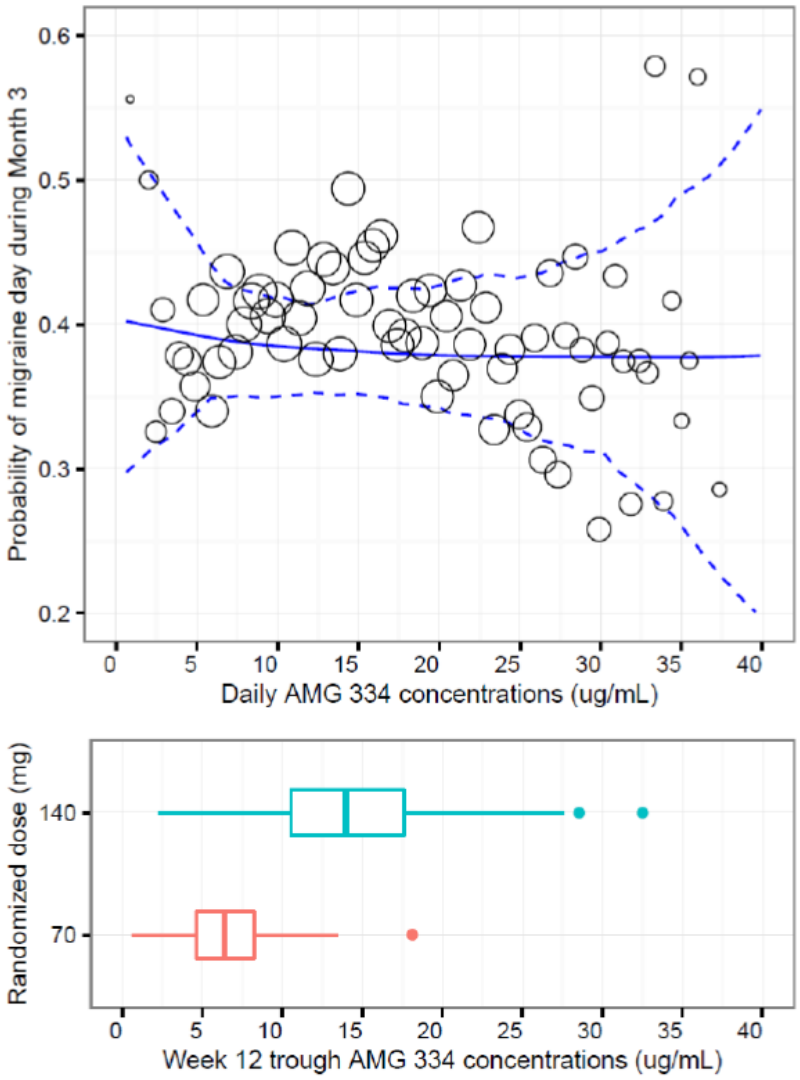
Figure 3-2 Least square mean changes from baseline in monthly migraine days by visit for pivotal study 2012-296 in episodic migraine (efficacy analysis set)



Source: Integrated Summary of Efficacy: Figure 20 on Page 261

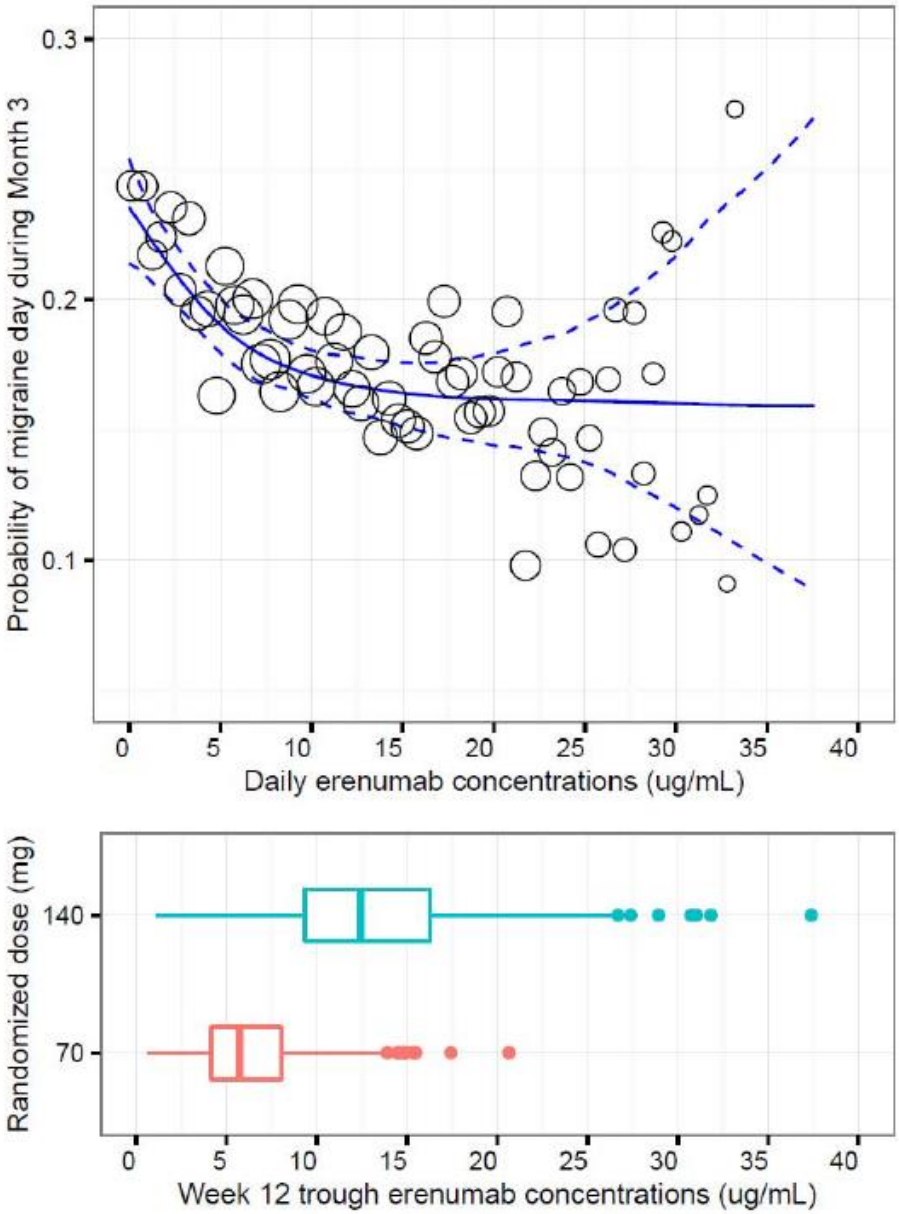
Exposure-response (E-R) analysis using average daily serum concentrations of erenumab and mean reduction from baseline over placebo in the monthly migraine days at the end of week 12 in chronic migraine or mean reduction from baseline over placebo in the mean monthly migraine days over months 4-6 in episodic migraine was conducted. There was a clear difference in exposures between the two dose levels (i.e., 70 mg and 140 mg) tested in these studies. The E-R analyses showed no apparent relationships between efficacy and erenumab concentrations and were consistent with the observed dose-response relationships.

Figure 3-3 **Probability of Migraine Day versus average Daily Erenumab Concentrations during Month 3 (Weeks 9-12) in Subjects with Chronic Migraine (Study 2012-0295)**



Legend: symbol= observed data with symbol size is proportional to square root of observations per bin of daily concentrations (500 ng/mL bins). Blue lines = mean prediction and 95% CI based on exposure-response model estimates; boxplots represent distributions of Month 3 trough concentrations for the corresponding dose group
Source: Summary of Clinical Pharmacology Studies, Figure 27, Page 100

Figure 3-4 Probability of Migraine Day versus average Daily Erenumab Concentrations During Month 3 (Weeks 9-12) in Subjects with Episodic Migraine (Studies 2012-0296, 2012-0297, and 2012-0178)



Legend: symbol= observed data with symbol size is proportional to square root of observations per bin of daily concentrations (500 ng/mL bins). Blue lines = mean prediction and 95% CI based on exposure-response model estimates; Summary of Clinical Pharmacology Studies, Figure 25, Page 96

Results from all four safety and efficacy studies confirmed a statistically significant greater mean reduction in the monthly migraine days from baseline with both 70 mg and 140 mg doses in comparison with placebo.

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 only for the 140 mg dose level. Based on the observed shallow dose/exposure-response relationships, the Office of Clinical Pharmacology review team is also recommending approval of the 70 mg administered once monthly (please see Appendix 4.2 for more details). The proposed once monthly regimen is identical to those used in pivotal trials for both episodic and chronic migraine.

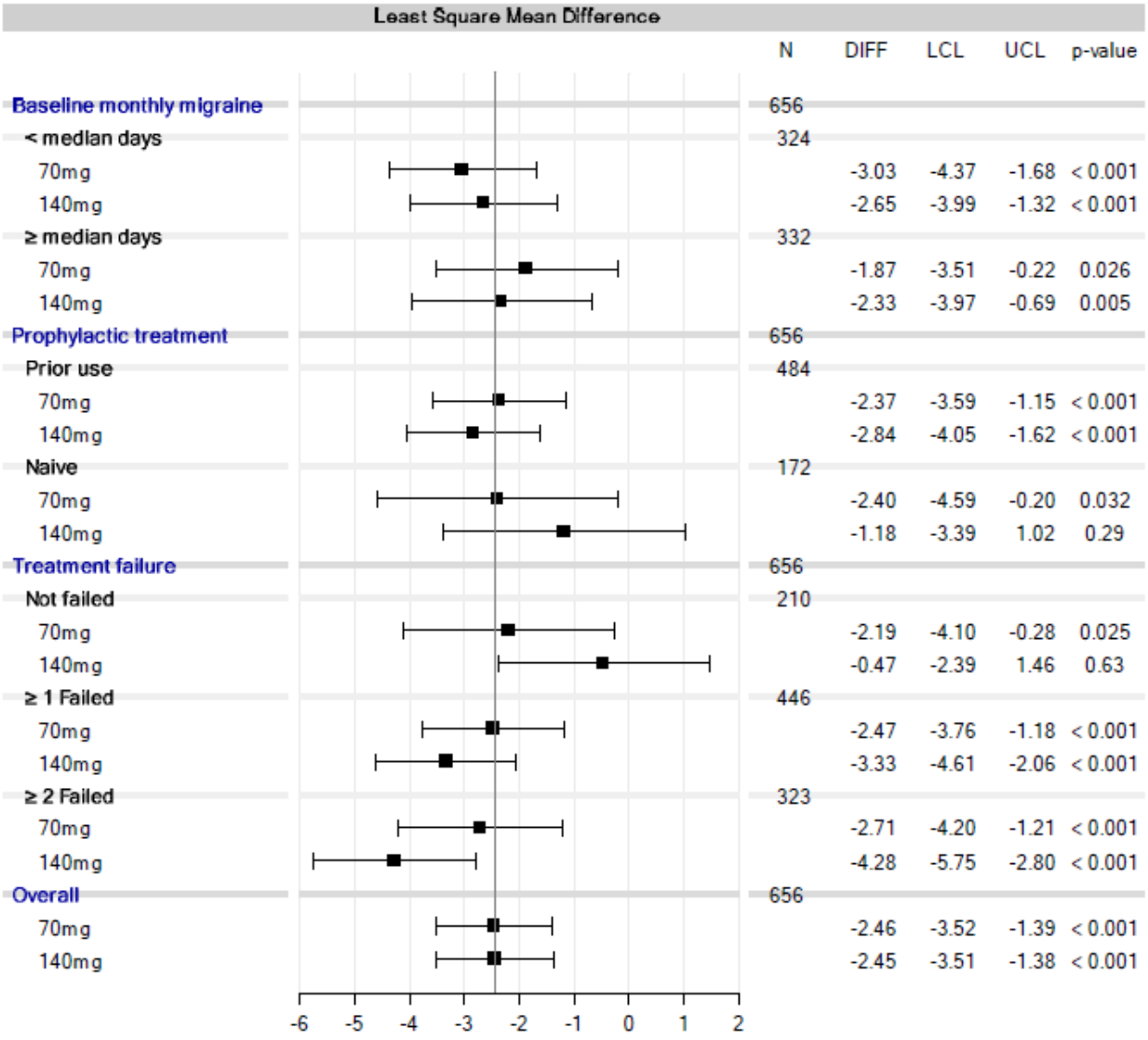
There was no difference in efficacy between two selected doses for chronic migraine indication (-2.46 vs -2.45 days). In addition, there was only a marginal numerical difference between two doses for episodic migraine (1.40 vs. 1.85 days). Secondary endpoints, such as ≥ 50% reduction from baseline in monthly migraine days, and change from baseline in monthly acute migraine-specific medication treatment days also showed no major differences between the 70 mg and 140 mg dose levels.

There seem to be numerical trends suggesting that some patients, e.g., patients who had treatment failure on prior prophylactic medication(s) may potentially derive additional benefit from the 140 mg monthly dose based on the applicant prespecified sub-group analyses in the respective pivotal trials. The forest plots are shown in Figure 3-5 and Figure 3-6 below. It should be noted that the results from these subgroup analyses be interpreted with caution, because adequate characterization of failure to prior treatment and identifying such patients may be clinically challenging. Please refer the clinical review by Dr. Laura Jawidzik and Dr. Heather Fitter for more details.

Overall, no major safety concerns were observed for both dose levels. The most commonly reported AEs include injection site reactions, constipation, pruritus and muscle spasms. The incidence rates for the injection site reactions in patients administered with 70 mg and 140 mg (as 2 × 70 mg) doses were comparable. However, the incidence rates for the rest of these commonly reported AEs in patients receiving 70 mg were comparable to placebo, while patients receiving 140 mg seem to be higher (2% or less).

In conclusion, erenumab 70 mg dose offers a similar efficacy to that of 140 mg dose in both chronic and episodic migraine, and thus we recommend approval of the lower dose (i.e., 70 mg) in addition to the higher dose (140 mg).

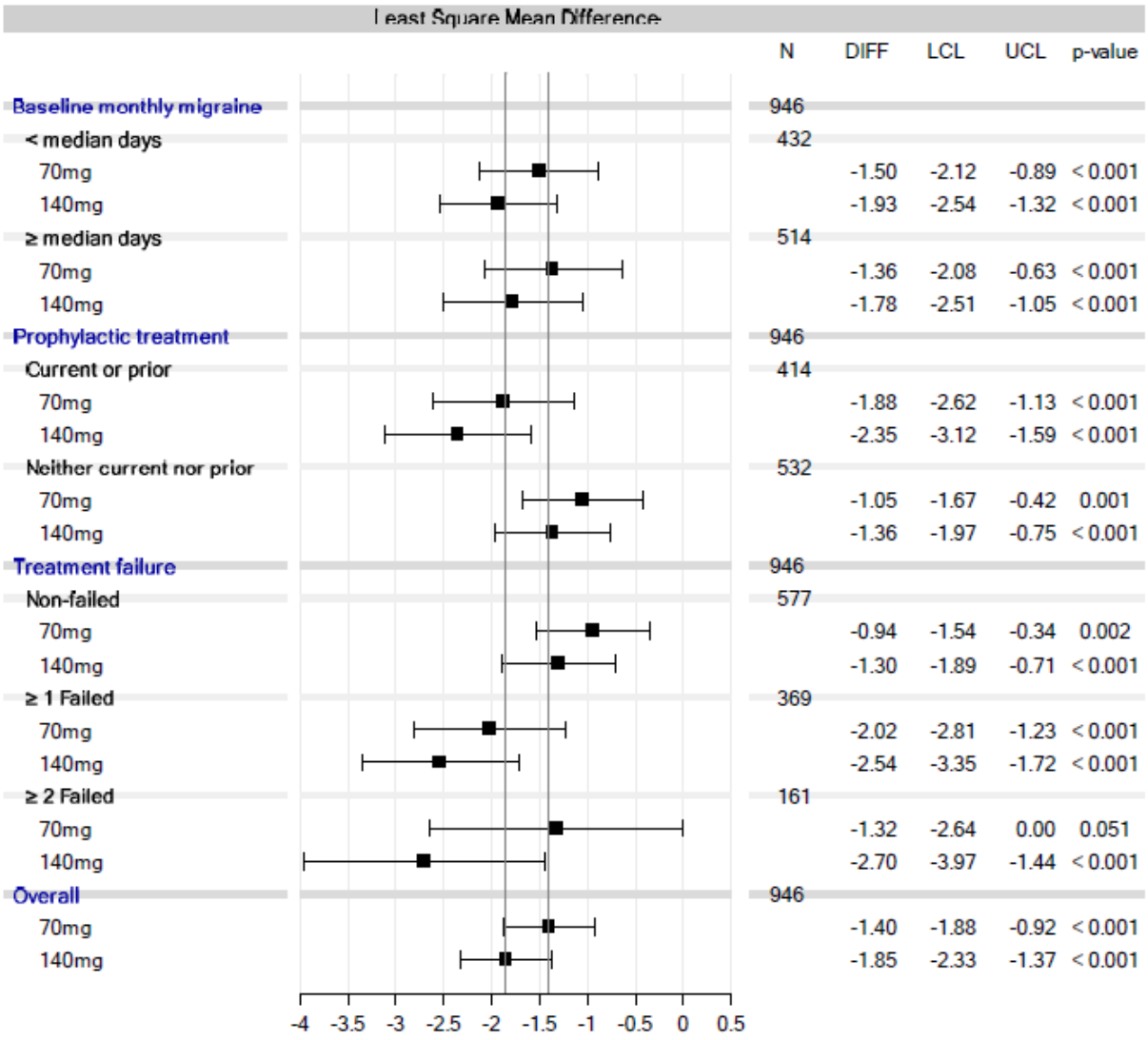
Figure 3-5 **Study 2012-0295 (Chronic Migraine): Forest plot of the least square mean difference (Erenumab 70 mg or 140 mg vs. Placebo) and 95% confidence interval for change from baseline in monthly migraine days at week 12 by disease-related subgroups (Efficacy analysis dataset)**



N = number of subjects in the model; DIFF = Least squares mean difference; LCL = Lower Confidence Limit; UCL = Upper Confidence Limit
Note: Week 12 reflects data collected during the 4 weeks preceding the week 12 visit. The pairwise comparisons compare each AMG 334 group vs. placebo (reference group).
Uses individual study data results
Least Squares Mean Differences < 0 favor AMG 334, > 0 favor Placebo.
Source: ISE Figure 14-4.1.405

Source: Summary of Clinical Efficacy, Figure – 6 on Page 91

Figure 3-6 **Study 2012-0296 (Episodic Migraine): Forest plot of the least square mean difference (Erenumab 70 mg or 140 mg vs. Placebo) and 95% confidence interval for change from baseline in monthly migraine days at week 24 by disease-related subgroups (Efficacy analysis dataset)**



N = number of subjects in the model; DIFF = Least squares mean difference; LCL = Lower Confidence Limit; UCL = Upper Confidence Limit.
Note: Week 24 reflects the average of data collected during months 4, 5, and 6. The pairwise comparisons compare each AMG 334 group vs. placebo (reference group).
Uses individual study data results
Least Squares Mean Differences < 0 favor AMG 334, > 0 favor Placebo.
Source: ISE Figure 14-4.1.406

Source: Summary of Clinical Efficacy, Figure – 8 on Page 93

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

No. Dose adjustment is not necessary based on intrinsic factors such as age, gender, bodyweight, BMI, renal or hepatic impairment. Population pharmacokinetic analysis did not reveal a significant impact of age, gender, bodyweight, BMI on the exposures of erenumab. In addition, there was no significant difference in the pharmacokinetics of erenumab in patients with mild or moderate renal impairment relative to those with normal renal function. Hepatic impairment is not expected to affect pharmacokinetics of erenumab.

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

Concomitant administration of erenumab with other drugs is not expected to result in clinically relevant drug interactions. Furthermore, it is unlikely to have an effect on drug metabolizing enzymes or transporters such as inhibition or induction and it is expected to be catabolized by general proteolytic degradation pathways. The applicant did not conduct specific in vitro permeability, in vitro metabolism, in vitro metabolic drug interaction, or nonclinical pharmacokinetic drug interaction studies. Erenumab is administered subcutaneously, and is not expected to be associated with clinically relevant food-drug interactions.

The applicant conducted two clinical studies to assess the potential for drug interactions between 1) erenumab and oral contraceptives (Study 2015-0334) and 2) erenumab and sumatriptan (Study 2014-0255).

A multicenter, open-label, drug interaction study (2015-0334) confirmed that the concomitant administration of erenumab does not affect the PK of the active components of a combined oral contraceptive (ethinylestradiol and norgestimate). In addition, the serum concentrations of luteinizing hormone, follicle-stimulating hormone, or progesterone were unaffected in healthy female subjects with concomitant administration oral contraceptive and erenumab.

Similarly, a randomized, double-blind, parallel-group, placebo-controlled, single-dose study (2014-0255) confirmed that the concomitant intravenous administration of 140 mg erenumab does not affect the pharmacokinetics sumatriptan in healthy subjects. No clinically meaningful differences in the primary endpoint of time-weighted averages of MAP and resting BP (systolic BP, diastolic BP, and MAP) were observed between subjects who received sumatriptan subcutaneously alone and those who received it concomitantly with intravenous erenumab.

Thus, from the pharmacokinetic perspective, there are no clinically relevant drug interactions associated with erenumab administration.

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?

During clinical safety and efficacy studies, the drug product was supplied in glass vials containing 70 mg/mL erenumab or glass prefilled syringe containing 70 mg/mL erenumab. Since the prefilled syringes were either used for SC injection or loaded into the SureClick autoinjector, the applicant used the glass prefilled syringe instead of autoinjector during most of the clinical

development. The applicant conducted relative bioavailability study (2014-0477) to assess bioequivalence between different clinical presentations (glass vial, prefilled syringe, and SureClick autoinjector) at 70 mg strength. The results from this study support bridging of data between the clinical trial formulations (glass vial and prefilled syringe) and the to-be-marketed 70 mg formulations (prefilled syringe and SureClick autoinjector).

A consult request for biopharmaceutic inspections of the analytical site for Study 2014-0477 was issued on 17-Jul-2017 to the Office of Study Integrity and Surveillance (OSIS). The Division of New Drug Bioequivalence Evaluation within the OSIS recommended accepting data on 16-Aug-2017 without on-site inspection because recent inspections of the analytical sites were completed and sites were classified as 'No Action Indicated'.

4 APPENDICES

4.1 Summary of Bioanalytical Method Validation

For the determination of serum erenumab levels, the Applicant used a validated enzyme-linked immunosorbent assay (ELISA) method. This method was developed and validated by the applicant and subsequently it was transferred (b) (4) where the method underwent partial method validations at each laboratory.

For the immunogenicity assessment, the Applicant used 2-stage approach with an initial screening followed by specificity assessment of binding antibodies. The applicant used an electrochemiluminescent bridging immunoassay to detect binding antibodies (screening assay) and confirm antibodies) capable of binding erenumab (confirmatory assay).

A consult request was issued on 27-Jul-2017 to the Division of Applied Regulatory Science (DARS) for assessing the suitability of bioanalytical assays including erenumab assay, its anti-drug antibodies assay, and neutralizing anti-drug antibodies assay. The DARS recommended accepting erenumab bioanalytical data confirming that the bioanalytical methods including the drug assay and ant-drug antibody assay were adequate to support clinical studies included in this submission (Please refer to consult reviews from Division of Applied Regulatory Sciences in DARRTS dated 12/05/2017 and 2/15/2018 for details on these analytical methods).

4.2 Pharmacometrics Assessment: Population PK Analyses

4.2.1 Sponsor's Population PK analysis:

Population PK (PopPK) analyses were conducted by the sponsor to characterize the PK of unbound AMG 334 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 AMG 334, which can potentially explain the interindividual differences in PK and aid in appropriate dose adjustment, if necessary; and (2) derive exposure metrics that can be used for subsequent exposure-response analyses of the efficacy and safety endpoints.

Data from 7 clinical studies, which included three phase 1 studies (20101267, 20101268 and 20120130), two phase 2 studies (20120178 and 20120295) and two phase 3 studies (20120296 and 20120297) were used in the population PK analyses. A brief description of these studies is given in **Table 3**.

Table 3 Summary of the characteristics of the studies used for PopPK analyses

Study ID	Subjects	Doses/Route	Description of data
20101267	Phase 1: Healthy subjects (N=6)	140 mg (IV)	Rich PK: Predose, 0.5 (IV), 1 (IV), 8 h, and 1, 2, 3, 4, 7, 11, 14, 21, 28, 42 days postdose. If dose ≥ 70 mg: 56, 63, 84, 98 days If dose ≥ 140 mg: 126 days If dose = 210 mg: 154 days
	Healthy subjects (N = 30)	1, 7, 21, 70, 140, 210 mg (SC)	
	Migraine patients (N = 6)	140 mg (SC)	
20101268	Phase 1: Healthy subjects (N = 24)	21, 70, 140 mg Q4W * 3 (SC) 280 mg * 1, 210 mg * 2 (SC)	Rich PK: Predose, 8 h, and 3, 4, 7, 11, 14, 21, 28 (predose), 35, 56 (predose and 8 h), 63, 70, 84, 98, 112 days If dose ≥70 mg: 126, 168 days If dose ≥140 mg: 196 days If dose 280 mg *1, 210 mg *2: 224 days
	Migraine patients (N=12)	21, 140 mg Q4W * 3 (SC)	
20120130	Phase 1: Healthy Japanese subjects (N = 18)	21, 70, 140 mg (SC)	Rich PK: Predose, 8 h, 1, 2, 3, 4, 7, 11, 14, 21, 28, 42, 63 days If dose ≥ 70 mg: 84 days

	Healthy Caucasian subjects (N = 6)	70 mg (SC)	If dose ≥ 140 mg: 112 days
20120178	Phase 2: Patients with episodic migraine (N = 427)	DB: 7, 21, 70 mg Q4W * 3 (SC) OL: 70 mg Q4W (SC)	Sparse PK: Predose, 2, 4, 8, 12, 36, 52, 64 weeks, every 6 months thereafter, and 16 weeks post last dose PK substudy: 7 and 63 days
20120295	Phase 2: Patients with chronic migraine (N =373)	70, 140 mg Q4W *3 (SC)	Sparse PK: Predose, 2, 4, 8, 12, 24 weeks PK substudy: 7 and 63 days
20120296	Phase 3: Patients with episodic migraine (N = 376)	DB: 70, 140 mg Q4W * 6 ATP: 70, 140 mg Q4W * 7	Sparse PK: Predose, 4, 12, 16, 24, 28, 36, 52 weeks, and 16 weeks post last dose PK substudy: 7 and 91 days
20120297	Phase 3: Patients with episodic migraine (N = 523)	DB: 70 mg Q4W * 3 OL: 70 mg Q4W	Sparse PK: Predose, 4, 12, 16, 24, 40 weeks and 12 weeks post last dose

Note: N: Number of subjects included in the PopPK analyses dataset; IV: Intravenous, SC: Subcutaneous, DB: Double-Blind (phase), OL: Open Label (phase); ATP: Active Treatment Phase; Source: Adapted from the PopPK report (123319), Table 12-1 on page 31

The final dataset for the PopPK analyses consists of a total of 9759 quantifiable AMG-334 PK samples from a total of 2061 subjects, of whom 84 were healthy subjects, 1601 were subjects with episodic migraine and 376 were subjects with chronic migraine. The PK samples in which the concentrations were below the limit of quantification (N = 48 samples, 0.5%) were excluded.

The PopPK data of AMG 334 was modeled using non-linear mixed effects in NONMEM. The structural model developed by the sponsor consists of a two-compartmental PK model whose:

a) absorption was characterized by a first order absorption rate constant (ka) and (absolute) bioavailability. The bioavailability was estimated only based on the PK data from one phase 1 study because of the limited availability of PK data following IV administration (N=6) that can support the (stable) estimation of bioavailability and peripheral distribution parameters.

b) distribution was characterized by apparent volumes of central (V_2) and peripheral compartments (V_3) and the inter-compartmental clearance (Q) between them
Note: Typical values of V_3, Q and bioavailability were fixed based on the estimation from only the intensive data in the subsequent steps of the model development

c) linear clearance (CL) (i.e., non-target specific drug elimination pathway) and a non-linear target-mediated elimination pathway, both from the central compartment. More specifically, the total amount of receptor (target) in the saturable elimination pathway was modeled as a

system of turnover rates of the unbound receptor and the association-dissociation of the antibody-receptor complex as:

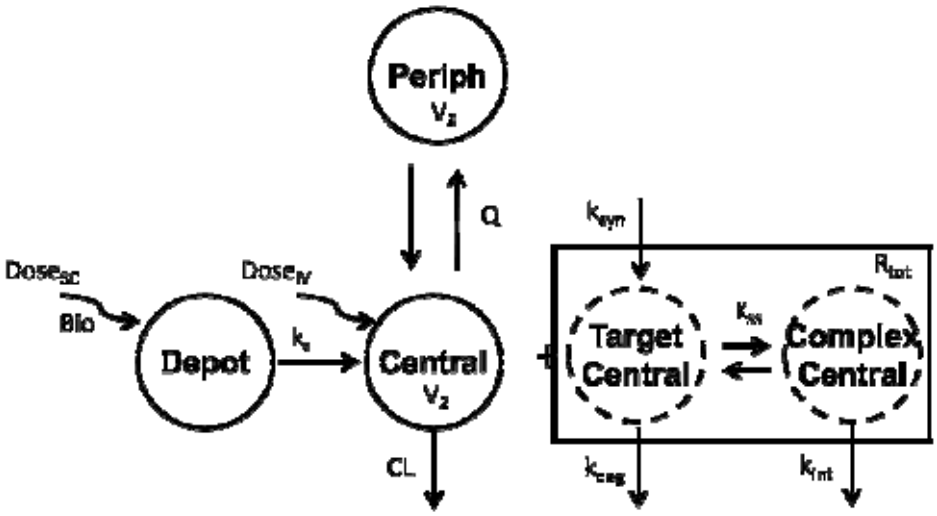
- the synthesis and elimination rate of the receptor were characterized by zero order (k_{syn}) and first order (k_{deg}) rate constant respectively
- a quasi-steady state equilibrium was assumed between the association-dissociation of the unbound receptor and the antibody-receptor complex, characterized by quasi-steady-state rate constant (K_{ss})
- the elimination of the antibody-receptor complex was characterized by a first-order rate constant (k_{int}).

d) residual error structure included proportional error component

The schematic for the structural model is shown in **Figure 7**. Covariate identification was performed in a stepwise manner and the list of covariates explored included age, estimated glomerular filtration rate (eGFR), sex, race, study population, injection site, presence of anti-drug antibodies. During the End-of-Phase 2 (EoP2) discussions with the agency, the sponsor stated that the phase 3 trials will offer patients and physicians the option of using different injection sites (i.e., abdomen, upper leg and upper arm) and such information will be collected and assessed as a covariate in the population analyses. In addition, it was noted that a single patient will utilize the same injection site for all subsequent injections throughout the study. It was found that the injection site had minimal impact in explaining the variance (<10%) of the PK parameters and therefore, was not retained in the final popPK model. Non-Caucasian subjects constituted only 9% of the subjects and binding anti-AMG 334 antibody incidence occurred in 7% of the subjects. Owing to these small sample sizes per category, race and anti-AMG 334 antibody status were not tested in the popPK model. Body weight was retained as a covariate on both CL and V_2 using allometry, whose coefficients were estimated. The parameter estimates of the final PopPK model are shown in **Table 4**.

The qualification of the final PopPK model was performed using the goodness of fit plots, shown in **Figure 8**. Furthermore, the individual prediction from simulation of 100 replicates with the same design using the estimates of the population means and variability from the final PopPK model were overlaid with the observed data and visualized using the Visual Predictive Check (VPC) shown in **Figure 9 - 15** (for individual studies).

Figure 7 Schematic of the structural PopPK model



k_a	first-order absorption rate of unbound antibody
Bio	Bioavailability of subcutaneous injections
CL	linear clearance or non-target specific drug elimination pathway
V_2	volume of distribution for the central compartment
V_3	volume of distribution for the peripheral compartment
Q	intercompartmental clearance between central and peripheral compartment
R_{max}	baseline apparent density of the total target in the peripheral compartment
k_{deg}	elimination rate constant of target
k_{int}	elimination rate constant of AMG 334-target complex
k_{syn}	synthesis rate constant of target
K_{ss}	quasi-steady-state constant

Source: Population PK report (123319) Figure-13-9 on Page 55

Table 4 Parameter estimates of the final PopPK model

Parameter Descriptions	Parameter (unit)	Mean	%RSE	95% CI[a]
Linear Clearance at 72.1 kg[b]	CL (mL/d)	198	1.82	(191 - 205)
Volume of distribution for central compartment at 72.1 kg[b]	V_2 (mL)	4350	3.47	(4054 - 4646)
Intercompartmental clearance (fixed)[c]	Q (mL/d)	959	-	-
Volume of distribution for peripheral compartment (fixed)[c]	V_3 (mL)	3250	-	-
First-order absorption rate constant	k_a (1/d)	0.298	9.13	(0.245 - 0.351)
Bioavailability (fixed)[c]	%	81.8	-	-
Production rate of target	k_{syn} (ng/mL/d)	66.3	8.25	(55.6 - 77.0)
Quasi-steady state constant	k_{ss} (ng/mL)	6.78	26.8	(3.21 - 10.3)
Elimination rate of AMG 334-target complex	k_{int} (1/d)	0.0509	14.2	(0.0367 - 0.0651)
Elimination rate of target	k_{deg} (1/d)	0.705	22.3	(0.397 – 1.01)
Effect of Bodyweight on CL		1.18	4.17	(1.08 - 1.28)
Effect of Bodyweight on V_2		1.46	6.01	(1.29 - 1.63)
Inter-subject variability in CL	ωCL (%CV)	27.6	7.93	(25.3 - 29.6)
Inter-subject variability in V_2	ωV_2 (%CV)	42.0	15.2	(35.2 - 47.8)
Inter-subject variability in k_{int}	ωk_{int} (%CV)	69.7	46.7	(20.3 - 96.5)
Inter-subject variability in k_a	ωk_a (%CV)	79.5	25	(56.8 - 97)
Inter-subject variability in k_{syn}	ωK_{syn} (%CV)	39.1	23.3	(28.8 - 47.2)
Covariance between η_{CL} and η_{V2}	Cov (η_{CL}, η_{V2})	0.0233	56.22	(-0.0024 - 0.049)
Residual error[d]	Prop. CV (%)	16.6	4.51	(15.1 - 18.1)
Residual error[e]	Prop. CV (%)	32.9	12	(25.1 - 40.7)
Residual error[f]	Prop. CV (%)	29.9	16.9	(20 - 39.8)

CV = coefficient of variation; RSE = relative standard error.

[a] 95% CI obtained from NONMEM asymptomatic standard errors.

[b] The final model included the following PK-parameter covariate relationships:

$$CL = 198 \cdot \left(\frac{BodyWeight}{72.1} \right)^{1.18}$$

$$V_2 = 4350 \cdot \left(\frac{BodyWeight}{72.1} \right)^{1.46}$$

[c] Intercompartmental clearance, volume of distribution for peripheral compartment, and bioavailability were estimated separately for 140 mg IV and SC, single and multiple-dose data in rich-sampling phase 1 PK studies for the same PK model (see Table 12-6)

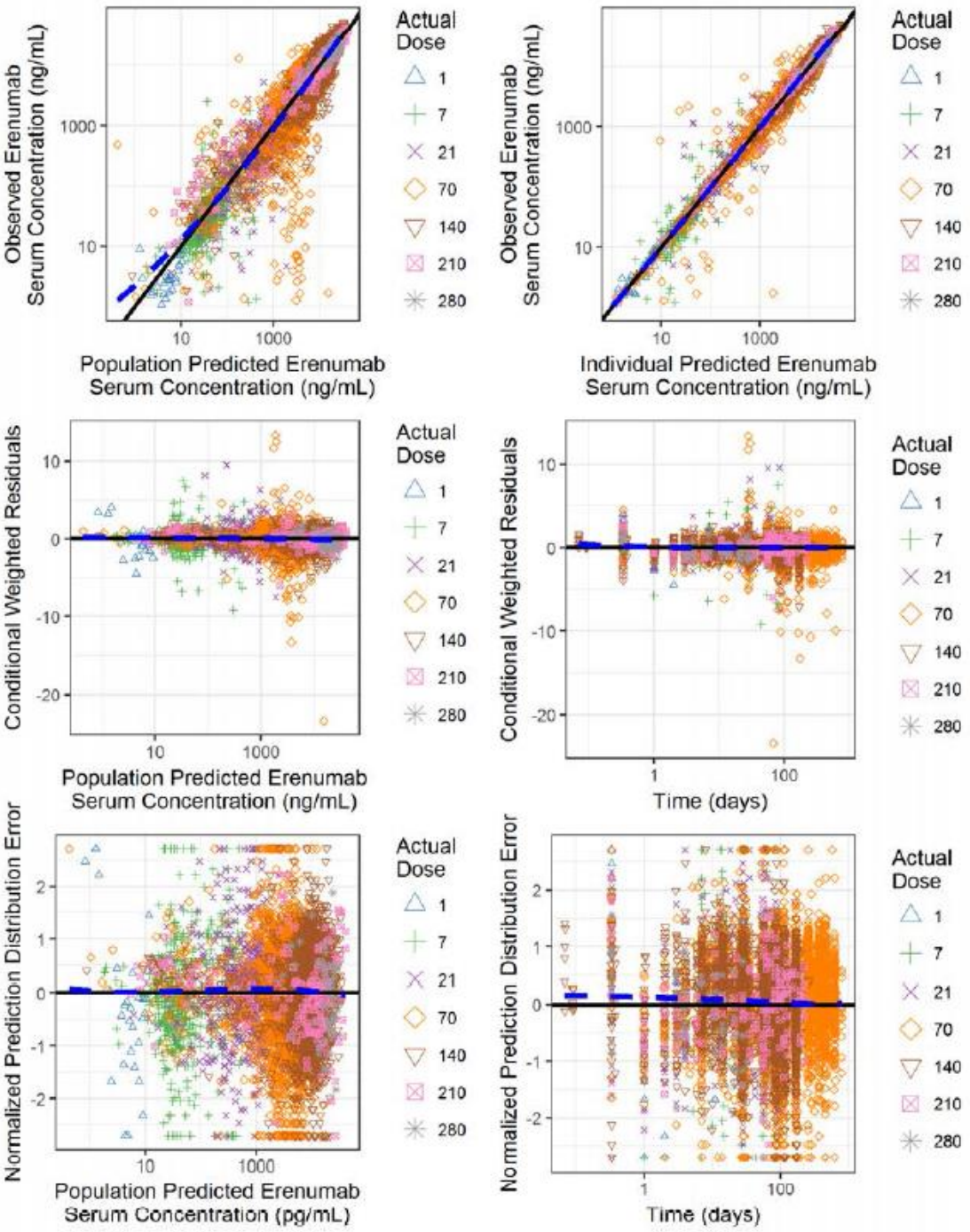
[d] Phase 1 studies 20101267, 20101268, and 20120130

[e] Studies 20120178, 20120295, and 20120297.

[f] Study 20120296.

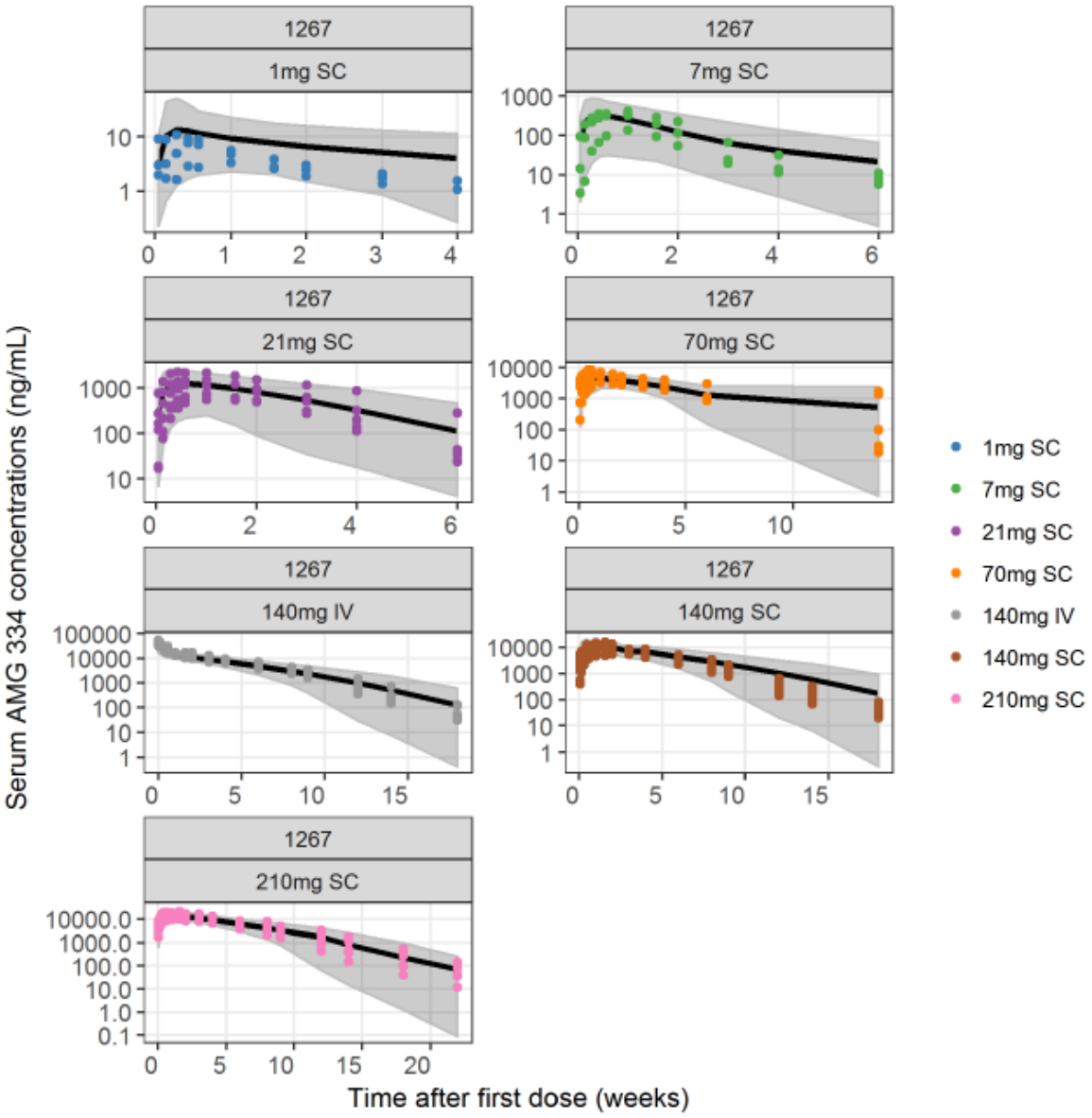
Source: Population PK report (123319) Table – 12-7 on Page 41

Figure 8 Goodness of fit plots for the final PopPK model



Source: Population PK report (123319) Figure13-15 on Page 70

Figure 9 VPC of final PopPK model for Study 20101267

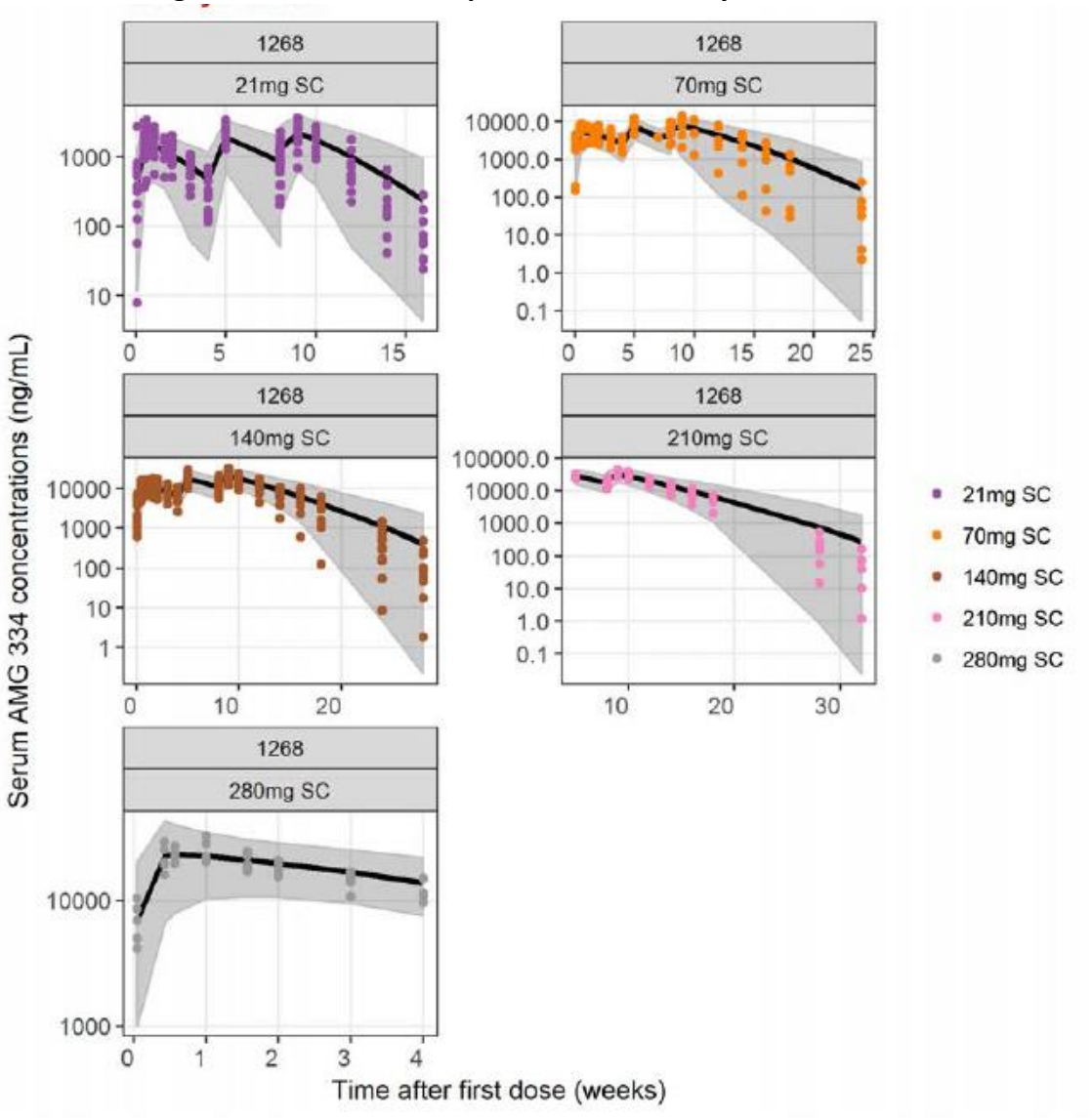


Page 1 of 7

Colored points are observed data. The simulated median is shown with a black line, and the 5th to 95th percentiles are shown in grey fill and grey lines. Study 1267 is Study 20101267.

Source: Population PK report (123319) Figure13-19 on Page 77

Figure 10 VPC of final PopPK model for Study 20101268



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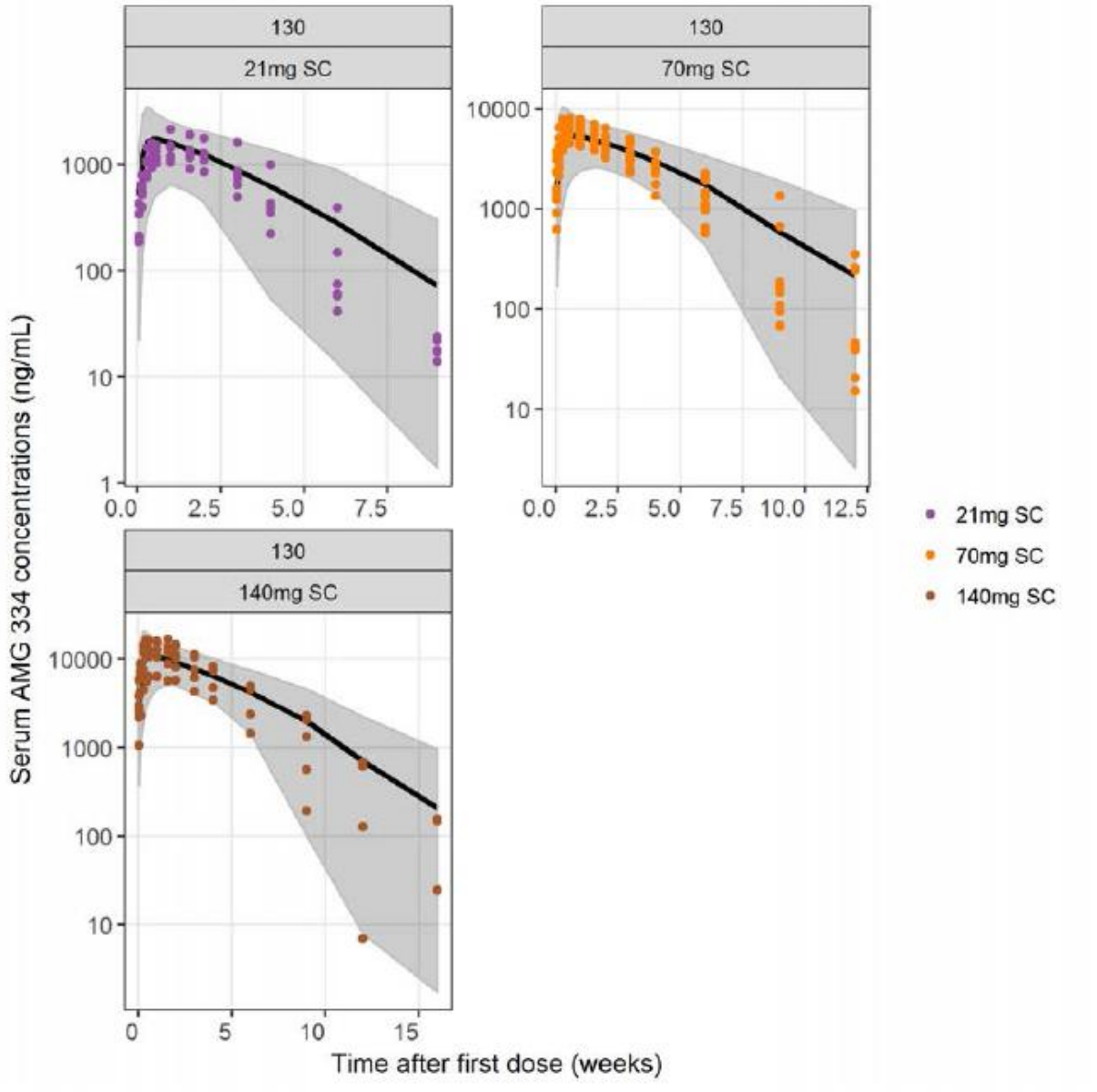
Colored points are observed data. The simulated median is shown with a black line, and the 5th to 95th percentiles are shown in grey fill and grey lines. Study 1268 is Study 20101268.

Source: Population PK report (123319) Figure13-19 on Page 78

Figure 11 VPC of final PopPK model for Study 20120130

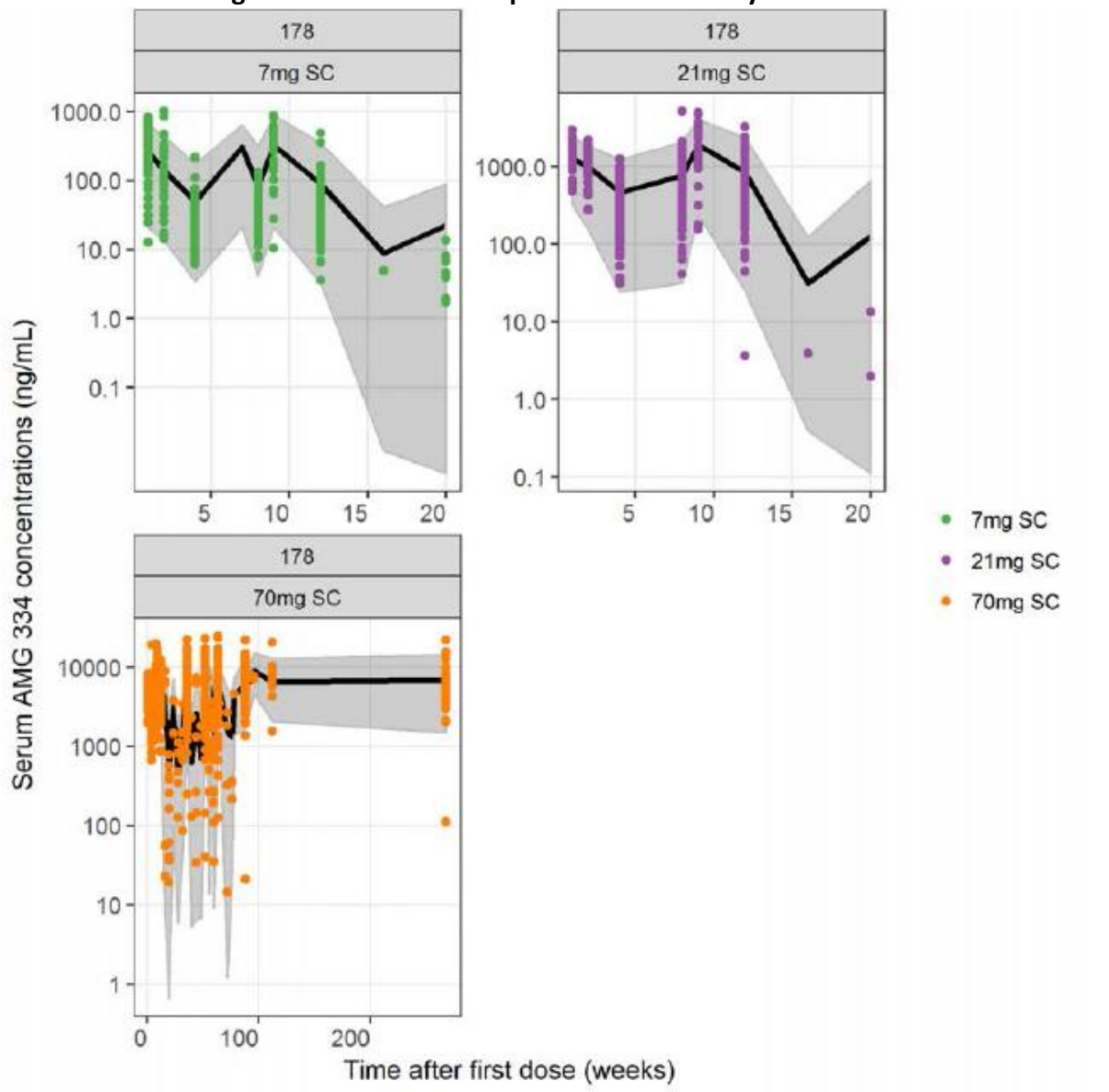


Page 3 of 7

Colored points are observed data. The simulated median is shown with a black line, and the 5th to 95th percentiles are shown in grey fill and grey lines. Study 130 is Study 20120130.

Source: Population PK report (123319) Figure13-19 on Page 79

Figure 12 VPC of final PopPK model for Study 20120178



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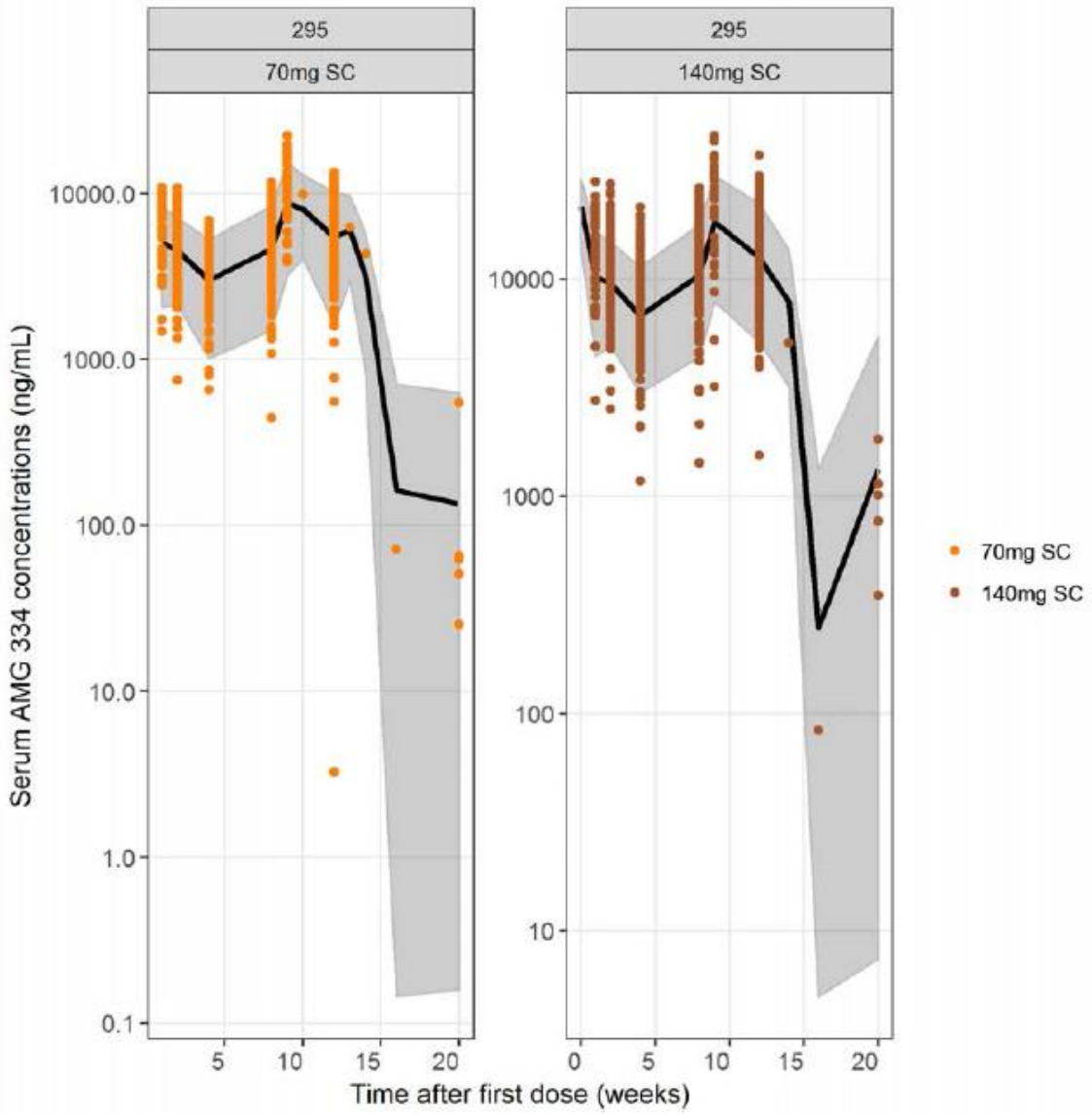
Colored points are observed data. The simulated median is shown with a black line, and the 5th to 95th percentiles are shown in grey fill and grey lines. Study 178 is Study 20120178.

Source: Population PK report (123319) Figure13-19 on Page 80

Figure 13 VPC of final PopPK model for Study 20120295

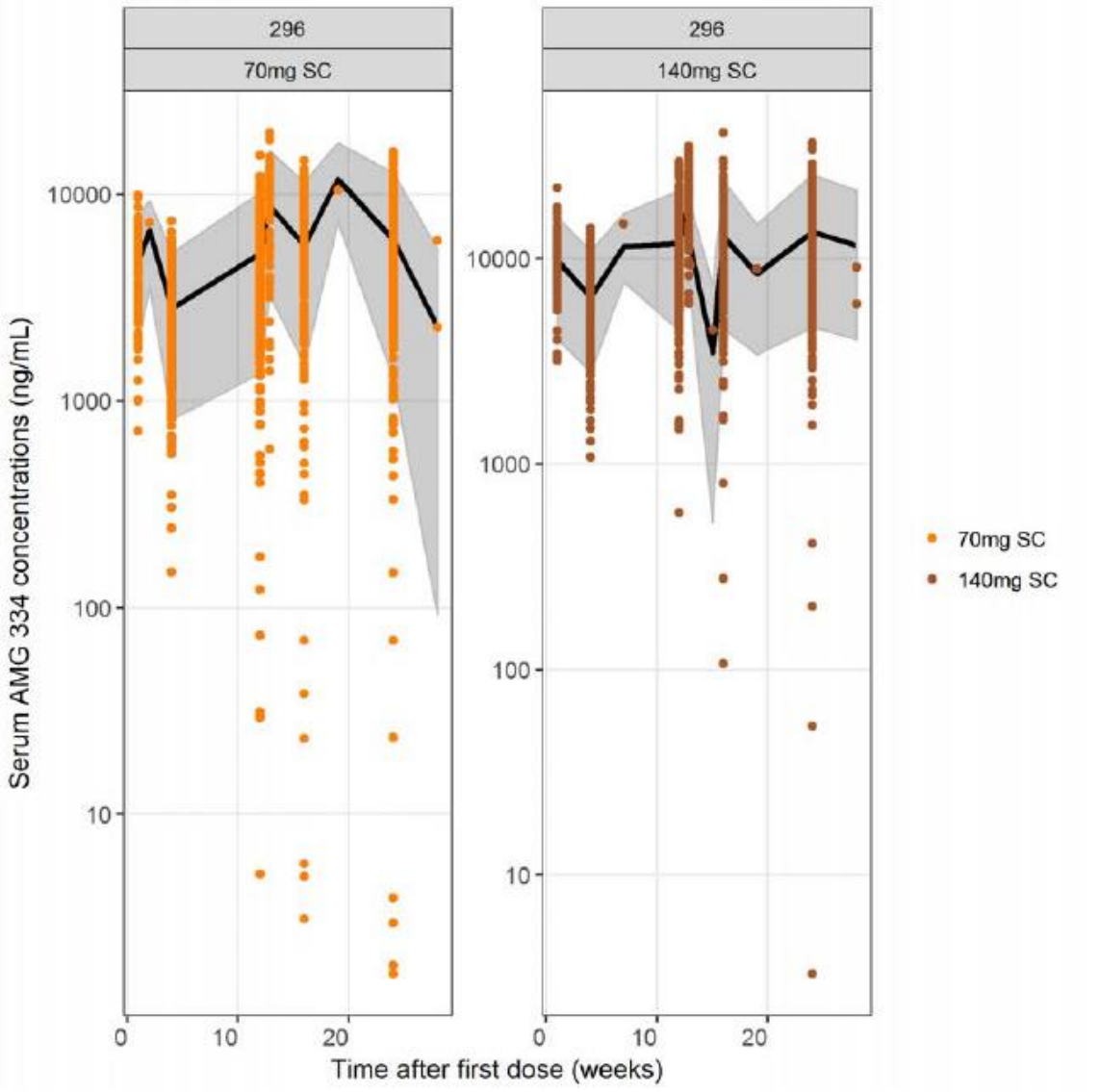


Page 5 of 7

Colored points are observed data. The simulated median is shown with a black line, and the 5th to 95th percentiles are shown in grey fill and grey lines. Study 295 is Study 20120295.

Source: Population PK report (123319) Figure13-19 on Page 81

Figure 14 VPC of final PopPK model for Study 20120296

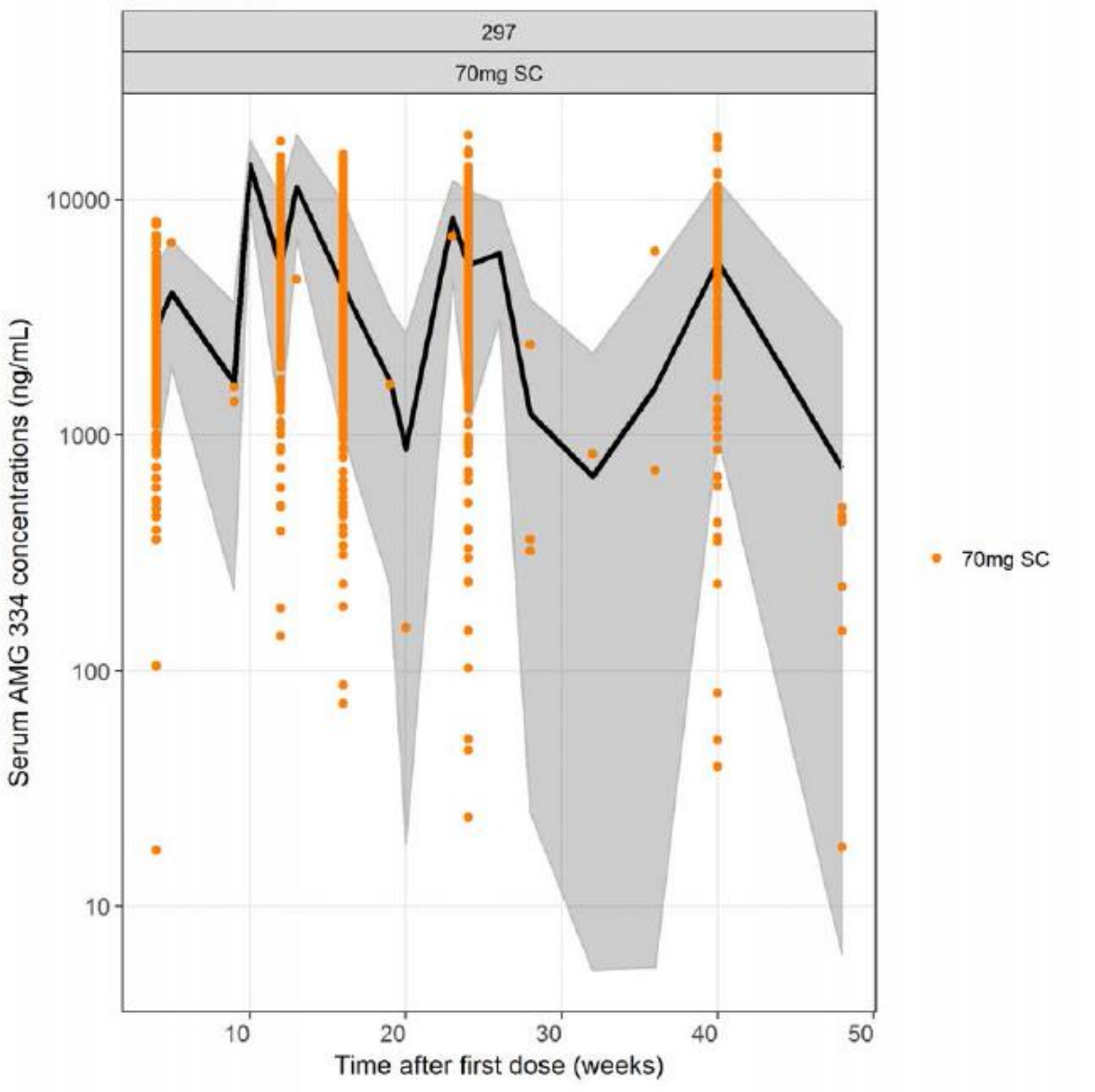


Page 6 of 7

Colored points are observed data. The simulated median is shown with a black line, and the 5th to 95th percentiles are shown in grey fill and grey lines. Study 296 is Study 20120296.

Source: Population PK report (123319) Figure13-19 on Page 82

Figure 15 VPC of final PopPK model for Study 20120297



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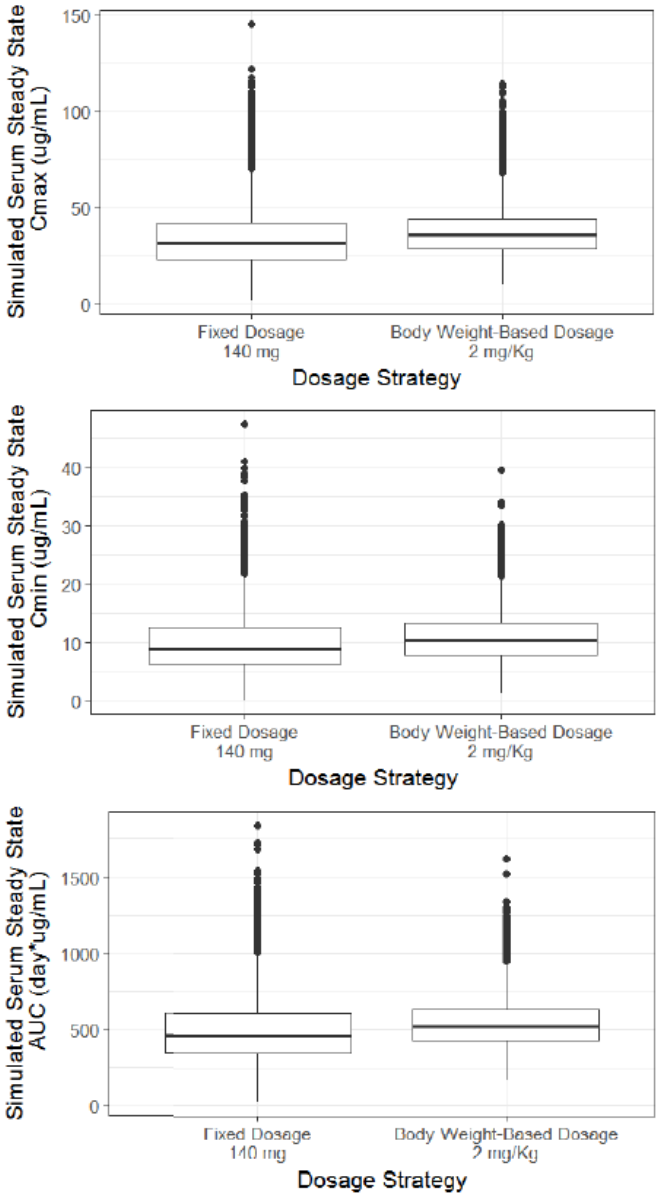
Colored points are observed data. The simulated median is shown with a black line, and the 5th to 95th percentiles are shown in grey fill and grey lines. Study 297 is Study 20120297.

Source: Population PK report (123319) Figure13-19 on Page 83

The sponsor performed simulations using the final PopPK model to support fixed dose recommendations. Steady-state exposures ($C_{min,}$ C_{max}, and AUC following 6 Q4W) were simulated for subjects in a bodyweight range of 40-163 kg and were compared to those after fixed dose regimen. The distribution of these exposures is shown in **Figure 16**

Figure 16 Simulated AMG 334 exposures (C_{max}, C_{min} and AUC) at steady-state for 140 mg SC Q4W and 2 mg/kg SC Q4W



Source: Population PK report (123319) Figure13-20 on Page 84

Reviewer's comments:

*The sponsor modeled the PK data of unbound serum AMG334 from studies listed in **Table 3**, which included both rich and sparse sampling designs in subjects with episodic and chronic migraine as well as healthy subjects. The dataset included n=6 subjects, in whom the AMG 334 was administered intravenously. During the structural model development, the PK data from only the rich PK sampling designs were fitted first to characterize the bioavailability, intercompartmental clearance and peripheral distribution parameters because it was collected from limited number of subjects. These model parameters estimates were fixed in the subsequent model development process, after they showed no systematic bias based on the goodness of fit plots (for the structural model). This approach seems reasonable, especially because PK data after intravenous administration were available from a limited number of subjects .*

*The final model parameter estimates and associated uncertainty in the estimation reported in **Table 4** seem reasonable for most of them. The estimates for interindividual variability in elimination rate constant of the AMG 334-receptor complex and absorption rate constant of AMG 334 seem to be particularly high. The covariate modeling results suggested that bodyweight was a significant covariate on the linear clearance (non-target mediated pathway) and peripheral volume of distribution. However, model-based simulations of fixed-dosing versus body weight based-dosing resulted in comparable exposures (**Figure 16**) and therefore, the sponsor proposed fixed doses. Given that the efficacy was similar across the two doses (relatively shallow exposure-response relationship for efficacy – please refer to Section 4.3 for additional details), the magnitude of the impact of bodyweight does not seem clinically meaningful and the fixed dosing recommendations proposed by the sponsor are acceptable. Apart from the low doses (1 mg), which are not clinically relevant, in study 20101267, the visual predictive checks across the rest of the studies (**Figure 9** - **Figure 15**) in general, suggest that the final popPK model was able to characterize the PK of unbound AMG-334 adequately.*

4.2. Exposure-Response Analyses

4.2.1 Exposure-Efficacy Analyses

4.2.1.1 Sponsor's Exposure-Efficacy Analyses

Exposure metrics, namely, daily serum concentrations of AMG 334 were derived from the final PopPK model such that they correspond to the days for which migraine observations were collected. Subsequently, relationships were explored between (logit function of) the probability of migraine headache day as a function of time-dependent effects during the baseline period, time-dependent placebo effects, AMG 334 exposures and patient-level covariates using a mixed effects logistic regression approach.

Episodic Migraine

Efficacy data from 3 episodic migraine studies (20120178, 20120296 and 20120297) were included for the exposure-response (ER) analyses and a brief description of the study characteristics are summarized in **Table 3**. In all studies, subjects used an electronic diary (eDiary) every day throughout the baseline and double-blind treatment phases to report various characteristics of each headache experienced by the subject, e.g., occurrence of migraine (with or without aura) or nonmigraine headache, times of onset and resolution, pain severity and features, associated symptoms (such as nausea, vomiting, photophobia, phonophobia) and their severity, and use of acute medication.

The final model characterizing the ER is discussed below and the model parameter estimates summarized in **Table 5**.

$$logit\left[p_i(m_{ij}=1)\,|\,\eta_i\right] = f_{bl} + f_{pbo} + 0.774 \cdot PrevMig - 0.564 \cdot \frac{\log(AMG334)^{10}}{\log(5150)^{10} + \log(AMG334)^{10}} + \eta_{ij}$$

where

$$f_{bl} = -0.923 \cdot nonfailed + -0.848 \cdot (1 - nonfailed) \cdot (1 - 0.0147 \cdot time[BL])$$

$$f_{pbo}(= -0.844 \cdot nonfailed + -0.529 \cdot (1 - nonfailed) + \eta_{pmax}) \cdot (1 - \exp(-0.0217 \cdot time[1 - BL]))$$

where time is in days since study entry; f_{bl} describes the daily migraine rate in the baseline period (BL=1 if baseline period else 0) as a function of time; f_{pbo} describes the daily migraine rate in the placebo arm as a function of time and prior prophylactic medication use (nonfailed=1 if the subject had 0 failed prior prophylactic medication use at baseline and 0 otherwise); *PrevMig* is the presence of a migraine on the previous day; and *AMG334* is individual serum concentration in ng/mL predicted for the corresponding day using the PopPK model.

Table 5 Parameter estimates in Episodic Migraine

Model components	Parameter descriptions (unit)	Estimate	%RSE
Baseline period	Time effect (1/day)	-0.0147	6.69
	Base at study entry for non-failed prophylactic medication (logit)	-0.923	1.98
	Base at study entry for failed ≥1 prophylactic medication (logit)	-0.848	2.43
Presence of previous migraine day	(logit)	0.774	2.69
Placebo effect	Maximum placebo effect for non-failed prophylactic medication (logit)	-0.844	4.41
	Maximum placebo effect for failed ≥1 prophylactic medication (logit)	-0.529	6.41
	Onset rate of placebo effect during double-blind period (d^{-1})	0.0217	7.92
	η_{pmax}, maximum placebo effect	0.515	7.63
	η-shrinkage (%)	13.8	NA
Drug related	Maximum effect, Emax (logit)	-0.564	12.3
	Concentration to achieve 50% of maximum effect ([EC50], ng/mL)	5148	26.1
	Hill coefficient	10 fixed	NA
Variability in individual response	η_{ij}	0.033	16.0
	η-shrinkage (%)	52.9	NA

CV = coefficient of variation; RSE = relative standard error of estimate; NA=not applicable
NONMEM output for efficacy model is in Appendix 15-2

Source: Exposure-response analyses report (123320) Table 12-6 on Page 45

The time-dependent effects during the 28-day baseline period were best characterized by a monotonic decreasing linear function both in the placebo as well as active-treatment arms. The estimated typical baseline probability of migraine day (on day 1 at study entry) was 0.369/day for non-failed and 0.386/day for failed prophylactic subjects, interpreted as 37% of the non-failed subjects and 39% of the failed subjects having migraine day at study entry respectively. This probability dropped to 0.28/day for non-failed and 0.295/day for failed subject at the end of the baseline period, i.e., one day prior to first dose of AMG 334. This observation (also referred to as the regression to the mean) was consistent across the dose groups prior to the AMG 334/placebo dose.

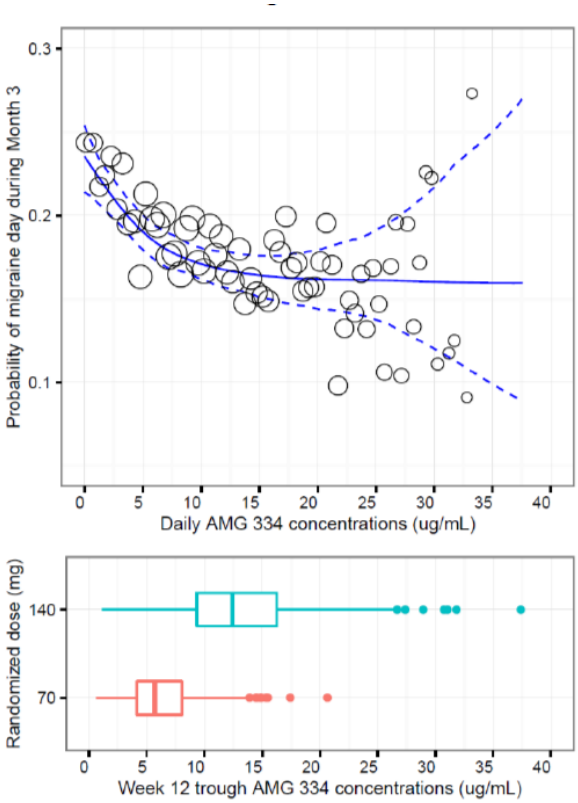
The time-dependent placebo effect during the placebo-treated arm was best characterized by a monotonic exponential function which plateaued to a maximum probability of 0.21/day (~-2 days/month) for non-failed subjects and 0.28/day (~-1.42 days/month) for failed prophylactic subjects. The average time to achieve 50% of the maximum placebo effect was approximately 32 days.

The daily AMG 334 concentration-dependent effect in the active treatment arm was best characterized by a sigmoidal Emax function with a significant hill coefficient estimate (and

therefore was fixed to a high value of ~10.5, suggesting an on-off like effect). The onset of drug effect is likely to be rapid as delayed drug effect model (e.g., effect compartment model) was not found to be significant. Assuming a constant placebo effect and concentration during the dosing interval, at steady-state, probability decreased to a maximum of -1.63 and -2.17 migraine days/month for non-failed and failed prior prophylactic medication use, respectively. These model parameter estimates suggest that the net concentration dependent effect seem to be larger for subjects with prior prophylactic medication use that is likely due to higher baseline and smaller placebo effect. The concentration at 50% maximal effect (EC_{50}) was estimated to be 5.1 µg/ml, which is near the trough concentrations at steady-state following 70 mg dose. It was reported that 97% of subjects in the 140 mg dose group and 64% of subjects in the 70 mg dose group achieved exposures greater than the EC_{50} within the first week of AMG 334 administration, and 61% subjects in the 140 mg dose group achieved exposures equivalent to EC_{50} on the same day of administration of the first dose (and none in the 70 mg dose group), also suggesting that the onset of the drug effect is rapid.

The qualification of the final ER model was performed using the goodness of fit plots, shown in **Figure 17** below.

Figure 17 Exposure response relationship at week 12 in episodic migraine

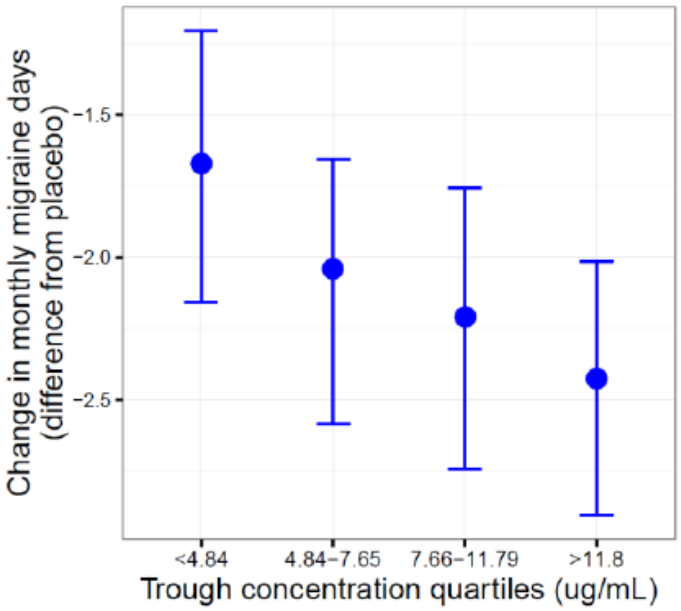


Legend: symbol= observed data with symbol size is proportional to square root of observations per bin of daily concentrations (500 ng/mL bins). Blue lines = mean prediction and 95% CI based on exposure-response model estimates; boxplots represent distributions of Month 3 trough concentrations for the corresponding dose group.

Source: Exposure-response analyses report (123320) Figure 13-12 on Page 64

Furthermore, the ER model predicted change in monthly migraine days (MMD) from baseline (primary efficacy endpoint) as a function of the quartiles of the predicted trough concentrations at week 12 in subjects with episodic migraine is shown in **Figure 18**.

Figure 18 Model predicted (mean ± 95%CI) change from baseline in the MMD by quartiles of trough concentrations in episodic migraine subjects



Source: Exposure-response analyses report (123320) Figure 13-19 on Page 73

Chronic Migraine

Efficacy data from one chronic migraine study 20120295 was included for the exposure-response (ER) analysis. The description of the study characteristics is in **Table 3**. The subjects used an electronic diary (eDiary) every day throughout the baseline and double-blind treatment phases to report various characteristics of each headache experienced by the subject, e.g., occurrence of migraine (with or without aura) or nonmigraine headache, times of onset and resolution, pain severity and features, associated symptoms (such as nausea, vomiting, photophobia, phonophobia) and their severity, and use of acute medication.

Owing to large variability in the placebo response, simultaneous estimation of placebo and treatment effects was not feasible. Therefore, the placebo effect was estimated based only on the placebo data, and these parameters were fixed in the subsequent estimation of the treatment effects. The final model characterizing the ER is discussed below and the model parameter estimates summarized in **Table 6**

$$logit\left[p_i(m_{ij}=1)|\eta_i\right] = (0.104+\eta_{base})\cdot(1+f_{bl}+f_{pbo})+0.799\cdot PrevMig-0.0564\cdot\log(AMG334)+\eta_{ij}$$

Where:

$$f_{bl} = (-0.0127\cdot time[BL])$$

$$f_{pbo} = -6.52\cdot(1-\exp(-0.014\cdot time[1-BL])$$

where *time* is in days since study entry; f_{bl} describes the daily migraine rate in the baseline period (*BL*=1 if baseline period else 0) as a function of time; f_{pbo} describes the daily migraine rate in the placebo arm as a function of time; *PrevMig* is the presence of a migraine on the previous day; and *AMG334* is individual serum concentration in ng/mL predicted for the corresponding day using the PopPK model.

Table 6 Parameter estimates in Chronic Migraine

Model components	Parameter descriptions (unit)	Estimate	%RSE
Placebo data only*			
Baseline period	Time effect during baseline period (1/day)	-0.0402	37.3
	Base at study entry (logit)	0.13	44.9
	η_{base}	1.82	27.9
	η-shrinkage (%)	20	NA
Placebo effect	Maximum placebo effect (logit)	-6.52	42.7
	Onset rate of placebo effect during double-blind period (d^{-1})	0.014	31.5
Presence of previous migraine day	(logit)	0.761	6.23
Variability in individual response	η_{ij}	0.524	18.9
	η-shrinkage (%)	12	NA
Treatment data only (placebo parameters fixed)**			
Baseline period	Time effect during baseline period (d^{-1})	-0.0401	22.1
	Base at study entry (logit)	0.103	21.4
	η_{base}	4.3	45.0
	η-shrinkage (%)	15.5	NA
Concentration effect	Slope (logit per ng/mL)	-0.0555	14
Presence of previous migraine day	(logit)	0.8	4.54
Variability in individual response	η_{ij}	0.458	14.7
	η-shrinkage (%)	11.9	NA

CV = coefficient of variation; RSE = relative standard error of estimate; NA= not applicable
* NONMEM output for efficacy model is in Appendix 15-3
** NONMEM output for efficacy model is in Appendix 15-4

Source: Exposure-response analyses report (123320) Table 12-8 on Page 49

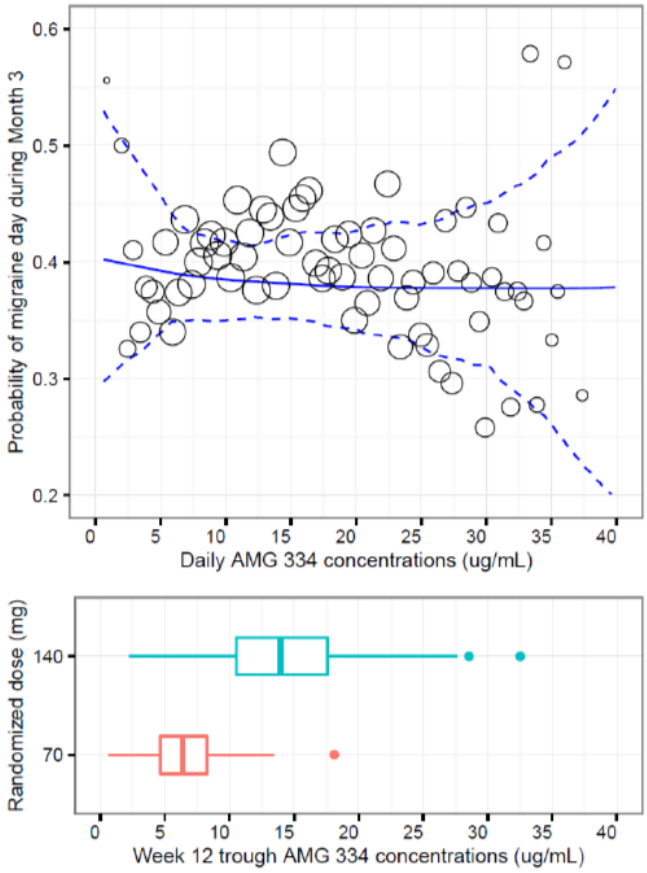
The time-dependent effects during the 28-day baseline period were best characterized by a monotonic decreasing linear function both in the placebo as well as active treatment arms. The estimated typical baseline probability of migraine day (on day 1 at study entry) was 0.623/day, interpreted as 62.3% of subjects having a migraine day at study entry. This probability dropped to 0.596/day at the end of the baseline period, i.e., one day prior to first dose of AMG 334. This observation (also referred to as the regression to the mean) was consistent across the dose groups prior to the AMG 334/placebo dose.

The time-dependent placebo effect during the placebo-treated arm was best characterized by a monotonic decreasing function which plateaus to a maximum probability of 0.49/day (~-3 days/month). The average time to achieve 50% of the maximum placebo effect was approximately 50 days.

The daily AMG 334 concentration-dependent effect in the active treatment arm was best characterized by a monotonic decreasing linear function of time. The onset of drug effect is likely to be rapid as delayed drug effect model, e.g., effect compartment model was not found to be significant. Assuming a constant placebo effect and concentration during the dosing interval, at steady-state, probability decreased to a maximum of 0.352/day.

The qualification of the final ER model was performed using the goodness of fit plots, shown in **Figure 19** below.

Figure 19 Exposure response relationship at week 12 in chronic migraine

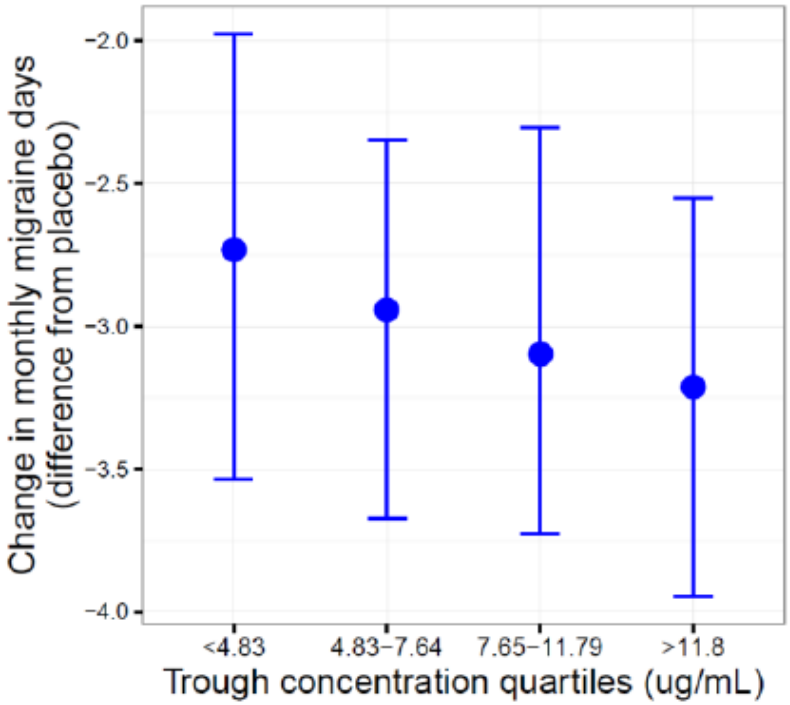


Legend: symbol= observed data with symbol size is proportional to square root of observations per bin of daily concentrations (500 ng/mL bins). Blue lines = mean prediction and 95% CI based on exposure-response model estimates; boxplots represent distributions of Month 3 trough concentrations for the corresponding dose group.

Source: Exposure-response analyses report (123320) Figure 13-17 on Page 71

Furthermore, the ER model predicted change in monthly migraine days (MMD) from baseline (primary efficacy endpoint) as a function of the quartiles of the predicted trough concentrations at week 12 in subjects with chronic migraine is shown in **Figure 20**.

Figure 20 Model predicted (mean ± 95%CI) change from baseline in the MMD by quartiles of trough concentrations in chronic migraine subjects



Source: Exposure-response analyses report (123320) Figure 13-19 on Page 73

Impact of Bodyweight

Bodyweight was evaluated directly in the ER model as a potential covariate, but was not found to be significant in either episodic or chronic migraine. The sponsor explored the adequacy of a fixed-dose (140 mg SC Q4W * 3) by re-sampling subjects 10000 times using the observed baseline bodyweight distribution for subjects with PK (40-163 kg) and baseline prior prophylactic medication use status (e.g., failed vs. non-failed) and sampling all the baseline covariates together in order to ensure the preservation of their correlation structures. The popPK model was used to simulate daily exposures corresponding to the migraine observations based on the actual dosing records. Subsequently, the simulated CFB in MMD (primary efficacy endpoint) at end of week 12 along with the exposures were compared for the quartiles of the bodyweight and shown in **Table 7**.

Table 7 Predicted exposures and MMD at Week 12 following AMG 334 SC at 140 mg Q4W Stratified by Bodyweight Quartiles

		1st Quartile (lighter subjects)		Interquartile		3rd Quartile (heavier subjects)	
		Weight < 63 kg		63 – 85 kg		Weight > 85 kg	
$AUC_{0\text{-}28d}$ (µg·d/mL)	Mean	594		447		303	
	CV%	24		26		31	
	Median	581		436		294	
	Min, Max	216, 1241		133, 962		41, 694	
Cmin (µg/mL)	Mean	16.8		12.2		7.92	
	CV%	29		32		38	
	Median	16.3		11.8		7.52	
	Min, Max	4.07, 37.5		3.02, 32.9		0.324, 21.3	
		Episodic	**Chronic**	**Episodic**	**Chronic**	**Episodic**	**Chronic**
Monthly migraine days (CFB)	Mean	-4.42	-7.01	4.08	-6.82	-3.83	-6.68
	SD	4.61	7.22	4.51	7.07	4.5	7.05
	Median	-5	-7	-4	-7	-4	-7
	Min, Max	-19, 17	-26, 15	-19, 19	-27, 17	-16, 16	-24, 19

Source: Exposure-response analyses report (123320) Table 12-9 on Page 50

Based on these simulations, it was observed that the 'lighter' subjects (<25th percentile: < 63 kg) had 33% higher systemic exposures, while 'heavier' subjects (>75th percentile: >85 kg) had 32% lower exposures than the subjects in the interquartile range (63-85 kg). It was found that the corresponding differences in change from baseline for the mean MMD days were comparable across the weight three groups of the weight quartiles, i.e., 'lighter', 'heavier' and subjects in the interquartile range. Therefore, the sponsor proposed fixed-dose based recommendations

Reviewer's comments:

While there seems to be a trend in the exposures (steady-state trough concentrations) of AMG 334 and the primary efficacy endpoint for episodic migraine, this seems to be less apparent for chronic migraine. These findings are consistent with the dose-response observations from P3 studies. The sponsor's ER analyses seem reasonable based on the model parameter estimates and associated uncertainty and model-based simulations for both episodic and chronic migraine indications.

4.2.2. Reviewer's Exposure-Efficacy Analyses

Introduction

Based on the primary efficacy endpoint results as well as the exposure-efficacy analyses, both the 70 and 140 mg doses seem appropriate for both chronic and episodic migraine indications. However, it was of interest to explore the possibility of some specific subgroups potentially benefiting more with a monthly dose of 140 mg dose. The reviewer carried out an independent analysis using the exposure and efficacy metrics across the quartiles of the covariates namely, BMI and age. Body size and age were selected as demographics of interest because of their potential influence on AMG 334 exposure and because of interest from the review team. A model-independent exploration was performed to detect potential trends in the data.

Objective

- To evaluate whether there is a subgroup of patients within a certain range of a covariates such as BMI and age, who may benefit more from receiving a monthly dose of 140 mg.

Datasets

Datasets used in the analyses are summarized in the **Table 8** below.

Table 8: Analysis Datasets

Study Number	Name	Link to EDR
20120295	adbase.xpt	\\cdsesub1\evsprod\BLA761077\0001\m5\datasets\20120295\analysis\adam\datasets
	admonpri.xpt	
	adpc.xpt	
	adsl.xpt	
	advs.xpt	
20120296	adbase.xpt	\\cdsesub1\evsprod\BLA761077\0001\m5\datasets\20120296-primary\analysis\adam\datasets
	admonpri.xpt	
	adpc.xpt	
	adsl.xpt	
	advs.xpt	

Software

The statistical software R version (3.3.1) were utilized for dataset compilation, analyses and generation of plots.

Methods

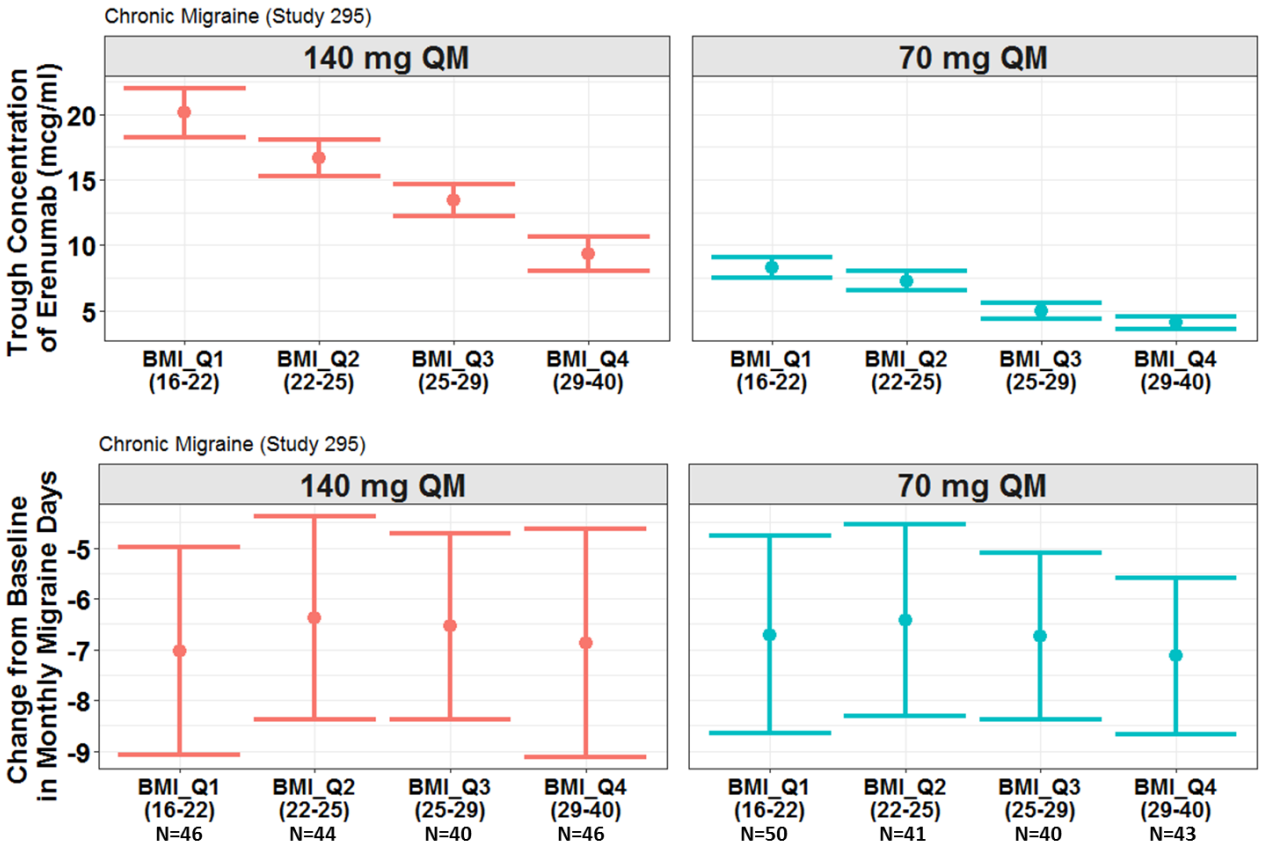
The quartiles of age and BMI were calculated based on the values reported at baseline for studies 20120295 (pivotal study for chronic migraine) and 20120296 (for episodic migraine). Additionally, the exposures, i.e., observed trough plasma concentration of erenumab either at the week 12 visit (chronic migraine) or the week 24 (episodic migraine) were also plotted.

Results

The results for the BMI quartiles across the doses are shown in **Figure 21**** for chronic migraine and in **Figure 22**** for episodic migraine. It can be noted that the primary efficacy endpoint results seem comparable across the BMI quartiles between 70 and 140 mg, consistent with the either no (chronic migraine) and shallow (episodic migraine) exposure-response relationship described above, despite higher exposures following 140 mg than 70 mg dose. Similar lack of trends were observed with the age quartiles across the doses for both chronic and episodic migraine (not shown here).

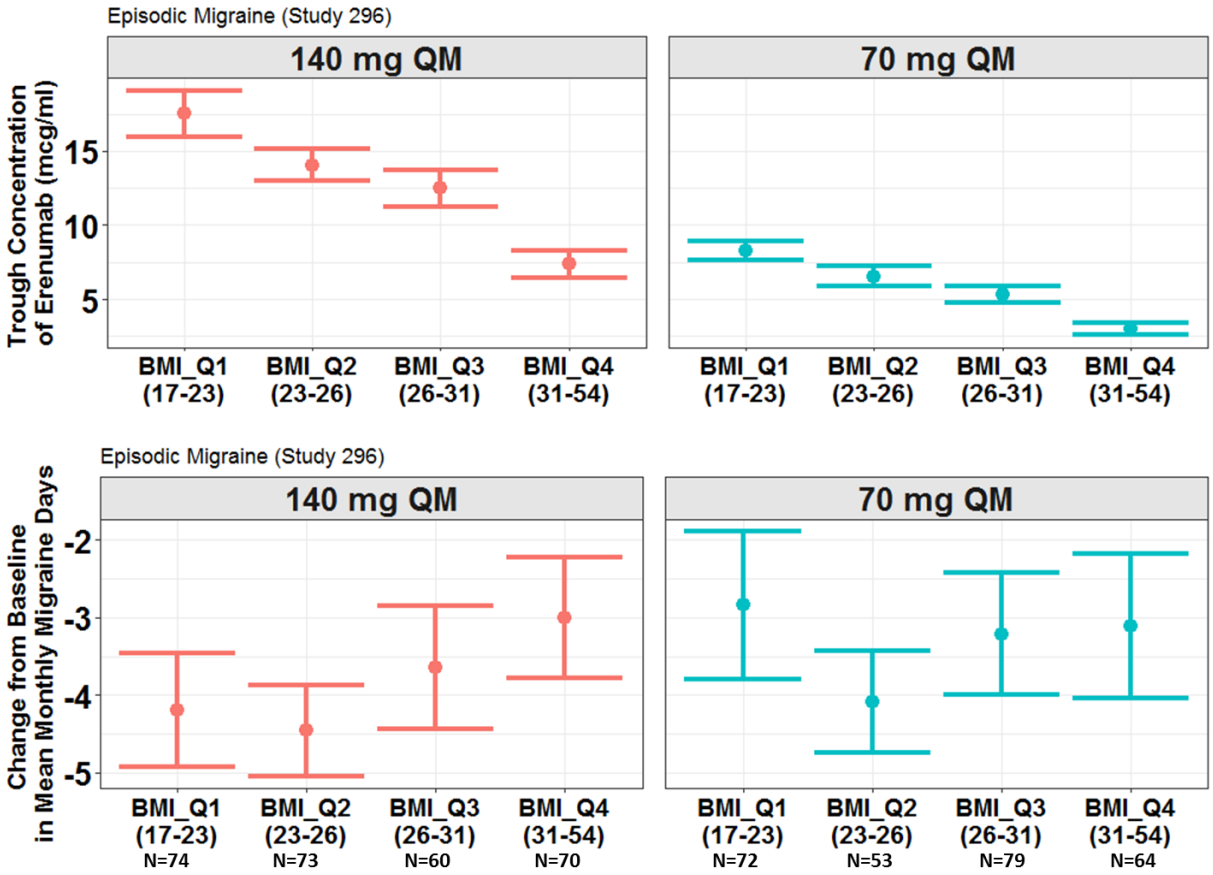
**Please note that figures 21, 22 show the change from the baseline in the MMD only in the treatment arms. The quartiles for the same endpoint were also explored in the placebo arm and an obvious trend was not observed (plots not included in the review).

Figure 21 Reviewer's analysis of the exposure and efficacy in different BMI quartiles across the doses in study 20120295 (chronic migraine)



Note: Numbers in the parenthesis reflect the range of the BMI in each quartile, and N stands for the number of subjects in each quartile

Figure 22 Reviewer's analysis of the exposure and efficacy in different BMI quartiles across the doses in study 20120296 (episodic migraine)



Note: Numbers in the parenthesis reflect the range of the BMI in each quartile, and N stands for the number of subjects in each quartile

.

List of Analysis Codes and Output files

Filename	Description	Link to PM Review Shared Drive
CM295_BMI_plots_final QBR.R	Analyses of BMI quartiles across the doses in study 20120295 in chronic migraine	\\cdsnas\Pharmacometrics\Reviews\Ongoing PM Reviews\Erenumab_BLA761077_GG\FDA Review\QBR
EM296_BMI_plots_final QBR.R	Analyses of BMI quartiles across the doses in study 20120296 in chronic migraine	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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Date: 26 September 2017

From: James L. Weaver PhD & Kristina Howard DVM, PhD; Division of Applied Regulatory Science/Office of Clinical Pharmacology (DARS/OCP)

Through: David Strauss MD, PhD, Director; DARS/OCP

To: Girish Bende; Division of Clinical Pharmacology I/OCP

Subject: Evaluation of assays for Erenumab (AMG-334), anti-drug antibodies and neutralizing anti-drug antibodies in BLA 761077

Executive Summary

Original Question: *Is the ELISA assay method used here acceptable for bioanalysis - Is it validated as per FDA guidelines? i.e., The assay used in analysis of Erenumab (AMG334), its antibody (ADA), and Anti-neutralizing Antibody are fit for purpose from bio-analytical validation perspective.*

The ELISA method used to measure AMG 334 levels in plasma was properly designed and was validated per FDA guidelines. Reports from clinical trial studies included appropriate detailed metrics of assay performance. The results of the studies evaluated in this report on measurement plasma levels of AMG-334 are acceptable.

The assays for ADA and neutralizing ADA were properly designed and validated. However, essentially no data were supplied on the performance of these two assays when being used to analyze clinical trial samples. Thus, the validity of the results for the ADA and neutralizing ADA assays performed on samples from the clinical trials evaluated for this consult cannot be assured.

Background

Erenumab (AMG 334, BLA 761077) is a monoclonal antibody intended to treat migraine headaches. The antibody binds to and inhibits the receptor of the calcitonin gene-related peptide (CGRP) but not the related amylin receptor (AMY1) (Schuster & Rapoport, 2017).

The clinical development pathway of this antibody is complex. The antibody was originally developed by Amgen, who also performed the initial development and validation of the assay to measure the drug in patient samples. The method developed by Amgen was subsequently transferred to three different companies: (b) (4) Each of the three companies performed a partial validation of the method developed by Amgen.

Evaluation

Is the ELISA assay method used here acceptable for bioanalysis - Is it validated as per FDA guidelines? i.e., The assay used in analysis of Erenumab (AMG334), its antibody (ADA), and Anti-neutralizing Antibody are fit for purpose from bio-analytical validation perspective.

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This question has multiple sub-parts, the assay validation performed by each of the four companies, the ADA assay and the anti-neutralizing antibody assay.

Measurement of AMG-334 in Serum

Assay Validation Studies

The assay for measurement of AMG-334 in serum is a standard ELISA format that relies on the specificity of two proprietary mouse anti-erenumab monoclonal antibodies that bind to Erenumab. One clone (1B6.1H) is bound to the ELISA plate as the capture antibody. The second biotin-conjugated clone (1F10.1) is used as the detection antibody with the detection reagent being streptavidin conjugated with horseradish peroxidase. All four companies used the same lot of capture and detection antibodies created and supplied by Amgen. Three companies (Amgen, (b) (4) used the same lot of AMG 334 while studies by (b) (4) used three different lots. An additional complication is that the studies appear to have crossed the issuance of the draft guidance for bio-analytical methods validation in 2013. As a result some studies were done under that guidance and some under the standard of the predecessor guidance issued in 2001.

The original or master assay validation studies were performed by Amgen and described in report # 116327. Acceptance criteria for the various parameters were set in agreement with the guidance. The assay range of quantitation was conservatively set at 1.0 to 100 ng/ml. The assay fully met all of the acceptance criteria.

The methods validation study by (b) (4) includes a partial validation of the Amgen method and a small cross validation study performed with Amgen. The assay as performed by (b) (4) met the acceptance criteria and the results were similar between the two companies. The cross validation study was fully successful.

The third validation effort was performed by (b) (4) This was a more basic partial validation and included a small cross validation study performed with (b) (4) The performance of the assay met the listed acceptance criteria.

The final validation of this series was performed by (b) (4) As with the previous efforts, the assay performance met the acceptance criteria.

Conclusion: The assay validation studies were performed in accordance with the Bioanalytical Methods Validation Guidance.

Measurement of AMG-334 in Serum – Performance in Clinical Studies

The clinical studies evaluated for this consult are listed in table 1 below. Performance of the assays was evaluated in all studies except 20130255. As this was an open label extension of the phase 2 study, no final report has been filed. However the assay performance in the main phase 2 study was fully acceptable. Incurred sample reanalysis (ISR) was done with Phase 1 and 2 studies but not in either phase 3 study.

Conclusion: The performance of the assay for drug levels of AMG-334 was properly evaluated and

reported. The data are fit for purpose.

Table 1 - Clinical trials performance metrics for measurement of AMG-334 in plasma

Study #	Description	File	Calibration	Fit parameter stats	Dilution QC	QC Results	ISR
20140477	Phase1 70 mg/ml dosage form comparison	161-131-csr-20140477-pk-info.pdf	OK	OK	OK	OK	OK
20120178	Phase 2 double blind placebo controlled with open label extension	CSR 20120178 - 16.1.13.1 Supportive Pharmacokinetic Information.pdf	OK	OK	OK	OK	OK
20120295	Phase 2 double blind placebo controlled	CSR 20120295 - 16.1.13.1 Supportive Pharmacokinetic Information.pdf	OK	OK	OK	OK	OK
20130255	Phase 2 open label extension of 20120295	No report					
20120296	Phase 3 double blind placebo controlled	CSR 20120296 Primary Analysis - 16.1.13.1 Supportive Pharmacokinetic Information.pdf	OK	OK	OK	OK	Not done
20120297	Phase 3 double blind placebo controlled	CSR 20120297 - 16.1.13.1 Supportive Pharmacokinetic Information.pdf	OK	OK	OK	OK	Not done

Detection of Anti-Drug Antibodies (ADAs) in Serum – Assay Validations:

Amgen Study # MVR-000443

The assay is a multi-step assay with an initial screening phase and a second specificity phase done only on samples that are positive in the screening phase. The screening assay starts with a serum sample diluted to 5% being treated with 300 mM acetic acid. This will dissociate any existing ADAs bound to AMG-334.

This sample is mixed with a solution containing AMG-334-biotin (AMG-334-B), AMG-334-Ruthenium (AMG-334-Ru) in a TRIS buffer, pH 9.5. This neutralizes the acetic acid and allows any ADAs to bind to any available AMG-334 species. Following this binding phase, the sample is added to a detection plate coated with streptavidin. All complexes containing AMG-B as well as any remaining free AMG-B will bind to the plate. The remaining complexes are washed away. Next ECL reagent is added allowing detection of complexes containing AMG-Ru. A polyclonal rabbit anti-AMG-334 is used as a positive control and normal human serum is used as a negative control.

For samples that tested positive a specificity check was performed by adding an excess of unlabeled AMG-334, this would generate combinations 4-6 from Table 2 and result in no detectable signal. This confirms that the detected ADAs are truly against AMG-334.

In the absence of AMG-334, the assay has a Lower Limit of Reliable Detection of 100 ng/ml of the polyclonal rabbit anti-AMG-334. The ability of unlabeled drug to interfere with the assay was determined and at the Lower Limit of Reliable Detection (LLRD), there was observable depletion at 50 µg/ml of AMG-334 (Table 21).

Interference by soluble receptor was tested and the assay performance was not affected by concentrations up to 20 µg/ml. Samples were stable through 5 freeze/thaw cycles or at 5 °C for up to 7 days. Inter and intra assay precision was acceptable, ranging from 5% to 16% CV, all comfortably under the acceptance criteria of 20%.

Design Evaluation
A clinical sample is likely to contain some amount of AMG-334 and may or may not contain some amount of ADAs. The ability to detect ADAs therefore is a function of the relative concentrations of AMG, AMG-B, AMG-Ru and the ADAs. The concentrations of AMG-B and AMG-Ru are fixed so that only the relative concentrations of AMG and ADAs affect the ability to detect ADAs. The most sensitive scenario is no AMG and a high concentration of ADAs. In contrast if there is a low concentration of ADAs and a high concentration of AMG then detection will not occur due to cold reagent block. When the assay is run, an individual ADA molecule has six possible outcome for which component binds to which of the two antigen binding sites on the antibody molecule (Table 2). Of these possible outcomes, only one of the six will generate a signal in the assay (#1).

As an example, for Table 11-1 from study 201296, concentrations of AMG-334 (140 mg) ranged from 0.0 to 41 µg/ml with median values from 6.5 to 18.1 µg/ml. The drug tolerance study found that at the LLRD, it took 50 µg/ml of AMG-334 to interfere with the assay in a detectable way. This demonstrates that the presence of drug at observed clinical levels will have no to minimal effects on the assay for ADAs. This suggests that outcomes 4 – 6 in table 2 below may be disregarded as real world outcomes. However this leaves outcomes 1 – 3 as plausible. Therefore the design is likely detecting 1/3 of the total ADAs present in the sample. The actual performance of the assay gives a detectable signal at 100 ng/ml of added antibody. A primary concern for ADAs is the ability to bind sufficient drug to affect clearance or function. If we take 10 µg/ml as a standard value for serum concentration of AMG-334, then the ADA assay is capable of detecting ADAs at an amount able to tie up 200 ng/ml or 2% of the standard serum concentration of the

drug.

Table 2 - ADA Assay possible binding combinations

	Binding to ADA Arm #		
Combo #	**Arm 1**	**Arm 2**	**Result**
1	AMG – B	AMG-Ru	Bound and detected
2	AMG – B	AMG – B	Bound, no detection
3	AMG-Ru	AMG-Ru	Washed away
4	AMG-Ru	AMG	Washed away
5	AMG – B	AMG	Bound, no detection
6	AMG	AMG	Washed away

Conclusion: The design and performance of the assay in validation studies performed by Amgen as reported in study MVR-000443 are acceptable.

(b) (4) *methods validation, report* (b) (4)
The ADAs detection method was transferred to (b) (4) and a methods validation study was performed to ensure acceptable performance.

Detection of Neutralizing Anti-Drug Antibodies in Serum –Amgen Study # MET-003420
Description
This assay was only performed on samples with a confirmed positive test in the ADA assay described above. The assay uses a cell line (SKNMC) that expresses a receptor for α-CGRP. This receptor is the target of the drug AMG-334. Treatment of SKNMC cells with the natural ligand α-CGRP leads to a significant rise in intracellular levels of cyclic Adenosine MonoPhosphate (cAMP). The drug AMG-334 binds to the receptor and blocks the α-CGRP from binding and in consequence reduces or eliminates the rise in cAMP. If there are neutralizing ADAs (nADAs) present then the ability of the drug to block the rise in cAMP will be reduced or eliminated. Positive results in this assay are confirmed by testing the ability of Protein-G and Protein-L coated beads to remove the neutralizing activity from the patient sample. As protein G binds all IgG molecules and protein-L binds antibody light chains, this removal confirms the identification of the neutralizing material as an antibody. Following the various treatments, the cells are lysed and cAMP is measured by a standard commercial ECL assay sourced from (b) (4)

Design Evaluation
Assay design is more for hazard ID and less for the quantitation of nADAs. A significant difference between the ADA assay and this nADA assay is the absence of the dissociation step to release any nADAs that are already bound to drug in the patient sample. Therefore this assay will only detect nADAs that are in excess of the amount of AMG-334 present in the test sample. That said, the assay otherwise will detect nADAs. The design is directly relevant to the intended mechanism of action of the drug and provides a readout that requires appropriate signaling in the SNKMC cells to generate the cAMP output.

Assay Validation - Amgen Study # MVR-000471
The assay validation paradigm set out in FDA guidance documents does not fit particularly well to the more complex assay design required for this nADA assay. The company did a credible job in describing how the concentrations of test and control reagents were set and the effects of free drug and free ligand on the assay. Interference by bilirubin, lipids or hemolysis were evaluated and found not to affect assay performance. Based on this set of experiments assay performance criteria were established for use in studies of samples from clinical trials.

LLRD for this study was set at 1.14 µg/ml of the positive control rabbit anti-AMG-334. As expected from the design, free drug will interfere with assay performance. The validation study shows that amounts of free AMG-334 above 10% of the nADA concentration will alter the results.

Conclusion: The design and performance of the assay for nADAs in validation studies performed by Amgen as reported in study MVR-000471 are acceptable.

Assay Validation - (b) (4) *Study #* (b) (4)
The Amgen method was transferred to (b) (4) who performed their own methods validation studies to ensure proper performance of the method. Critical reagents were obtained from Amgen or were obtained from the same supplier used by Amgen. The validation studies were cloned directly from the Amgen document. Observed values from (b) (4) were highly similar to the values from the original Amgen study. A limited cross validation study was performed (n=18) with complete agreement between (b) (4) and Amgen as to positive and negative samples.

Conclusion: The performance of the assay for nADAs in secondary validation studies performed by (b) (4) as reported in study (b) (4) is acceptable.

Assay Validation - (b) (4) *Study #* (b) (4)
The Amgen method was transferred to (b) (4) who performed a methods validation study as well. Critical reagents were obtained from Amgen or were obtained from the same supplier used by Amgen. The validation studies were cloned directly from the Amgen document. Observed values from (b) (4) were highly similar to the values from the original Amgen study. A limited cross validation study was performed (n=18) with complete agreement between (b) (4) and Amgen as to positive and negative samples.

Conclusion: The performance of the assay for nADAs in secondary validation studies performed by (b) (4) as reported in study (b) (4) is acceptable.

Detection of Anti-Drug and neutralizing Anti-Drug Antibodies in Serum – Performance in Clinical Studies
The specific reports examined are listed in table 3 below. As these reports document performance metrics for both ADA and nADA methods these will be discussed together. No reports provided individual run performance metrics or statistical analysis of performance for either assay. When reported assay performance was reported only as the percent meeting method acceptance criteria. A quote of the entire Section 3.3 Assay Performance from study 20140477: "In the binding antibody assay, 39 out of 42 assays (92.85%) met method acceptance criteria. In the neutralizing antibody assay, 5 out of 6 assays (83.3%) met

method acceptance criteria." No mention is made of what happened following assays that did not meet acceptance criteria. There is also no mention of ISR for any of the samples in any study.

Table 3 - Clinical trials performance metrics for measurement of ADAs and nADAs in plasma

Study #	Description	File	# samples	Parameters reported
20140477	Phase1 70 mg/ml dosage form comparison	CSR 20140477 - 16.1.13.2 Anti-AMG 334 Antibody Assays Report.pdf	1548	LLRD, Assay sensitivity, % pass
20120178	Phase 2 double blind placebo controlled with open label extension	161-132-csr-20120178-antibody-rpt.pdf	Not reported	Assay sensitivity, drug tolerance
20120295	Phase 2 double blind placebo controlled	CSR 20120295 - 16.1.13.2 Anti-AMG 334 Antibody Assays Report.pdf	2794	Not reported
20130255	Phase 2 open label extension of 20120295	CSR 20130255 Interim Analysis - 16.1.13.1 Anti-AMG 334 Antibody Assays Report.pdf	1616	LLRD, assay sensitivity, % pass
20120296	Phase 3 double blind placebo controlled	CSR 20120296 Primary Analysis - 16.1.13.2 Anti-AMG 334 Antibody Assays Report.pdf	4256	LLRD, assay sensitivity, % pass
20120297	Phase 3 double blind placebo controlled	CSR 20120297 - 16.1.13.2 Anti-AMG 334 Antibody Assays Report.pdf	2452	LLRD, assay sensitivity, % pass

Conclusion: The documentation of the performance of the ADA and nADA assays on clinical study samples is not acceptable. Judging by the assay performance during validation studies, the assay results are likely to be reasonable, however due to the lack of data on performance as supplied in the study reports, the results cannot be assured.

Summary and Conclusions

The assay for measurement of AMG-334 in plasma was of acceptable design and was properly validated across the four companies who performed the assay. The assay validation studies were performed according to the Bioanalytical Methods Validation guidance. In the clinical trials evaluated the assay performed well within the listed acceptance criteria. Appropriate standards and controls were included and properly reported. The data on measurement of AMG-334 in these clinical trials is acceptable.

The assays for measurement of ADAs and nADAs were acceptably designed and appropriate validation studies were performed. However, the documentation of the performance of these two assays on clinical trials samples is not acceptable. Essentially no data were reported on the performance of the assays and therefore the validity of the results cannot be assured.

References and Supporting Documents

Schuster NM & Rapoport AM. (2017) Calcitonin gene-related peptide-targeted therapies for migraine and cluster headache: A review. *Clin Neuropharmacol* **40**, 169-174.

Multiple study reports from BLA761077, listed by study number in the body of the report.

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