CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number:	BLA 761077 / Serial Number 0001-
Drug Name:	AMG 334 (Erenumab)
Indication(s):	Chronic Migraine
Applicant:	Amgen
Date(s):	May 17, 2017 (date received by CDER)
Review Priority:	Standard Review
Biometrics Division:	Division of Biostatistics 1
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Table of Contents

LIST OF TABLES

1 EXECUTIVE SUMMARY

This BLA submission is to obtain marketing authorization for AMG334 (Erenumab) in the treatment and prevention of chronic migraine. The study doses are 70 mg and 140 mg SC (subcutaneously) self-injection monthly in the form of 2 pre-filled 70 mg syringes.

For the clinical studies, the disease indication of chronic migraine is divided into a less severe indication called EM (episodic migraine) with an average of 8 migraine days per month and a more severe indication called CM (chronic migraine) where patients may have an average of 18 migraine days per month with other bothersome symptoms also more severe. Please refer to the clinical review for a more precise definition.

The pivotal efficacy evidence is from three studies: two phase 3 studies for EM, and one phase 2 study for CM.

1.1 Conclusions and Recommendations

The pivotal studies in patients with EM and CM presented statistical evidence that AMG334, at once monthly dose of 70 mg, or 140 mg, is efficacious for the treatment of EM and CM based on reduction in monthly migraine days (MMD). The two dose levels show similar efficacy result.

1.2 Brief Overview of Clinical Studies

The Phase 3 study 20120296 is a 24-week study for EM with two dose levels 70 mg and 140 mg, The Phase 3 study 20120297 is a 12-week study for EM with one dose level 70 mg.

The Phase 2 study 20120295 is a 12-week study for CM with two dose levels 70 mg and 140 mg.

All three studies are multi-center, randomized, double-blinded, parallel group and placebo controlled. All 3 studies are complete and included in the current submission.

1.3 Statistical Issues and Findings

No major statistical issues were found.

2 INTRODUCTION

Three studies: 20120295, 20120296 and 20120297 are included in this statistical review for efficacy evaluation.

2.1 Overview

AMG 334 is a human monoclonal immunoglobulin G2 (IgG2) that is directed against the calcitonin gene-related peptide (CGRP) receptor complex and inhibits the action of CGRP. Due to its long half-life, it is anticipated that AMG 334 will selectively antagonize the CGRP receptor for prolonged periods, therefore preventing and/or reversing the activation of the trigeminal-vascular system. This prolonged CGRP receptor inhibition could be particularly useful for migraine prevention.

Table 1 List of All Studies included in Review

Study Number	Phase and Design	Treatment Period	Dose Levels	# of Subjects per Arm	Study Population
20120295	Phase 2	12 weeks	140 mg, 70 mg, placebo	187, 188, 281	CM
20120296	Phase 3	24 weeks	140 mg, 70 mg, placebo	318, 312, 316	EM
20120297	Phase 3	12 weeks	70 mg, placebo	282, 288	EM

All 3 studies are multi-center, randomized, double-blinded, parallel group and placebo controlled. The one phase 2 study is part of the pivotal evidence.

2.2 Data Sources

All documents reviewed for this NDA submission are in electronic form. In GS review, the BLA number 761077 will locate all documents of this BLA submitted by the sponsor including data files and programming code files in the CDER Electronic Document Room.

At the time of review the following is the link to the EDR Location:
\\CDSESUB1\evsprod\BLA761077\0001

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy Study - 20120295

3.1.1 Description of the Study

This study had its first subject enrolled on 5 March 2014, last subject last visit on 28 April 2016, and the study report was created on the date of 15 September 2016.

The purpose of this study was to evaluate the effect of AMG 334 70 mg and 140 mg compared to placebo on the change from baseline in MMD (monthly migraine days) in subjects with CM (chronic migraine).

Study 20120295 was a phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel group study of subjects with CM. The study was conducted at 69 centers in North America (US and Canada) and Europe (Czech Republic, Denmark, Germany, Finland, Norway, Poland, Sweden, and United Kingdom). Eligible subjects identified in the screening phase commenced a 4-week baseline phase. After the baseline period, eligible subjects were randomized in a 3:2:2 ratio to receive placebo, AMG 334 70 mg, or AMG 334 140 mg QM (every 4 weeks) by SC injection for the duration of the 12-week double-blind treatment phase. Randomization was stratified by region (North America or Europe) and medication overuse (yes or no) at baseline.

This study was originally designed as a phase 2 study but was amended to meet the standards required for it to serve as a pivotal study.

Eligible subjects were adults 18 to 65 years of age with history of migraine with or without aura who experienced >= 15 headache days per month, with >= 8 migraine days per month. Approximately 651 eligible subjects were planned to be randomized with a ratio of 3:2:2 to placebo, AMG 334 70 mg, or AMG 334 140 mg.

3.1.2 Efficacy Variables

3.1.2.1 Primary Endpoint

The primary endpoint for this study was the change in MMD (monthly migraine days) from baseline to the last 4 weeks of the 12-week double-blind treatment phase.

3.1.2.2 Secondary Endpoints

Secondary efficacy endpoints included:

1) Achievement of at least a 50% reduction from baseline in MMD in the last 4 weeks.
2) Change from baseline in monthly acute migraine-specific medication treatment days in the last 4 weeks.
3) Change from baseline in cumulative monthly headache hours in the last 4 weeks.

Subjects used an electronic diary (e-Diary) every day throughout the baseline and double-blind treatment phases to report information about their migraine and nonmigraine headaches and acute medication use. In-clinic visits were scheduled at weeks 2, 4, 8 and 12 during the double-blind treatment phase.

3.1.3 Statistical Analysis Methods

Efficacy analyses were based on the Efficacy Analysis Set, which included subjects who received at least 1 dose of investigational product and completed at least 1 postbaseline monthly e-Diary measurement. Subjects were grouped based on the assigned treatment.

3.1.3.1 Analysis of the Primary Endpoint and Secondary Endpoints

The primary and continuous secondary endpoints were analyzed using a MMRM (generalized linear mixed effects model) including treatment group, baseline value, stratification factors, scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data. For the primary endpoint, the least squares mean (LSM) change from baseline for each treatment group, and the treatment difference, 95% CI, and p-value were reported. For the 50% responder endpoint, a stratified Cochran-Mantel-Haenszel (CMH) test was used after the missing data were imputed as nonresponse.

3.1.3.2 Multiplicity Adjustment

The multiplicity adjustment method was pre-specified and deemed adequate.

A sequential testing procedure, specifically, hierarchical gate-keeping procedures and the Hochberg method, was pre-specified to maintain the 2-sided study-wise type I error at 0.05 between the 2 AMG 334 doses and the primary and secondary endpoints.

The test for the primary endpoint will be initially tested at significance level 0.04 for the 70 mg group, and 0.01 for the 140 mg group, separately.

If the primary endpoint is statistically significant for at least one of the doses, the corresponding secondary endpoints will be tested using the Hochberg method at significance level 0.04 for the AMG 334 70 mg group, and 0.01 for the AMG 334 140 mg group, separately. The Hochberg method is applied when there is more than 1 endpoint in that tier of secondary endpoints to be tested.

3.1.4 Patient Results

3.1.4.1 Patient Disposition

Due to the usage of MMRM model for the primary analysis, any patients with at least 1 post baseline monthly measurement will be included in the efficacy analysis set. The per protocol

analysis set will be the data set where only patients who complete the entire study with all 3 post baseline monthly measurement will be included.

Of the 953 subjects screened, 286 were enrolled but not randomized; 667 subjects were randomized to receive placebo (286 subjects), AMG 334 70 mg (191 subjects), or AMG 334 140 mg (190 subjects). A total of 660 subjects (99.0%) received 1 or more doses of investigational product (AMG 334 or placebo), 637 (95.5%) completed investigational product (ie, completed the week 8 dose), and 23 (3.4%) discontinued investigational product for the following reasons: subject request, ineligibility determined, lost to follow-up, adverse event, and non-compliance.

Overall, 631 subjects (94.6%) completed the study (ie, completed the week 12 assessment); 36 (5.4%) discontinued the study for the following reasons: withdrawal of consent from study, decision from sponsor, and lost to follow-up.

Table 2 Patient Disposition - Study 20120295 (Source: Table 9-2 of sponsor's study report)

		AMG 334		
	Placebo (N = 286) n (%)	70 mg (N = 191) n (%)	140 mg (N = 190) n (%)	Total (N = 667) n (%)
Efficacy analysis set inclusion	281 (98.3)	188 (98.4)	187 (98.4)	656 (98.4)
Efficacy analysis set exclusion	5 (1.7)	3 (1.6)	3 (1.6)	11 (1.6)
Did not receive at least one dose of IP	4 (1.4)	1 (0.5)	2 (1.1)	7 (1.0)
Did not complete at least one post-baseline monthly migraine day measurement during DBTP	5 (1.7)	3 (1.6)	3 (1.6)	11 (1.6)
Safety analysis set inclusion	282 (98.6)	190 (99.5)	188 (98.9)	660 (99.0)
Safety analysis set exclusion	4 (1.4)	1 (0.5)	2 (1.1)	7 (1.0)
Did not receive at least one dose of IP	4 (1.4)	1 (0.5)	2 (1.1)	7 (1.0)
Per protocol analysis set inclusion	262 (91.6)	173 (90.6)	177 (93.2)	612 (91.8)
Per protocol analysis set exclusion	24 (8.4)	18 (9.4)	13 (6.8)	55 (8.2)
Excluded from efficacy analysis set	5 (1.7)	3 (1.6)	3 (1.6)	11 (1.6)
Incomplete data on primary endpoint	19 (6.6)	13 (6.8)	8 (4.2)	40 (6.0)
Did not receive IP at the primary time point per protocol	15 (5.2)	7 (3.7)	6 (3.2)	28 (4.2)
Migraine or headache frequency at baseline did not meet eligibility criteria	4 (1.4)	2 (1.0)	1 (0.5)	7 (1.0)
Important deviation from eligibility criteria	1 (0.3)	0 (0.0)	1 (0.5)	2 (0.3)
Received excluded therapies	3 (1.0)	3 (1.6)	2 (1.1)	8 (1.2)
Important GCP deviations	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)

DBTP = double-blind treatment phase; GCP = good clinical practice; IP= investigational product.
Note: Reasons for exclusion from an analysis set are not mutually exclusive. The per protocol set includes patients who complete the study.

3.1.4.2 Patient Baseline Demographic Characteristics

Of the 667 randomized subjects, 82.8% were women, 94.2% were white, and the mean (minimum to maximum) age was 42.1 (18 to 66) years. The treatment groups were balanced for these baseline demographic characteristics.

Table 3 Patient Baseline Demographic Characteristics - Study 20120295 (Source: Table 9-3 of sponsor's study report)

		AMG 334		
	Placebo (N = 286)	70 mg (N = 191)	140 mg (N = 190)	Total (N = 667)
Sex - n (%)				
Male	60 (21.0)	25 (13.1)	30 (15.8)	115 (17.2)
Female	226 (79.0)	166 (86.9)	160 (84.2)	552 (82.8)
Ethnicity - n (%)				
Hispanic/Latino	9 (3.1)	7 (3.7)	10 (5.3)	26 (3.9)
Not Hispanic/Latino	277 (96.9)	184 (96.3)	180 (94.7)	641 (96.1)
Race - n (%)				
Asian	4 (1.4)	4 (2.1)	0 (0.0)	8 (1.2)
Black or African American	11 (3.8)	10 (5.2)	6 (3.2)	27 (4.0)
White	268 (93.7)	176 (92.1)	184 (96.8)	628 (94.2)
Other	3 (1.0)	1 (0.5)	0 (0.0)	4 (0.6)
Age (years)				
Mean (SD)	42.1 (11.3)	41.4 (11.3)	42.9 (11.1)	42.1 (11.3)
Median	43.0	42.0	45.0	43.0
Q1, Q3	33.0, 50.0	33.0, 50.0	37.0, 50.0	34.0, 50.0
Minimum, Maximum	18, 66	18, 64	18, 64	18, 66
Body mass index (BMI, kg/m²)				
Mean	26.32 (5.07)	26.03 (5.34)	26.02 (5.40)	26.15 (5.24)
Median	25.73	24.98	25.21	25.38
Q1, Q3	22.59, 29.07	21.81, 28.44	21.96, 30.43	22.10, 29.07
Minimum, Maximum	15.8, 39.9	15.6, 40.0	17.1, 40.0	15.6, 40.0

3.1.4.3 Patient Baseline Disease Characteristics

Baseline disease characteristics were consistent with a CM patient population and were balanced across the treatment groups.

The mean (SD) number of monthly migraine days at baseline was 18.22 (4.73), 17.85 (4.39), and 17.78 (4.72) days in the placebo, AMG 334 70-mg, and AMG 334 140-mg groups, respectively.

The mean (SD) number of monthly headache days at baseline was 21.12 (3.93), 20.49 (3.82), and 20.73 (3.83) days, respectively.

Table 4 Patient Baseline Disease Characteristics - Study 20120295 (Source: Table 9-4 of sponsor's study report)

		AMG 334		
	Placebo (N = 286)	70 mg (N = 191)	140 mg (N = 190)	Total (N = 667)
Targeted neurological disease diagnosis - n (%)				
Migraine with aura	124 (43.4)	81 (42.4)	71 (37.4)	276 (41.4)
Migraine without aura	254 (88.8)	166 (86.9)	164 (86.3)	584 (87.6)
Menstrual migraine	45 (15.7)	34 (17.8)	30 (15.8)	109 (16.3)
Depression	46 (16.1)	41 (21.5)	31 (16.3)	118 (17.7)
Anxiety	36 (12.6)	20 (10.5)	27 (14.2)	83 (12.4)
Vertigo	21 (7.3)	9 (4.7)	15 (7.9)	45 (6.7)
Migraine acute headache medications used during baseline phase - n (%)				
None	4 (1.4)	0 (0.0)	2 (1.1)	6 (0.9)
Any acute medication	282 (98.6)	191 (100.0)	188 (98.9)	661 (99.1)
Migraine specific	225 (78.7)	143 (74.9)	149 (78.4)	517 (77.5)
Non-migraine specific	246 (86.0)	167 (87.4)	161 (84.7)	574 (86.1)
Prior treatment with migraine prophylactic medication - n (%)				
Previously never failed prophylactic treatment	86 (30.1)	64 (33.5)	64 (33.7)	214 (32.1)
Failed ≥ 1 prior prophylactic medication class	200 (69.9)	127 (66.5)	126 (66.3)	453 (67.9)
Failed ≥ 2 prior prophylactic medication classes	142 (49.7)	93 (48.7)	92 (48.4)	327 (49.0)
Prior migraine prophylactic medication - n (%)				
Yes	218 (76.2)	138 (72.3)	136 (71.6)	492 (73.8)
No	68 (23.8)	53 (27.7)	54 (28.4)	175 (26.2)
Disease duration of migraine with or without aura (years)				
Mean (SD)	22.21 (12.63)	20.71 (12.83)	21.92 (11.80)	21.70 (12.46)
Median	20.00	19.00	21.00	20.00
Q1, Q3	12.00, 32.00	10.00, 31.00	13.00, 32.00	11.00, 31.40
Minimum, Maximum	0.0, 55.0	0.0, 52.0	1.2, 47.0	0.0, 55.0
Monthly migraine days at baseline				
Mean (SD)	18.22 (4.73)	17.85 (4.39)	17.78 (4.72)	17.99 (4.63)
Median	18.00	17.50	17.63	17.92
Q1, Q3	14.56, 21.78	15.00, 20.28	14.48, 21.00	14.56, 21.00
Minimum, Maximum	5.6, 28.0	8.1, 28.0	8.1, 28.0	5.6, 28.0
Monthly headache days at baseline				
Mean (SD)	21.12 (3.93)	20.49 (3.82)	20.73 (3.83)	20.83 (3.88)
Median	21.00	20.00	20.22	20.53
Q1, Q3	18.00, 24.00	17.23, 23.00	17.73, 23.63	17.82, 23.85
Minimum, Maximum	9.3, 28.0	11.2, 28.0	11.2, 28.0	9.3, 28.0
Monthly acute migraine-specific medication use in days at baseline				
Mean (SD)	9.46 (7.58)	8.76 (7.16)	9.66 (7.02)	9.32 (7.31)
Median	9.00	9.66	10.40	9.33
Q1, Q3	2.00, 15.00	0.00, 14.00	2.07, 15.56	1.87, 15.00
Minimum, Maximum	0.0, 27.0	0.0, 26.0	0.0, 23.6	0.0, 27.0

3.1.5 Efficacy Results

3.1.5.1 Efficacy Results of the Primary Endpoint

The primary analysis of MMD included 656 patients. The results reported by the sponsor were confirmed. There was a statistically significant greater mean reduction in the change in monthly migraine days from baseline to the last 4 weeks of the 12-week double-blind treatment phase for AMG 334 70 mg and AMG 334 140 mg compared with placebo. The difference in least squares mean (LSM) (95% CI) was −2.46 (−3.52, −1.39) days for AMG 334 70 mg vs placebo and −2.45 (−3.52, −1.38) days for AMG 334 140 mg vs placebo ($p < 0.001$ for both).

Table 5 Results from Analysis of MMD – Study 20120295 (Source: Table 10-1 of sponsor's study report)

		AMG 334	
	Placebo (N = 281)	70 mg (N = 188)	140 mg (N = 187)
Baseline			
Mean (SE)	18.24 (0.28)	17.94 (0.32)	17.78 (0.34)
Median	18.06	17.68	17.63
Q1, Q3	14.82, 21.78	15.00, 20.37	14.48, 21.00
Minimum, Maximum	5.6, 28.0	8.1, 28.0	8.1, 28.0
Change from baseline at week 12 (month 3)			
n	267	178	182
Mean (SE)	-4.24 (0.38)	-6.63 (0.45)	-6.53 (0.50)
Median	-3.75	-7.26	-6.52
Q1, Q3	-8.00, 0.07	-11.25, -2.00	-10.81, -1.14
Minimum, Maximum	-21.8, 9.0	-20.3, 10.6	-26.1, 7.0
Adjusted analysis[a]			
LSM estimate	-4.18	-6.64	-6.63
(95% CI of LSM)	(-4.86, -3.50)	(-7.47, -5.81)	(-7.45, -5.80)
Difference in LSM	–	-2.46	-2.45
(95% CI of difference)	–	(-3.52, -1.39)	(-3.51, -1.38)
p-value	–	< 0.001	< 0.001

Adjusted analysis utilizes a generalized linear mixed model which includes treatment, visit, treatment by visit interaction, stratification factors region and medication overuse, and baseline value as covariates and assuming a first-order autoregressive covariance structure. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment.

3.1.5.2 Missing Data and Sensitivity Analysis

About how to handle missing data, pre-specified rules were adequate. The overall missing rate was very low for this study as can be seen from the following table which shows the monthly patient counts for each group.

If less than 14 days of e-Diary out of the 28-day interval is recorded, then the monthly measurement will be set as missing.

If at least 14 days of e-Diary out of 28-day interval is recorded, then the monthly measurement will be prorated to 28-day or computed as average from the available observed days of data.

Table 6 Monthly Patient Counts – Study 20120295 (source: Table 14 -4.4.1.1 from sponsor's study report)

	randomized	Baseline	Month 1	Month 2	Month 3	Month 3 (%)
placebo	286	281	279	271	267	95.02%
70mg	191	188	188	183	178	94.68%
140mg	190	187	187	184	182	97.33%

In the sensitivity analysis on primary and secondary efficacy endpoints during the DBTP, missing continuous efficacy endpoints will be handled using last observation carried forward (LOCF) method, multiple imputation and inverse probability weighting (IPW) generalized estimation equations (GEE) method respectively. Missing dichotomous endpoints will be analyzed using the non-responder imputation (NRI), derived dichotomous data based on multiple imputation (MI) for continuous variable, and inverse probability weighting (IPW) generalized estimation equations (GEE) method respectively.

In MI, all post-baseline missing continuous efficacy endpoints will be imputed resulting in multiple complete sets by the Markov Chain Monte Carlo (MCMC) method. The multiple imputation will be stratified by stratification variables and treatment groups.
If the proportion of missing data in primary endpoint is high (e.g., > 20% for primary analysis at week 12), further analysis will be performed to

- examine the frequency and reason of missing data
- determine if there are any patterns in the missing data
- distinguish true missing values from other unknown values (e.g., due to measurement or sample processing error).

Results for the sensitivity analyses were consistent with those observed for the primary analysis. Results from the per-protocol analysis were consistent with the efficacy analysis.

3.1.5.3 Efficacy Results of the Secondary Endpoints

>= 50% Reduction in Monthly Migraine Days from Baseline

The proportion of subjects with at least a 50% reduction in monthly migraine days from baseline to the last 4 weeks of the 12-week double-blind treatment phase was 23.5%, 39.9%, and 41.2% for the placebo, AMG 334 70-mg, and AMG 334 140-mg groups, respectively; results were statistically significant for each AMG 334 group vs placebo ($p < 0.001$ for both).

Table 7 Responder Rate: >= 50% Reduction in MMD from Baseline, NRI, CMH Test – Study 20120295 (Source: Table 10-5 from sponsor's study report)

		AMG 334	
	Placebo (N = 281)	70 mg (N = 188)	140 mg (N = 187)
Week 12 (month 3)			
N1	281	188	187
Responder - n (%)	66 (23.5)	75 (39.9)	77 (41.2)
Difference in responder (AMG 334 vs Placebo) - %	–	16.4	17.7
Adjusted odds ratio (AMG 334 vs Placebo)[a]	–	2.18	2.34
(95% CI)	–	(1.46, 3.27)	(1.56, 3.51)
p-value	–	< 0.001	< 0.001

NRI = non-responder imputation.
CMH test = Cochran-Mantel-Haenszel test.
The adjusted odds ratios and p-values are obtained from a CMH test after the missing data are imputed as non-response, stratified by stratification factors region and medication overuse. The same analysis is repeated for each visit. P-values for pairwise comparisons are nominal p-values obtained from the CMH test using data including placebo and corresponding AMG 334 dose group only.

Change from Baseline in Monthly Acute Migraine-specific Medication Treatment Days

There was a statistically significant greater mean reduction in the change in monthly acute migraine-specific medication treatment days from baseline to the last 4 weeks of the 12-week double-blind treatment phase for AMG 334 70 mg and AMG 334 140 mg compared with placebo. The difference in LSM (95% CI) was −1.86 (−2.60, −1.13) days for AMG 334 70 mg vs placebo and −2.55 (−3.28, −1.82) days for AMG 334 140 mg vs placebo ($p < 0.001$ for both).

Change from Baseline in Cumulative Monthly Headache Hours

There was no statistically significant mean difference.

3.2 Evaluation of Efficacy - Study 20120296

3.2.1 Description of the Study

This study had its first subject enrolled on 17 July 2015, last subject last visit on 5 September 2016, and the study report was created on the date of 20 February 2017.

The primary objective was to evaluate the effect of AMG 334 compared to placebo on the change from baseline in mean monthly migraine days in subjects with EM (Episodic Migraine).

This was a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study of subjects with EM. The study was conducted at 121 centers in North America (US and Canada), Europe (Austria, Belgium, Czech Republic, Finland, Germany, Poland, Slovakia, Sweden, the UK), and Turkey. Eligible subjects identified in the screening phase commenced a 4-week baseline phase. After the baseline period, eligible subjects were randomized in a 1:1:1 ratio to receive placebo, AMG 334 70 mg, or AMG 334 140 mg QM (every 4 weeks) by SC injection for the duration of the 24-week double-blind treatment phase. Randomization was stratified by region (North America or 'Other' [Europe and Turkey]) and treatment status with migraine prophylactic medication (prior only, current, or neither prior nor current).

Eligible subjects were adults 18 to 65 years of age with history of migraine with or without aura for ≥ 12 months who experienced >= 4 to < 15 migraine days per month with < 15 headache days per month.

Approximately 852 eligible subjects were planned to be randomized, in a 1:1:1 ratio, to placebo, AMG 334 70 mg, or AMG 334 140 mg, with a planned number of 284 subjects in each treatment group.

3.2.2 Efficacy Variables

3.2.2.1 Primary Endpoint

The primary endpoint for this study was the change in MMD (monthly migraine days) from baseline to the last 3 months of the 24-week double-blind treatment phase.

3.2.2.2 Secondary Endpoints

1) Achievement of at least a 50% reduction from baseline in mean monthly migraine days over the last 3 months (months 4, 5, and 6) of the 24-week double-blind treatment phase

2) Change from baseline in mean monthly acute migraine-specific medication treatment days over the last 3 months (months 4, 5, and 6) of the 24-week double-blind treatment phase

3) Change from baseline in mean monthly average physical impairment domain scores over the last 3 months (months 4, 5, and 6) of the double-blind treatment phase as measured by the MPFID (Migraine Physical Function Impact Diary)

4) Change from baseline in mean monthly average impact on everyday activities domain scores over the last 3 months (months 4, 5, and 6) of the double-blind treatment phase as measured by the MPFID

Subjects used an e-Diary throughout the baseline and treatment phases to report information about their migraine and nonmigraine headaches and acute medication use. In-clinic visits were scheduled at weeks 2, 4, 8, 12, 16, 20, and 24 during the double-blind treatment phase.

3.2.3 Statistical Analysis Methods

Efficacy analyses and analyses of PROs were based on the Efficacy Analysis Set, which included subjects who received at least 1 dose of investigational product and had at least 1 change from baseline measurement in monthly migraine days during the double-blind treatment phase. For efficacy analyses, subjects were analyzed based on their randomized treatment, regardless of the treatment received.

3.2.3.1 Analysis of the Primary Endpoint and Secondary Endpoints

The primary and continuous secondary endpoints were analyzed using a MMRM (generalized linear mixed effects model) including treatment group, baseline value, stratification factors, scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data. For the primary endpoint, the least squares mean (LSM) change from baseline for each treatment group, and the treatment difference, 95% CI, and p-value were reported. For the 50% responder endpoint, a stratified Cochran-Mantel-Haenszel (CMH) test was used after the missing data were imputed as nonresponse.

3.2.3.2 Multiplicity Adjustment

The multiplicity adjustment method was pre-specified and deemed adequate.

A sequential testing procedure, specifically, hierarchical gate-keeping procedures and the Hochberg method, was pre-specified to maintain the 2-sided study-wise type I error at 0.05 between the 2 AMG 334 doses and the primary and secondary endpoints.

The test for the primary endpoint will be initially tested at significance level 0.04 for the 70 mg group, and 0.01 for the 140 mg group, separately.

If the primary endpoint is statistically significant for at least one of the doses, the corresponding secondary endpoints will be tested using the Hochberg method at significance level 0.04 for the AMG 334 70 mg group, and 0.01 for the AMG 334 140 mg group, separately. The Hochberg method is applied when there is more than 1 endpoint in that tier of secondary endpoints to be tested.

3.2.4 Patient Results

3.2.4.1 Patient Disposition

Due to the usage of MMRM model for the primary analysis, any patients with at least 1 post baseline monthly measurement will be included in the efficacy analysis set. The per protocol analysis set will be the data set where only patients who complete the entire study with all 3 post baseline monthly measurement will be included.

Of the 1492 subjects screened, 955 subjects were randomized to receive placebo (319 subjects), AMG 334 70 mg (317 subjects), or AMG 334 140 mg (319 subjects).

In the double-blind treatment phase, 952 subjects (99.7%) received 1 or more doses of investigational product, 865 (90.6%) completed investigational product (i.e., completed the week 20 dose or investigational product temporarily withheld at week 20 and continued to receive investigational product during active treatment phase), and 87 (9.1%) discontinued investigational product for the following reasons: subject request (no further information available) (4.7%), adverse event (2.1%), lost to follow-up (1.2%), pregnancy (0.3%), non-compliance (0.3%), ineligibility determined (0.2%), protocol-specified criteria (0.2%), and decision by sponsor (0.1%).

Overall, 858 subjects (89.8%) completed the double-blind treatment phase of the study (ie, completed the week 24 assessment), and 97 (10.2%) discontinued the study for the following reasons: subject request (8.0%), lost to follow-up (1.9%), decision by sponsor (0.3%).
A total of 946 subjects was included in the Efficacy Analysis Set.

Table 8 Patient Disposition - Study 20120296 (Source: Table 9-2 of sponsor's study report)

		AMG 334		
	Placebo (N = 319) n (%)	70 mg (N = 317) n (%)	140 mg (N = 319) n (%)	Total (N = 955) n (%)
Efficacy analysis set inclusion	316 (99.1)	312 (98.4)	318 (99.7)	946 (99.1)
Efficacy analysis set exclusion	3 (0.9)	5 (1.6)	1 (0.3)	9 (0.9)
Did not receive at least one dose of IP	0 (0.0)	3 (0.9)	0 (0.0)	3 (0.3)
Did not have at least one change from baseline measurement in monthly migraine day during DBTP	3 (0.9)	5 (1.6)	1 (0.3)	9 (0.9)
Safety analysis set inclusion	319 (100.0)	314 (99.1)	319 (100.0)	952 (99.7)
Safety analysis set exclusion				
Did not receive at least one dose of IP	0 (0.0)	3 (0.9)	0 (0.0)	3 (0.3)
Active treatment phase safety analysis set inclusion	277 (86.8)	280 (88.3)	287 (90.0)	844 (88.4)
Active treatment phase safety analysis set exclusion				
Did not receive at least one dose of ATP IP	42 (13.2)	37 (11.7)	32 (10.0)	111 (11.6)
Per protocol analysis set inclusion	262 (82.1)	273 (86.1)	273 (85.6)	808 (84.6)

Per protocol analysis set exclusion	57 (17.9)	44 (13.9)	46 (14.4)	147 (15.4)
Excluded from efficacy analysis set	3 (0.9)	5 (1.6)	1 (0.3)	9 (0.9)
Incomplete data on primary endpoint	39 (12.2)	33 (10.4)	35 (11.0)	107 (11.2)
Did not receive IP at the primary time point per protocol	39 (12.2)	31 (9.8)	28 (8.8)	98 (10.3)
Migraine or headache frequency at baseline did not meet eligibility criteria	1 (0.3)	2 (0.6)	2 (0.6)	5 (0.5)
Important deviation from eligibility criteria	4 (1.3)	1 (0.3)	3 (0.9)	8 (0.8)
Received excluded therapies	7 (2.2)	6 (1.9)	3 (0.9)	16 (1.7)
Important GCP deviations	1 (0.3)	2 (0.6)	1 (0.3)	4 (0.4)

Note: Reasons for exclusion from an analysis set are not mutually exclusive. The per protocol set includes patients who complete the study.
ATP = Active treatment phase; DBTP = Double-blind treatment phase; GCP = good clinical practice;
IP = Investigation product.
Note: For the ATP, subjects are presented by their randomization group in the DBTP; the subjects' allocation in the ATP remains blinded.

3.2.4.2 Patient Baseline Demographic Characteristics

Of the 955 randomized subjects, 85.2% were women, 89.1% were white, and the mean (minimum to maximum) age was 40.9 (18 to 65) years. The treatment groups were balanced for these baseline demographic characteristics.

Table 9 Patient Baseline Demographic Characteristics - Study 20120296 (Source: Table 9-3 of sponsor's study report)

		AMG 334		
	Placebo (N = 319)	70 mg (N = 317)	140 mg (N = 319)	Total (N = 955)
Sex - n (%)				
Male	45 (14.1)	49 (15.5)	47 (14.7)	141 (14.8)
Female	274 (85.9)	268 (84.5)	272 (85.3)	814 (85.2)
Ethnicity - n (%)				
Hispanic/Latino	32 (10.0)	26 (8.2)	22 (6.9)	80 (8.4)
Not Hispanic/Latino	287 (90.0)	291 (91.8)	297 (93.1)	875 (91.6)
Race - n (%)				
American Indian or Alaska Native	2 (0.6)	0 (0.0)	1 (0.3)	3 (0.3)
Asian	8 (2.5)	5 (1.6)	4 (1.3)	17 (1.8)
Black or African American	24 (7.5)	24 (7.6)	18 (5.6)	66 (6.9)
Multiple	2 (0.6)	1 (0.3)	0 (0.0)	3 (0.3)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
White	277 (86.8)	281 (88.6)	293 (91.8)	851 (89.1)
Other	6 (1.9)	6 (1.9)	2 (0.6)	14 (1.5)
Age (years)				
Mean	41.3	41.1	40.4	40.9
SD	11.2	11.3	11.1	11.2
Median	41.0	42.0	41.0	42.0
Q1, Q3	33.0, 49.0	33.0, 50.0	31.0, 49.0	32.0, 49.0

Min, Max	18, 65	18, 63	19, 65	18, 65
Age group - n (%)				
18 - 64 years	317 (99.4)	317 (100.0)	317 (99.4)	951 (99.6)
65 - 74 years	2 (0.6)	0 (0.0)	2 (0.6)	4 (0.4)
Body mass index (BMI, kg/m^2)				
Mean	27.14	27.28	27.03	27.15
SD	6.31	5.85	6.22	6.13
Median	25.64	26.56	25.52	25.87
Q1, Q3	22.79, 30.21	22.55, 30.48	22.27, 30.68	22.63, 30.32
Min, Max	16.6, 53.0	16.7, 48.4	18.0, 54.7	16.6, 54.7

3.2.4.3 Patient Baseline Disease Characteristics

Baseline disease characteristics were consistent with a EM patient population and were balanced across the treatment groups.
The mean (SD) number of monthly migraine days at baseline was 8.23 (2.51), 8.29 (2.47), and 8.34 (2.48) days in the placebo, AMG 334 70-mg, and AMG 334 140-mg groups, respectively. The mean (SD) number of monthly headache days at baseline was 9.26 (2.58), 9.07 (2.61), and 9.28 (2.54) days, respectively.

Table 10 Patient Baseline Disease Characteristics - Study 20120296 (Source: Table 9-4 of sponsor's study report)

		AMG 334		
	Placebo (N = 319)	70 mg (N = 317)	140 mg (N = 319)	Total (N = 955)
Monthly migraine days at baseline				
n	318	316	319	953
Mean	8.23	8.29	8.34	8.29
SD	2.51	2.47	2.48	2.48
Median	8.00	8.00	8.00	8.00
Q1, Q3	6.00, 10.00	6.40, 10.00	6.76, 10.00	6.32, 10.00
Min, Max	3.0, 14.9	2.7, 14.5	3.2, 16.0	2.7, 16.0
Monthly headache days at baseline				
n	318	316	319	953
Mean	9.26	9.07	9.28	9.20
SD	2.58	2.61	2.54	2.58
Median	9.00	9.00	9.00	9.00
Q1, Q3	7.23, 11.00	7.00, 10.84	7.2	7.2
Min, Max	4.0, 15.9	2.7, 15.4	4.0, 17.0	2.7, 17.0
Monthly acute migraine-specific medication use in days at baseline				
n	318	316	319	953
Mean	3.41	3.21	3.41	3.34
SD	3.43	3.39	3.48	3.43
Median	3.15	3.00	3.00	3.00
Q1, Q3	0.00, 6.00	0.00, 5.79	0.00, 6.00	0.00, 6.00
Min, Max	0.0, 12.0	0.0, 14.0	0.0, 12.6	0.0, 14.0
Monthly MPFID impact on everyday activities scores at baseline[b]				

n	318	316	319	953
Mean	13.66	13.99	13.05	13.56
SD	9.07	8.89	8.25	8.74
Median	11.85	11.63	11.03	11.66
Q1, Q3	6.48, 18.37	8.08, 17.17	7.14, 17.28	7.36, 17.97
Min, Max	0.0, 49.4	0.1, 52.3	0.0, 46.2	0.0, 52.3
Monthly MPFID physical impairment scores at baseline[b]				
n	318	316	319	953
Mean	12.24	12.57	12.03	12.28
SD	9.43	9.64	8.99	9.35
Median	10.16	10.16	10.30	10.18
Q1, Q3	5.31, 16.55	5.93, 15.58	5.18, 16.43	5.59, 16.29
Min, Max	0.3, 51.2	0.0, 62.2	0.0, 47.3	0.0, 62.2

Impact on Everyday Activities (EA) domain score and Physical Impairment (PI) domain score ranges from 0 to 100. Higher scores represent greater impact of migraine (ie, higher burden).

3.2.5 Efficacy Results

3.2.5.1 Efficacy Results of the Primary Endpoint

The primary analysis of MMD included 946 patients. The results reported by the sponsor were confirmed.

There was a statistically significant greater mean reduction in the change in mean monthly migraine days from baseline to the last 3 months (months 4, 5, and 6) of the 24-week double-blind treatment phase for AMG 334 70 mg and AMG 334 140 mg as compared with placebo. The difference in least squares mean (LSMs) (95% CI) was -1.40 (–1.88, –0.92) days for AMG 334 70 mg vs placebo and –1.85 (–2.33, –1.37) days for AMG 334 140 mg versus placebo ($p < 0.001$ for both).

Table 11 Results from Analysis of MMD – Study 20120296 (Source: Table 10-1 of sponsor's study report)

		AMG 334	
	Placebo (N = 316)	70 mg (N = 312)	140 mg (N = 318)
Baseline			
n	316	312	318
Mean (SD)	8.25 (2.51)	8.31 (2.45)	8.33 (2.48)
Median	8.00	8.00	8.00
Q1, Q3	6.00, 10.00	6.40, 10.00	6.76, 10.00
Minimum, Maximum	3.0, 14.9	3.5, 14.5	3.2, 16.0
Mean over month 4, 5 and 6			
n	289	296	302
Mean (SE)	6.33 (0.22)	4.95 (0.21)	4.48 (0.18)
Median	5.71	4.31	3.82
Q1, Q3	3.59, 8.49	2.14, 7.13	2.08, 6.52
Minimum, Maximum	0.0, 20.7	0.0, 19.0	0.0, 15.6

Change from baseline in mean over month 4, 5 and 6			
n	289	296	302
Mean (SE)	-1.95 (0.22)	-3.36 (0.21)	-3.83 (0.18)
Median	-1.95	-3.65	-3.96
Q1, Q3	-4.26, 0.20	-5.66, -1.50	-6.09, -1.86
Minimum, Maximum	-12.0, 12.4	-13.4, 9.0	-13.0, 6.6
Adjusted analysis[a] [b]			
LSM estimates	-1.83	-3.23	-3.67
(95% CI of LSM)	(-2.18, -1.48)	(-3.58, -2.88)	(-4.02, -3.33)
Difference in LSMs	--	-1.40	-1.85
(95% CI of difference)	--	(-1.88, -0.92)	(-2.33, -1.37)
p-value	--	< 0.001	< 0.001

a Adjusted analysis utilizes a generalized linear mixed model which includes treatment, visit, treatment by visit interaction, stratification factors region and prior/current treatment with migraine prophylactic medication, and baseline value as covariates and assuming a first-order autoregressive covariance structure. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment.
b Adjusted analysis results for mean over month 4, 5, and 6 are obtained from the same generalized linear mixed model using contrasts.

3.2.5.2 Missing Data and Sensitivity Analyses

About how to handle missing data, pre-specified rules were adequate. The overall missing rate was very low for this study as can be seen from the following table which shows the monthly patient counts for each group.

If less than 14 days of e-Diary out of the 28-day interval is recorded, then the monthly measurement will be set as missing. If at least 14 days of e-Diary out of 28-day interval is recorded, then the monthly measurement will be prorated to 28-day or computed as average from the available observed days of data.

Table 12 Monthly Patient Counts – Study 20120296 (source: Table 14 -4.4.1.1 from sponsor's study report)

	randomized	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 6 (%)
placebo	319	316	316	308	299	288	284	283	89.56%
70mg	317	312	311	306	301	296	293	284	91.03%
140mg	319	318	318	313	304	299	296	287	90.25%

In the sensitivity analysis on primary and secondary efficacy endpoints during the DBTP, missing continuous efficacy endpoints will be handled using last observation carried forward (LOCF) method, multiple imputation and inverse probability weighting (IPW) generalized estimation equations (GEE) method respectively. Missing dichotomous endpoints will be analyzed using the non-responder imputation (NRI), derived dichotomous data based on multiple imputation (MI) for continuous variable, and inverse probability weighting (IPW) generalized estimation equations (GEE) method respectively.

In MI, all post-baseline missing continuous efficacy endpoints will be imputed resulting in multiple complete sets by the Markov Chain Monte Carlo (MCMC) method. The multiple imputation will be stratified by stratification variables and treatment groups.

If the proportion of missing data in primary endpoint is high (e.g., > 20% for primary analysis at week 12), further analysis will be performed to
• examine the frequency and reason of missing data
• determine if there are any patterns in the missing data
• distinguish true missing values from other unknown values (e.g., due to measurement or sample processing error).

Results for the sensitivity analyses were consistent with those observed for the primary analysis.

Results from the per-protocol analysis were consistent with the efficacy analysis.

3.2.5.3 Efficacy Results of the Secondary Endpoints

The results presented by the sponsor has been confirmed.

The COA related endpoints did not show any statistically significant result.

>= 50% Reduction in Monthly Migraine Days from Baseline

The proportion of subjects who achieved at least a 50% reduction in mean monthly migraine days from baseline to the last 3 months (months 4, 5, and 6) of the 24-week double-blind treatment phase was 26.6%, 43.3%, and 50.0% for the placebo, AMG 334 70-mg, and AMG 334 140-mg groups, respectively; results were statistically significant for each AMG 334 group vs placebo ($p < 0.001$ for both).

Table 13 Responder Rate: >= 50% Reduction in MMD from Baseline, NRI, CMH Test – Study 20120296 (Source: Table 10-4 from sponsor's study report)

	Placebo (N = 316)	AMG 334	
		70 mg (N = 312)	140 mg (N = 318)
Months 4, 5, and 6			
N1	316	312	318
Responder - n (%)	84 (26.6)	135 (43.3)	159 (50.0)
Difference in responder (AMG 334 vs Placebo) - %	--	16.7	23.4
Common odds ratio (AMG 334 vs Placebo)[a]	–	2.13	2.81
(95% CI)	–	(1.52, 2.98)	(2.01, 3.94)
p-value	–	< 0.001	< 0.001

NRI = non-responder imputation.

CMH test = Cochran-Mantel-Haenszel test.
[a] The common odds ratios and p-values are obtained from a CMH test, stratified by stratification factors region and prior/current treatment with migraine prophylactic medication. The same analysis is repeated for each visit. P-values for pairwise comparisons are nominal p-values obtained from the CMH test using data including placebo and corresponding AMG 334 dose group only. Breslow-day test for homogeneity of the odds ratio cross strata for responder derived from the mean over month 4, 5, and 6 is 0.84 for 70 mg and 0.82 for 140 mg.
The pairwise comparisons compare each AMG 334 group vs placebo (reference group).

Change from Baseline in Monthly Acute Migraine-specific Medication Treatment Days

There was a statistically significant greater mean reduction in mean monthly acute migraine-specific medication treatment days from baseline to the last 3 months (months 4, 5, and 6) of the 24-week double-blind treatment phase for AMG 334 70 mg and AMG 334 140 mg compared with placebo. The difference in LSMs (95% CI) was -0.94 (-1.23, –0.64) days for AMG 334 70 mg vs placebo and –1.42 (–1.71, –1.12) days for AMG 334 140 mg vs placebo ($p < 0.001$ for both).

Table 14 Change from Baseline in Monthly Acute Migraine-specific Medication Treatment Days- Study 20120296 (Source: Table 10-5 from sponsor's study report)

	Placebo (N = 316)	AMG 334	
		70 mg (N = 312)	140 mg (N = 318)
Baseline			
n	316	312	318
Mean (SD)	3.43 (3.43)	3.24 (3.40)	3.42 (3.48)
Median	3.29	3.00	3.00
Q1, Q3	0.00, 6.00	0.00, 5.87	0.00, 6.00
Minimum, Maximum	0.0, 12.0	0.0, 14.0	0.0, 12.6
Mean over month 4, 5 and 6			
n	289	296	302
Mean (SE)	3.31 (0.22)	2.25 (0.17)	1.75 (0.14)
Median	2.33	1.00	0.35
Q1, Q3	0.00, 5.67	0.00, 3.69	0.00, 3.05
Minimum, Maximum	0.0, 14.2	0.0, 13.4	0.0, 11.8
Change from baseline at Months 4, 5, and 6			
n	289	296	302
Mean (SE)	-0.26 (0.14)	-1.12 (0.13)	-1.64 (0.13)
Median	0.00	0.00	-0.38
Q1, Q3	-1.35, 0.22	-2.45, 0.00	-3.43, 0.00
Minimum, Maximum	-8.3, 7.5	-7.8, 6.3	-9.3, 2.9
Adjusted analysis[a,b]			
LSM estimate	-0.20	-1.13	-1.61
(95% CI of LSM)	(-0.41, 0.02)	(-1.34, -0.92)	(-1.83, -1.40)

Difference in LSM	--	-0.94	-1.42
(95% CI of difference)	--	(-1.23, -0.64)	(-1.71, -1.12)
p-value	--	< 0.001	< 0.001

a Adjusted analysis utilizes a generalized linear mixed model which includes treatment, visit, treatment by visit interaction, stratification factors region and prior/current treatment with migraine prophylactic medication, and baseline value as covariates and assuming a first-order autoregressive covariance structure. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment.
b Adjusted analysis results for mean over month 4, 5, and 6 are obtained from the same generalized linear mixed model using contrasts.

Change from Baseline in Mean Monthly Average Physical Impairment Domain Scores as Measured by MPFID

The analysis presented in the submission did not follow the prespecified method.

(b) (4)

From the presented analysis result one can deduce the nominal p-value for the required test would **not** be significant, since the 95% confidence interval for the estimated score change did not cover the value -5, as you can see from the sponsor's result as the following: The difference in LSMs (95% CI) was –1.86 **(–2.95, –0.77)** for AMG 334 70 mg vs placebo and –2.43 **(-3.51, -1.35)** for AMG 334 140 mg vs placebo.

Change from Baseline in Mean Monthly Average Impact on Everyday Activities Score as Measured by MPFID

The analysis presented in the submission did not follow the prespecified method.

(b) (4)

From the presented analysis result one can deduce the nominal p-value for the required test would **not** be significant, since the 95% confidence interval for the estimated score change did not cover the value -5, as you can see from the sponsor's result as the following: The difference in LSMs (95% CI) was -2.22 **(–3.28, –1.16)** for AMG 334 70 mg vs placebo and –2.57 **(-3.62, -1.51)** for AMG 334 140 mg vs placebo.

3.3 Evaluation of Efficacy - Study 20120297

3.3.1 Description of the Study

This study had its first subject enrolled on 20 July 2015, last subject last visit on 11 July 2016 And the study report was created on the date of 21 December 2016.

The primary objective was to evaluate the effect of AMG 334 compared to placebo on the change from baseline in mean monthly migraine days in subjects with EM (Episodic Migraine).

This was a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study of subjects with EM. The study was conducted at 69 centers in North America (US and Canada), Europe (Denmark, France, Greece, Portugal, Spain, and Switzerland), and the Russian Federation. Eligible subjects identified in the screening phase commenced a 4-week baseline phase. After the baseline period, eligible subjects were randomized in a 1:1 ratio to receive placebo, AMG 334 70 mg QM (every 4 weeks) by SC injection for the duration of the 12-week double-blind treatment phase. Randomization was stratified by region (North America or 'Other' [Europe and Russia]) and treatment status with migraine prophylactic medication (prior only, current, or neither prior nor current).

Eligible subjects were adults 18 to 65 years of age with history of migraine with or without aura for ≥ 12 months who experienced >= 4 to < 15 migraine days per month with < 15 headache days per month, on average across the 3 months prior to screening.

Approximately 540 eligible subjects were planned to be randomized, in a 1:1 ratio, to placebo, AMG 334 70 mg, with a planned number of 270 subjects in each treatment group.

3.3.2 Efficacy Variables

3.3.2.1 Primary Endpoint

The primary endpoint for this study was the change in MMD (monthly migraine days) from baseline to the last month of the 12-week double-blind treatment phase.

3.3.2.2 Secondary Endpoints

1) Achievement of at least a 50% reduction from baseline in mean monthly migraine days over the last month of the 12-week double-blind treatment phase

2) Change from baseline in mean monthly acute migraine-specific medication treatment days over the last month of the 12-week double-blind treatment phase

3) Change from baseline in mean monthly average physical impairment domain scores over the last month of the 12-week double-blind treatment phase as measured by the MPFID

4) Change from baseline in mean monthly average impact on everyday activities domain scores over the last month of the 12-week double-blind treatment phase as measured by the MPFID

Subjects used an e-Diary throughout the baseline and treatment phases to report information about their migraine and nonmigraine headaches and acute medication use. In-clinic visits were scheduled at weeks 2, 4, 8, and 12 during the double-blind treatment phase.

3.3.3 Statistical Analysis Methods

Efficacy analyses and analyses of PROs were based on the Efficacy Analysis Set, which included subjects who received at least 1 dose of investigational product and had at least 1 change from baseline measurement in monthly migraine days during the double-blind treatment phase. For efficacy analyses, subjects were analyzed based on their randomized treatment, regardless of the treatment received.

3.3.3.1 Analysis of the Primary Endpoint and Secondary Endpoints

The primary and continuous secondary endpoints were analyzed using a MMRM (generalized linear mixed effects model) including treatment group, baseline value, stratification factors, scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data. For the primary endpoint, the least squares mean (LSM) change from baseline for each treatment group, and the treatment difference, 95% CI, and p-value were reported. Dichotomous efficacy endpoints were analyzed using a stratified CMH test after missing data were imputed as nonresponse.

3.3.3.2 Multiplicity Adjustment

The multiplicity adjustment method was pre-specified and deemed adequate but did not have much impact for the study conclusion in this case since the study result produced p-values either very small as <0.001 or very large as > 0.05 for each of the hypothesis test.

A sequential testing procedure, specifically, hierarchical gate-keeping procedures and the Hochberg method, was used to maintain the 2-sided study-wise type I error at 0.05 the primary and secondary endpoints.

3.3.4 Patient Results

3.3.4.1 Patient Disposition

Due to the usage of MMRM model for the primary analysis, any patients with at least 1 post baseline monthly measurement will be included in the efficacy analysis set. The per protocol analysis set will be the data set where only patients who complete the entire study with all 3 post baseline monthly measurement will be included.

Of the 887 subjects screened, 577 subjects were randomized to receive placebo (291 subjects) or AMG 334 70 mg (286 subjects).

In the double-blind treatment phase, a total of 572 subjects (99.1%) received 1 or more doses of investigational product (289 subjects [99.3%] received placebo and 283 subjects [99.0%] received AMG 334), 544 (94.3%) completed investigational product (ie, completed the week 8 dose [541 subjects] or temporarily withholding investigational product at week 8 and continuing to receive investigational product during open-label treatment phase [3 subjects], and 28 (4.9%) discontinued investigational product for the following reasons: subject request, lost to follow-up, adverse event, ineligibility determined, and non-compliance. Overall, 546 subjects (94.6%) completed the double-blind treatment phase of the study (ie, completed the week 12 follow-up assessment), and 31 (5.4%) discontinued the double-blind treatment phase of the study for the following reasons: subject request, lost to follow-up, and decision by sponsor.

A total of 570 subjects was included in the Efficacy Analysis Set.

Table 15 Patient Disposition - Study 20120297 (Source: Table 9-2 of sponsor's study report)

	Placebo (N = 291) n (%)	AMG 334 70 mg (N = 286) n (%)	Total (N = 577) n (%)
Efficacy analysis set inclusion	288 (99.0)	282 (98.6)	570 (98.8)
Efficacy analysis set exclusion	3 (1.0)	4 (1.4)	7 (1.2)
Did not receive at least one dose of IP	2 (0.7)	3 (1.0)	5 (0.9)
Did not have at least one change from baseline measurement in monthly migraine day during DBTP	3 (1.0)	3 (1.0)	6 (1.0)
Safety analysis set inclusion	289 (99.3)	283 (99.0)	572 (99.1)
Safety analysis set exclusion	2 (0.7)	3 (1.0)	5 (0.9)
Did not receive at least one dose of IP	2 (0.7)	3 (1.0)	5 (0.9)
Open label treatment phase set inclusion	270 (92.8)	268 (93.7)	538 (93.2)
Open label treatment phase set exclusion	21 (7.2)	18 (6.3)	39 (6.8)
Did not receive at least one dose of OLTP IP	21 (7.2)	18 (6.3)	39 (6.8)
Per protocol analysis set inclusion	260 (89.3)	262 (91.6)	522 (90.5)
Per protocol analysis set exclusion	31 (10.7)	24 (8.4)	55 (9.5)
Excluded from efficacy analysis set	3 (1.0)	4 (1.4)	7 (1.2)
Incomplete data on primary endpoint	21 (7.2)	18 (6.3)	39 (6.8)
Did not receive IP at the primary time point per protocol	19 (6.5)	17 (5.9)	36 (6.2)
Migraine or headache frequency at baseline did not meet eligibility criteria	5 (1.7)	3 (1.0)	8 (1.4)
Important deviation from eligibility criteria	1 (0.3)	0 (0.0)	1 (0.2)
Received excluded therapies	4 (1.4)	2 (0.7)	6 (1.0)
Important GCP deviations	0 (0.0)	0 (0.0)	0 (0.0)

DBTP = double-blind treatment phase; GCP = good clinical practice; IP = investigational product; OLTP = open-label treatment phase.
Reasons for exclusion from an analysis set are not mutually exclusive.
The per protocol set includes patients who complete the study.

3.3.4.2 Patient Baseline Demographic Characteristics

Of the 577 randomized subjects, 85.3% were women, 89.8% were white, and the mean (minimum to maximum) age was 42.3 (18 to 65) years.

The treatment groups were balanced for these baseline demographic characteristics.

Table 16 Patient Baseline Demographic Characteristics - Study 20120297 (Source: Table 9-3 of sponsor's study report)

	Placebo (N = 291)	AMG 334 70 mg (N = 286)	Total (N = 577)
Sex – n (%)			
Male	44 (15.1)	41 (14.3)	85 (14.7)
Female	247 (84.9)	245 (85.7)	492 (85.3)
Ethnicity – n (%)			
Hispanic/Latino	34 (11.7)	23 (8.0)	57 (9.9)
Not Hispanic/Latino	257 (88.3)	263 (92.0)	520 (90.1)
Race – n (%)			
Asian	0 (0.0)	2 (0.7)	2 (0.3)
Black or African American	27 (9.3)	24 (8.4)	51 (8.8)
Multiple	2 (0.7)	1 (0.3)	3 (0.5)
Native Hawaiian or Other Pacific Islander	1 (0.3)	0 (0.0)	1 (0.2)
White	259 (89.0)	259 (90.6)	518 (89.8)
Other	2 (0.7)	0 (0.0)	2 (0.3)
Age (years)			
Mean (SD)	42.2 (11.5)	42.3 (11.4)	42.3 (11.4)
Median	43.0	43.5	43.0
Q1, Q3	32.0, 51.0	35.0, 50.0	33.0, 51.0
Minimum, Maximum	18, 65	19, 65	18, 65
Body mass index (BMI, kg/m^2)			
N	288	284	572
Mean (SD)	27.37 (6.12)	27.37 (6.32)	27.37 (6.21)
Median	25.77	26.25	25.98
Q1, Q3	22.93, 31.14	22.76, 30.99	22.83, 31.13
Minimum, Maximum	16.0, 49.3	16.6, 54.7	16.0, 54.7

3.3.4.3 Patient Baseline Disease Characteristics

Baseline disease characteristics were consistent with a EM patient population and were balanced across the treatment groups.

The mean (SD) number of monthly migraine days at baseline was 8.38 (2.60) and 8.14 (2.65) days in the placebo and AMG 334 70-mg groups, respectively. The mean (SD) number of monthly headache days at baseline was 9.30 (2.72) and 9.08 (2.68) days, respectively. The mean (SD) disease duration of migraine with or without aura was 20.03 (12.08) and 21.70 (12.62) years, respectively. Mean (SD) monthly acute migraine-specific medication use at baseline was 3.42 (3.59) and 3.70 (3.64) days, respectively.

Mean monthly MPFID scores were also collected at baseline. Domain scores range from 0 to 100 with higher scores representing greater impact of migraine (ie, higher burden). Mean (SD) monthly MPFID impact on everyday activity scores at baseline were 13.16 (8.86) in the placebo group and 12.64 (8.63) in the AMG 334 70-mg group, while mean (SD) monthly MPFID physical impairment scores at baseline were 11.51 (9.23) and 10.82 (9.13), respectively.

Table 17 Patient Baseline Disease Characteristics - Study 20120297 (Source: Table 9-4 of sponsor's study report)

	Placebo (N = 291)	AMG 334 70 mg (N = 286)	Total (N = 577)
Monthly migraine days at baseline			
Mean (SD)	8.38 (2.60)	8.14 (2.65)	8.26 (2.62)
Median	8.24	8.00	8.00
Q1, Q3	6.46, 10.00	6.32, 9.66	6.40, 10.00
Min, Max	2.8, 16.6	0.0, 16.3	0.0, 16.6
Monthly headache days at baseline			
Mean (SD)	9.30 (2.72)	9.08 (2.68)	9.19 (2.70)
Median	9.00	9.00	9.00
Q1, Q3	7.20, 11.00	7.00, 11.00	7.20, 11.00
Min, Max	2.8, 18.7	2.9, 16.3	2.8, 18.7
Monthly acute migraine-specific medication use in days at baseline			
Mean (SD)	3.42 (3.59)	3.70 (3.64)	3.56 (3.62)
Median	2.55	3.45	2.80
Q1, Q3	0.00, 6.76	0.00, 6.79	0.00, 6.79
Min, Max	0.0, 12.4	0.0, 13.5	0.0, 13.5
Monthly MPFID impact on everyday activities scores at baseline			
Mean (SD)	13.16 (8.86)	12.64 (8.63)	12.90 (8.74)
Median	11.07	10.46	10.71
Q1, Q3	6.55, 17.73	6.83, 16.18	6.65, 17.12
Min, Max	0.0, 53.7	0.2, 48.3	0.0, 53.7
Monthly MPFID physical impairment scores at baseline			
Mean (SD)	11.51 (9.23)	10.82 (9.13)	11.17 (9.18)
Median	8.75	8.61	8.75
Q1, Q3	4.82, 16.07	4.12, 14.64	4.31, 15.58
Min, Max	0.0, 53.8	0.0, 53.2	0.0, 53.8

Randomization was stratified by region and treatment status with migraine prophylactic medication. Of the randomized subjects, 338 (58.6%) were in North America and 239 subjects (41.4%) were in other regions.

3.3.5 Efficacy Results

3.3.5.1 Efficacy Results of the Primary Endpoint

The primary analysis of MMD included 570 patients. The results reported by the sponsor were confirmed. There was a statistically significant greater mean reduction in the change in mean monthly migraine days from baseline to the last month of the 12-week double-blind treatment phase for AMG 334 70 mg as compared with placebo. The difference in least squares mean (LSMs) (95% CI) was -1.04 (–1.61, –0.47) days for AMG 334 70 mg vs placebo ($p < 0.001$).

Table 18 Results from Analysis of MMD – Study 20120297 (Source: Table 10-1 of sponsor's study report)

		AMG 334
	Placebo (N = 288)	70 mg (N = 282)
Baseline		
n	288	282
Mean (SD)	8.38(2.58)	8.13 (2.57)
Median	8.24	8.00
Q1, Q3	6.50, 10.00	6.32, 9.66
Minimum, Maximum	2.8, 16.6	2.4, 15.4
Change from baseline at week 12 (month 3)		
n	270	268
Mean (SE)	-1.96 (0.25)	-2.89 (0.23)
Median	-2.26	-3.11
Q1, Q3	-4.21, 0.64	-5.13, -0.89
Minimum, Maximum	-12.4, 14.7	-13.5, 16.4
Adjusted analysis[a b]		
LSM estimates	-1.84	-2.88
(95% CI of LSM)	(-2.25, -1.43)	(-3.30, -2.47)
Difference in LSMs	--	-1.04
(95% CI of difference)	--	(-1.61, -0.47)
p-value	--	< 0.001

[a] Adjusted analysis utilizes a generalized linear mixed model which includes treatment, visit, treatment by visit interaction, stratification factors region and prior/current treatment with migraine prophylactic medication, and baseline value as covariates and assumes a first-order autoregressive covariance structure. P-values are nominal p-values without multiplicity adjustment.

3.3.5.2 Missing Data and Sensitivity Analyses

About how to handle missing data, pre-specified rules were adequate. The overall missing rate was very low for this study as can be seen from the following table which shows the monthly patient counts for each group.
If less than 14 days of e-Diary out of the 28-day interval is recorded, then the monthly measurement will be set as missing.
If at least 14 days of e-Diary out of 28-day interval is recorded, then the monthly measurement will be prorated to 28-day or computed as average from the available observed days of data.

Table 19 Monthly Patient Counts – Study 20120297 (source: Table 14 -4.4.1.2 from sponsor's study report)

	randomized	Baseline	Month 1	Month 2	Month 3	Month 3 (%)
placebo	291	288	287	280	270	93.75%
70mg	286	282	280	275	268	95.04%

In the sensitivity analysis on primary and secondary efficacy endpoints during the DBTP, missing continuous efficacy endpoints will be handled using last observation carried forward (LOCF) method, multiple imputation and inverse probability weighting (IPW) generalized estimation equations (GEE) method respectively. Missing dichotomous endpoints will be analyzed using the non-responder imputation (NRI), derived dichotomous data based on multiple imputation (MI) for continuous variable, and inverse probability weighting (IPW) generalized estimation equations (GEE) method respectively.
In MI, all post-baseline missing continuous efficacy endpoints will be imputed resulting in multiple complete sets by the Markov Chain Monte Carlo (MCMC) method. The multiple imputation will be stratified by stratification variables and treatment groups.
If the proportion of missing data in primary endpoint is high (eg, > 20% for primary analysis at week 12), further analysis will be performed to

- examine the frequency and reason of missing data
- determine if there are any patterns in the missing data
- distinguish true missing values from other unknown values (eg, due to measurement or sample processing error).

Results for the sensitivity analyses were consistent with those observed for the primary analysis. Results from the per-protocol analysis were consistent with the efficacy analysis.

3.3.5.3 Efficacy Results of the Secondary Endpoints

There was statistically significant difference between the treatment group and placebo in the MMD related secondary endpoints.

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There was no statistically significant difference between the treatment group and placebo in the MPFID related secondary endpoints.

>= 50% Reduction in Monthly Migraine Days from Baseline

The proportion of subjects who achieved at least a 50% reduction in monthly migraine days from baseline to the last month of the 12-week double-blind treatment phase was 29.5% for the placebo group and 39.7% for the AMG 334 70-mg treatment group; results were statistically significant for the AMG 334 70-mg group vs placebo (p = 0.010).

Table 20 Responder Rate: >= 50% Reduction in MMD from Baseline, NRI, CMH Test – Study 20120297 (Source: Table 10-4 from sponsor's study report)

	Placebo (N = 288)	AMG 334 70 mg (N = 282)
Week 12 (month 3)		
N1	288	282
Responder - n (%)	85 (29.5)	112 (39.7)
Difference in responder (AMG 334 vs Placebo) - %	--	10.2
Common odds ratio (AMG 334 vs Placebo)[a]	--	1.59
(95% CI)	--	(1.12, 2.27)
p-value	--	0.010

NRI = non-responder imputation
[a] The common odds ratios and p-values are obtained from a Cochran-Mantel-Haenszel (CMH) test, stratified by stratification factors region and prior/current treatment with migraine prophylactic medication. The same analysis is repeated for each visit. P-values are nominal p-values obtained from the CMH test.
Breslow-day test for homogeneity of odds ratios across strata at week 12 (month 3) is 0.89.

Change from Baseline in Monthly Acute Migraine-specific Medication Treatment Days

There was a statistically significant greater reduction in the change from baseline in monthly acute migraine-specific medication treatment days in the last month of the 12-week double-blind treatment phase for AMG 334 70 mg as compared with placebo. The difference in LSM (95% CI) was –0.59 (–0.96, –0.21) days for AMG 334 70 mg vs placebo (p = 0.002)

3.3.5.4 Efficacy Results for Exploratory Endpoints (MPFID)

There was no statistically significant difference between the treatment group and placebo.

The proportion of subjects who achieved at least a 5-point reduction from baseline to the last month of the double-blind treatment phase in the average impact on everyday activities domain scores by MPFID was numerically larger for AMG 334 70 mg compared to placebo, but the difference was not statistically significant.

The proportion of subjects who achieved at least a 5-point reduction from baseline to the last month of the double-blind treatment phase in the average physical impairment domain scores by MPFID was numerically larger for AMG 334 70 mg, but the difference was not statistically significant.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age

Of the three studies, the median age of the subjects was between 41 and 45 years, with the majority being female with percentage between 79% and 87%, and the majority being white with percentage between 86.8% and 96.8%.

Table 21 Age, Gender and Race Summary of the Three Studies by Treatment Group

	Study 95			Study 96			Study 97		
	Age (Median)	Gender (%F)	Race (%W)	Age (Median)	Gender (%F)	Race (%W)	Age (Median)	Gender (%F)	Race (%W)
placebo	43.0	79.0	93.7	41.0	85.9	86.8	43.0	79.0	93.7
70 mg	42.0	86.9	92.1	42.0	84.5	88.6	43.5	86.9	92.1
140 mg	45.0	84.2	96.8	41.0	85.3	91.8	Not Applicable		

For the two phase 3 studies, analyses for the treatment effect of AMG 334 vs placebo on change in MMD across clinically meaningful subsets defined by baseline covariates such as age (< median or not), gender, race (white and others) were performed.

Table 22 Findings in Subgroup Populations – Age, Gender and Race – Study 20120295

MMD	Baseline Mean(SE)	Change at Week 12	Effect diff (95% CI)	Baseline Mean(SE)	Change at Week 12	Effect diff (95% CI)
	Age < Median			Age >= Median		
placebo	18.32 (0.40)	-4.65		18.16 (0.39)	-3.8	
70mg	18.29 (0.43)	-8.02	-3.37 (-4.95, -1.79)	17.58 (0.47)	-5.24	-1.45 (-2.88, -0.02)
140mg	18.72 (0.60)	-7.23	-2.58 (-4.25, -0.91)	17.11 (0.39)	-6.18	-2.39 (-3.76, -1.02)
	Gender = Female			Gender = Male		
placebo	18.25 (0.31)	-4.13		18.21(0.70)	-4.41	
70mg	17.96(0.35)	-6.75	-2.62 (-3.79, -1.45)	17.78(0.60)	-6.18	-1.76 (-4.56, 1.03)
140mg	17.99(0.35)	-6.59	-2.46 (-3.64, -1.29)	16.62(1.1)	-6.83	-2.42 (-5.03, 0.18)
	Race = White			Race = Other		
placebo	18.30(0.29)	-4.17		17.39 (1.28)	-4.39	
70mg	17.96(0.33)	-6.48	-2.30 (-3.41, -1.19)	17.77 (1.05)	-8.31	-3.92 (-7.86, 0.01)
140mg	17.84(0.35)	-6.61	-2.44 (-3.53, -1.34)	16.00 (1.67)	-7.51	-3.12 (-8.27, 2.02)

Table 23 Findings in Subgroup Populations – Age, Gender and Race – Study 20120296

MMD	Baseline Mean(SE)	Change over Month 4,5 and 6	Effect Diff (95% CI)	Baseline Mean(SE)	Change over Month 4,5 and 6	Effect Diff (95% CI)
	Age < Median			Age >= Median		
placebo	8.52 (2.58)	-1.81		7.98 (2.41)	-1.9	
70mg	8.23 (2.40)	-2.93	-1.12 (-1.83, -0.42)	8.39 (2.50)	-3.47	-1.57 (-2.24, -0.90)
140mg	8.13 (2.36)	-3.41	-1.60 (-2.30, -0.90)	8.53 (2.58)	-3.86	-1.96 (-2.63, -1.28)
	Gender = Female			Gender = Male		
placebo	8.31 (2.55)	-1.73		7.89 (2.20)	-2.48	
70mg	8.32 (2.46)	-3.36	-1.62 (-2.15, -1.09)	8.28 (2.37)	-2.5	-0.02 (-1.25, 1.21)
140mg	8.40 (2.47)	-3.7	-1.97 (-2.49, -1.44)	7.92 (2.49)	-3.49	-1.00 (-2.24, 0.24)
	Race = White			Race = Other		
placebo	8.31 (2.51)	-1.56		7.88 (2.47)	-4.43	
70mg	8.29 (2.40)	-3.19	-1.63 (-2.14, -1.11)	8.47 (2.85)	-4.17	0.26 (-1.26, 1.77)
140mg	8.28 (2.43)	-3.73	-2.17 (-2.67, -1.66)	8.84 (2.99)	-3.65	0.77 (-0.86, 2.41)

(Source: Table 39, 40, 41 from sponsor's ISE report)

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The three pivotal studies collectively provided sufficient statistical evidence that AMG334 at doses 70 mg or 140 mg is effective in treating patients with chronic migraine. No major statistical issues were identified.

5.2 Conclusions and Recommendations

The efficacy results obtained from the statistical analyses of the three pivotal studies support the conclusion that AMG334 is effective in treating patients with chronic migraine.

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/s/

JINNAN LIU
02/05/2018

KUN JIN
02/05/2018
I concur with the review.

HSIEN MING J HUNG
02/05/2018