

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761077Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 116,098

MEETING MINUTES

Amgen, Inc.
Attention: Vanessa Shurn
601 13th Street, N.W.
Washington, D.C. 20005

Dear Ms. Shurn:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AMG 334.

We also refer to the meeting between representatives of your firm and the FDA on January 31, 2017. The purpose of the meeting was to discuss the clinical aspects of your development program.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Lana Chen, Regulatory Project Manager at (301) 796-796-1056.

Sincerely,

{See appended electronic signature page}

Eric Bastings, M.D.
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date: January 31, 2017
Meeting Location: FDA White Oak

Application Number: IND 116,098
Product Name: AMG 334/ erenumab
Indication: Migraine
Sponsor/Applicant Name: Amgen

Meeting Chair: Billy Dunn, M.D.
Meeting Recorder: Lana Chen, R.Ph.

FDA ATTENDEES

Division of Neurology Products

Billy Dunn, MD, Director
Eric Bastings, MD, Deputy Director
Heather Fitter, MD, Clinical Team Leader
Laura Jawidzik, MD, Clinical Reviewer
Sally Jo Yasuda, MS, PharmD, Safety Team Leader
Lourdes Villalba, MD, Safety Team Reviewer (via phone)
Lois Freed, PhD, Supervisory Pharmacologist
Edmund Nesti, PhD, Pharmacology Reviewer
Lana Chen, RPh, Project Manager

Joslyn Brunelle, PhD, Product Quality Team Leader (via phone)
Andrea Franco, PhD, Product Quality Reviewer (via phone)
Junshan Qiu, PhD, Statistical Reviewer
Xinning Yang, PhD, Clinical Pharmacology Reviewer
Gopichand Gottipati, PhD, Pharmacometric Reviewer
Kevin Krudys, PhD, Pharmacometric Team Leader
Patricia Love, MD, Deputy Director, Office of Combination Products (OCP)
Sarrit M. Kovacs, Ph.D., Clinical Outcome Assessments Reviewer, COA Staff
(formerly SEALD)
Thomas Birkner, PhD, Biometrics COA Point Person
Laura Lee Johnson, Ph.D., Deputy Director, Division of Biometrics III
Joshua Hunt, PharmD, Senior Regulatory Reviewer, Controlled Substance Staff (via phone)

Corwin Howard, PharmD, Safety Regulatory Project Manager, Office of Surveillance and Epidemiology (via phone)

Division of Risk Management (DRISK)

Laura Zendel, PharmD, BCPS, Risk Management Analyst

Yasmeen Abou-Sayed, PharmD, Risk Management Analyst

Division of Medication Error Prevention and Analysis (DMEPA)

Ebony Whaley, PharmD, BCPPS, Safety Evaluator

Irene Chan, PharmD, BCPS, Deputy Director

SPONSOR ATTENDEES

Amgen

Daniel Mikol, MD, PhD, Executive Medical Director, Global Development

Rob Lenz, MD, PhD, Vice-President, Global Development

Hernan Picard, MD, PhD, Medical Director, Global Development

Osa Eisele, MD, MPH, Director, Global Safety

Marie-Louise Trotman, MS, Director, Global Biostatistical Science

Ed Lee, PhD Director, Clinical Pharmacology

Sandhya Sapra, PhD Director, Global Health Economics, Product Lead

Brian Ortmeier, PharmD, PhD, Executive Director, Global Health Economics

Vanessa Shurn, Senior Manager, Regulatory Affairs

Mark Taisey, Vice-President, Global Regulatory Affairs

Paul Nitschmann, Executive Director, Regulatory Affairs

Drew Badger, PhD, DABT, Director, Regulatory Affairs

Lori de los Reyes, MSN, JD, Director, Regulatory Affairs Device

Novartis

Molly Shea, PhD, Novartis, Executive Director, Regulatory Affairs, Global Therapeutic Area Lead, DRA Neuroscience I

DISCUSSION

Clinical

Question 1. An overview of the clinical studies to be included in the BLA, including the status and type of reports to be provided for each study, are presented in the briefing document. Does the FDA require any clarifications regarding Amgen's approach for inclusion of information from completed and ongoing studies in the BLA submission (Section 6.1)?

FDA Response:

1. Please include in the BLA submission a clear schematic or table of each of the phase 2 and 3 study designs and duration, along with number of patients enrolled by treatment group, in the base studies and the extensions, to better explain the characteristics of this database. In addition, please include a table showing the numbers of patients in each of the following groups:

- a) 70 mg during the double-blind treatment phase (DBTP) only
- b) 140 mg during the DBTP only
- c) 70 mg during the DBTP and 70 mg during the open-label treatment phase (OLTP) or active treatment phase(ATP)
- d) 70 mg during the DBTP and 140 mg during the ATP
- e) 70 mg during the DBTP, 70 mg during the OLTP and then 140 mg during the OLTP
- f) 140 mg during the DBTP, 70 mg during the OLTP and then 140 mg during the OLTP
- g) 140 mg during the DBTP and 140 mg during the OLTP

Amgen Response: We will provide a schematic or table explaining the subject flow of all the phase 2/3 studies and this will be provided in the initial filing as part of the SCS. For your reference, we have provided the study schemas as Attachment 1 and plan on reviewing them briefly to help address multiple agency questions below.

2. Table 35 of the briefing document includes the data cut-off for analyses of ongoing studies for the 120-day safety update. Please provide the data cut-off for analyses in Table 36 (Estimated Exposure to AMG 334 at the Time of the Initial Marketing Application).

Amgen Response: The data cut-off dates that correspond to the estimated exposures in Table 36 of the briefing book are provided below.

Study	Data Cutoff Date	Snapshot/lock date
20120178	9/1/16	10/14/16
20120295	4/28/16	5/25/16
20120296	1/19/17	2/9/17
20120297	7/11/16	9/14/16
20130255	1/23/17	2/16/17

For ease of reference, Table 36 from the briefing book is provided below.

Table 36. Estimated Exposure to AMG 334 at the Time of the Initial Marketing Application

Study Number	Phase /Migraine Type	Anticipated Number of Subjects					
		Exposed to AMG 334 (All doses ^a)	Exposed to AMG 334 (≥ 70 mg)	Exposed to AMG 334 ≥ 1 year (≥ 70 mg)	Exposed to AMG 334 (140 mg)	Exposed to AMG 334 ≥ 6 months (140 mg)	Exposed to AMG 334 ≥ 1 year (140 mg) ^b
20120296	phase 3 / episodic	910	910	330	598	484	82 ^c
20120297	phase 3 / episodic	553	553	–	–	–	–
20120178	phase 2 / episodic	439	401	310	235	–	–
20120295 / OLE 20130255	phase 2 / chronic	634	634	482	373	167	23
Subtotal		2536	2498	1102	1206	631	105
Phase 1 Program Exposure ^b		688	658		189		
Total		3224	3156	1102	1395	631	105

OLE = open-label extension.

^a Doses up to 210 mg.

^b Healthy volunteers and subjects with migraine who received ≥ 1 dose of AMG 334 in studies 20101267, 20101268, 20120130, 20120180, 20140255, 20140477, 20150149 and 20150334.

^c Continuous exposure to 140 mg. For ongoing subjects assumes a 5% drop-out rate.

3. For the data provided regarding exposure for 6 months and for 1 year, please provide information in the BLA to clarify whether that represents continuous exposure to a given dose, or the most commonly administered dose during that period, or a different representation. Please also provide information to show how many patients received all of the doses for 6 or 12 months, and how many received fewer than the number of doses expected (e.g., how many received 11 doses, how many received 10 doses, etc.). If patients received fewer than the expected number of doses, provide information regarding the time gap between doses.

Amgen Response: The exposure data presented in Tables 36 and 37 of the briefing book represent continuous exposure at the respective doses. A table summarizing number of doses received will be included in the ISS to provide additional information on the summary of exposure duration.

4. Please clarify the time frame (days after last dose) used for collection and analyses of adverse events in each of the studies included in the ISS? Please provide this information at the pre-BLA meeting and include this information in the BLA submission.

Amgen Response: This information is included in the protocol for each individual study. In general, AEs are collected for 12 weeks after last dose in studies where 70 mg is the highest dose and for 16 weeks in studies where 140 mg is the highest dose. The ISS SAP specifies the time frame for AEs included in the ISS analyses.

Meeting Discussion (for all parts of Question 1 above):

The sponsor presented schematics for individual phase 2 and 3 studies. Exact numbers of patients were not provided, but will be included with the BLA submission. The sponsor stated that there were few missed doses overall. The sponsor clarified that the exposure data in Table 36 of the briefing packet represents continuous dosing at the doses specified.

Question 2. It is Amgen's position that the results of the pivotal studies in CM (20120295) and EM (20120296) provide an adequate basis for the initial BLA submission to support approval of 140 mg AMG 334 for the indication of prophylaxis of migraine in adults, consistent with FDA EOP2 discussions. Does the FDA agree that the results of Studies 20120295, and 20120296, along with supplemental data from Study 20120297, Study 20120178 and Study 20130255 provide an adequate basis to support a BLA submission of AMG 334 for the prophylaxis of migraine in adults (Section 6.2)?

FDA Response:

On face, it appears that these studies have the potential to support an initial filing application for your BLA for AMG 334. Review of the information requested above at the time of filing will determine whether the safety database is sufficient. The exact dose(s) marketed will be a matter of review, based on the totality of evidence presented in the BLA.

At the time of BLA submission, your application should include complete study reports for all studies required to support approval. If Study 20140254 is necessary to support approval, it should be included with the original BLA submission.

Amgen Response: Amgen acknowledges the feedback. Please see Amgen's response to Question 6 regarding a clarification on the content of the Study 20140254 CSR at the time of initial filing.

Meeting Discussion: None.

Question 3. Based on the safety and efficacy results of the pivotal studies, Amgen has recommended a commercial dose of 140 mg. Beyond the information provided in this background package, are there any additional analyses the FDA needs to support this recommendation (Section 6.3)?

FDA Response:

At this time, we are not requesting any additional analyses; however, this may change when we review your BLA.

Amgen Response: Amgen appreciates the feedback.

Meeting Discussion:

The Division understands the sponsor's rationale for proposing the 140 mg dose for marketing, but Division will consider the safety and efficacy at both the 70 mg and 140 mg dose. The Division suggested that efficacy and safety analyses be provided by the sponsor for both doses. In some cases, when an unexpected safety issue arises in a development program at a higher dose, it is useful to have a lower dose option. The final dose recommended for marketing is a matter of review.

Question 4. In spite of our efforts, we were unable to reach the target of 80 subjects enrolled into the clinical home use (CHU) substudy of the CM Study 20130255 (80 is the sample size previously agreed upon with FDA to support patient self-administration). As a result of unexpected delays in IRB/ethics committee approvals of the amendment that increased the AMG 334 dose from 70 mg to 140 mg and introduced the CHU substudy, 1/3 of the planned countries not participating in the substudy, and subjects discontinuing treatment, the number of subjects eligible for consent decreased from 245 (initially projected) to 134 (actual); in the end, 61 subjects consented and 53 subjects enrolled in the CHU substudy of Study 20130255. As such, Amgen is supplementing the clinical home use database with an additional substudy of identical design as part of EM Study 20120178. Does the FDA agree that a combined dataset from clinical home use substudies in CM Study 20130255 (53 subjects) and EM Study 20120178 (83 subjects) reported in a single CSR is acceptable to support patient self-administration at initial launch? (Section 6.4)?

FDA Response:

On face, this appears acceptable. Please clarify how many patients in the CHU sub-study self-administered two injections of 70 mg for a total single dose of 140 mg monthly.

Amgen Response: The sub-study was designed such that all subjects would administer two injections of 70 mg for a total dose of 140mg; 136 subjects were enrolled in the CHU sub-study.

Meeting Discussion: None.

Question 5. Amgen plans to submit an initial safety data package with the BLA filing. The 120-day safety update is proposed to include updated safety data from all ongoing studies as described in Table 35. Does the FDA agree with Amgen's proposal for the studies' planned analyses and proposed data cutoff dates for inclusion in the 120-day safety update (Section 6.5.1)?

FDA Response:

In Section 6.5.1 of the background package, you state that the 120 day safety update (SUR) will be an amendment with new data and that there will not be an updated integrated summary of safety (ISS) analysis based on the cumulative data. The SUR must include an updated integrated ISS along with the pertinent datasets to support the analyses.

Amgen Response: Amgen appreciates the feedback. All relevant sections of the ISS will be updated in the SUR submission.

Meeting Discussion: None.

Post-meeting note: Please confirm that the updated ISS datasets will also be submitted with the SUR.

Question 6. Study 20140254 is an ongoing phase 2a treadmill cardiovascular safety study to assess AMG 334 in patients with stable angina. As this study is ongoing, but is no longer screening subjects, Amgen intends to submit the Study 20140254 primary analysis CSR at the time of the initial filing, and the final analysis CSR as supportive data with the 120-day safety update. *Does the FDA agree that this approach is acceptable and will not delay the filing review (Section 6.5.1.1)?*

FDA Response:

We recommend that you include the complete study report and all analyses for this trial with your initial submission. We cannot directly respond to your question above because we are uncertain of what you are referring to as the “primary analysis CSR” and how that differs from the “final analysis CSR”.

Amgen Response: The objective of conducting the study was to assess the effects of a single 140mg iv dose of AMG 334 on exercise tolerance and duration in a stable angina patient population. Final results of all primary and secondary endpoints and safety from the exercise tolerance test will be included in the primary analysis CSR. The primary analysis CSR will also contain all available safety data from the 12-week safety follow-up period that follows after the single dose.

A Final Analysis CSR will only include an updated analysis of the safety (e.g. adverse events, concomitant medications) obtained during the 12-week safety follow-up period.

Meeting Discussion:

The sponsor clarified the content of the treadmill study that will be available at the time of filing and at the time of the 120 day safety update. The sponsor has asserted that no treatment-emergent adverse events have occurred thus far, and that at filing they will have at least a 2-week follow up on 94% of subjects, leaving 6% with only initial data at the time of filing. The Division agreed that if the sponsor provides data consistent with what was described during this meeting discussion, this should not be a filing issue. The sponsor will provide the final CSR for the treadmill study at the 120-day safety update.

Question 7. Does the FDA concur with Amgen's approach to the proposed risk minimization and post-marketing safety strategy (Section 6.5.2)?

FDA Response:

We agree that a post-marketing safety study looking at outcomes in pregnancy would be of value. However, until we review the safety data in its entirety, we cannot agree prospectively that no additional risk mitigation measures would be needed.

Amgen Response: Amgen acknowledges the feedback.

Meeting Discussion: None.

Clinical Pharmacology

Question 8. A summary of the clinical pharmacology information will be included in the BLA, including descriptions of AMG 334 pharmacokinetics (PK), pharmacodynamics (PD), intrinsic factors and extrinsic factors, dose selection rationale, and population PK/PD. A listing of the studies and supportive information are included in this briefing document in [Section 6.6](#). *Does the FDA agree that the clinical pharmacology studies constitute a complete package that supports the submission of the AMG 334 BLA?*

FDA Response:

In general, we agree. Please perform the analysis to evaluate the effect of injection sites on PK and efficacy of AMG334 as previously discussed during the EOP2 meeting.

Your proposed table of contents (Appendix 6) does not include the reports for the population PK/PD and exposure-response analyses. These reports and accompanying datasets and model codes should be included in the BLA.

All datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariate model, final model and validation model. These files should be submitted as ASCII files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt).

Amgen Response: At the EOP2 meeting we discussed assessing the effects of injection site on PK. Although we did not discuss the impact on efficacy, Amgen agrees to assess the effects of injection site on PK in a pop-PK analysis. If injection site is determined to have a significant effect on PK, we will subsequently assess the effect on monthly migraine days (efficacy) in a pop-PK/PD analysis. We also agree to provide the datasets and files as requested.

Meeting Discussion: The Division agreed that, on face, the sponsor's proposal is acceptable.

Patient Reported Outcomes (MPFID)

Question 9. The following is an overview of the current approach to support the clinical interpretation of changes on the MPFID:

Using Study 20120297 pooled data, we will explore change scores for the MPFID (change from baseline to end of double-blind phase) between clinically distinct groups (e.g., subjects with a 30%, 50%, or 70% reduction from baseline in monthly migraine days vs those without). These estimates will provide a range of *average* clinically important differences in MPFID scores that will help contextualize the 'observed' differences in the MPFID mean scores in Studies 20120297 and 20120296.

In addition, Amgen will develop a within-patient definition of response on the MPFID (b) (4) from baseline in the MPFID score that corresponds to a clinically meaningful change in external anchors. Additional details are provided in Section 7.

Does the FDA agree that the proposed approaches are sufficient to support the clinical meaningfulness of the MPFID?

FDA Response:

Determination of the clinical meaningfulness of the MPFID will be evaluated during the review of your BLA and the complete MPFID evidence dossier. We suggest that you provide your rationale for using the anchor scales that you have proposed for determining within-patient change in your BLA submission. When doing so, we suggest that you use data from your existing qualitative research with migraine patients and observational psychometric evaluation study. We also suggest that you establish thresholds using the MPFID domain point change, (b) (4) in line with the endpoint definition (b) (4)

With regard to your proposed plans for supportive analyses to evaluate clinical meaningfulness of between-group differences, we have the following recommendations:

- a. Refrain from applying a threshold developed from a set of data to the same set of data.
- b. Base the analyses on a point change (b) (4) from baseline in MPFID domain scores.

Conclusions from the proposed analyses will be considered exploratory.

Amgen Response: Amgen would like the agency to please clarify the comment 'Conclusions from the proposed analyses will be considered exploratory'?

We agree with the FDA on presenting point change [REDACTED] (b) (4) for the supportive analyses to evaluate clinical meaningfulness of between-group differences in MPFID domain score.

Amgen will continue to explore thresholds using the MPFID domain score point change to support clinical meaningfulness. Is this consistent with the agency's recommendation?

We also agree with the agency in not applying a threshold developed from a set of data to the same set of data. We would like to highlight that the proposed analyses described here and in section 7 of the Pre BLA briefing book are being conducted on pooled 20120297 data (and in observational study 20140136). Data from these analyses will be included in the PRO dossier. Rationale for selected anchors will also be provided in the PRO dossier.

Meeting Discussion:

The Division clarified that 'supportive' is the more accurate term (compared to 'exploratory') to describe the proposed analyses. The Division stated that whether the MPFID measures can be included in labeling will be a matter of review. At this time, there is no generally accepted anchor-based method to determine clinically meaningful between-group differences. As previously stated, a statistically significant change on an MPFID measure would not be necessarily be sufficient to support inclusion of this finding in labeling. There would also have to be sufficient evidence provided that the measured change on the MPFID represents a clinically meaningful change.

The sponsor asked whether the Division agrees that the psychometric properties of the MPFID are acceptable, but that meaningfulness of the MPFID change scores still needs to be reviewed. The Agency replied that acceptability of the psychometric properties and performance of the MPFID (i.e., reliability, validity, and ability to detect change) will be determined during the BLA review, when the evidence dossier is submitted.

Labeling

Question 10. While a draft USPI is not yet available for inclusion in this briefing book, the following label concept is provided for the FDA's consideration.

a) [REDACTED] (b) (4)

(b) (4)

(b) (4)

FDA Response:

Whether information about this study will be included in the label is a matter of review. If this study is described in labeling, any description of the findings will be based on the specific results of the study. It is premature to prospectively agree on specific language for labeling. We recommend that you submit the full study report at the time of the BLA submission to allow sufficient time for an adequate review and for consideration for inclusion in the label.

Amgen Response: Please refer to our response to Question 6 regarding the content of the study report at the time of initial filing.

Meeting Discussion: None.

Question 11. Given the safety profile of the drug (Section 6.2.2) and based on the requirements of CFR 208.1(c), Amgen does not consider that a Medication Guide is required for AMG 334. Does the FDA agree?

FDA Response:

It is premature to consider this question. Whether a Medication Guide will be required is a matter of review.

Amgen Response: Amgen acknowledges the response, no further discussion is needed.

Meeting Discussion: None.

Regulatory

Question 12. The planned AMG 334 BLA for the prophylaxis of migraine in adults will be based on results from the pivotal phase 2 CM Study 20120295, phase 3 Studies 20120296 and 20120297 in EM, and long-term safety data provided in the phase 2 EM Study 20120178 and phase 2 OLE Study 20130255 in CM. The AMG 334 migraine clinical development program also includes 7 phase 1 studies and 2 additional phase 2 studies. The proposed Table of Contents discusses the BLA structure of the nonclinical and clinical modules in further detail. Does the

FDA agree with the proposed content and placement of the clinical and nonclinical packages for the marketing application (Section 8.2 and Appendix 6)?

FDA Response:

Please refer to responses provided at the Type C meeting from September 2016 and to Attachment 2 of this document that includes the current recommendations from the Division of Neurology Products for submission of safety data.

In addition, based on the statistical analysis plan (SAP) submitted in August 2016, we have the following comments related to the safety analysis:

- a. Proposed pools for the ISS: We suggests adding two additional pools: Study 20120296 (24 weeks controlled data) and a long term pool for patients exposed consecutively for >6 months. The pools should separately include patients treated with 70 mg, with 140 mg, and an all treated group. Please clarify how the 70 and 140 mg groups will be defined in the long term pools.

Amgen Response: It should be noted that the 24 week controlled data for study 20120296 is included in the study primary CSR, however Amgen agrees to provide a separate pool for study 20120296 in the ISS.

For the long-term pool for patients exposed consecutively for >6months, Amgen would like to clarify the following points:

- “AMG 334 through open-label extension pool” provides safety data across different exposure periods (double-blind treatment period and/or open-label extension/active treatment period) for subjects who received at least 1 dose of AMG 334 70 mg, 140 mg or both.
- Because all Phase 2 and 3 studies allowed safety extensions and very low discontinuation rates were observed in the double-blind portions of the Phase 2 and 3 studies, a vast majority of subjects who received 1 or more doses of AMG 334 would have had > 6 month continuous exposure to either the 70mg or 140mg.

For subjects with long-term exposure beyond the double-blind treatment period, the exposure-adjusted subject incidence of adverse events was tabulated by the dose level of AMG 334 that the subject was receiving on the onset date for a specific adverse event. The time of the first occurrence of the adverse event within each dose determined the dose level. If a subject had multiple occurrences of the same adverse event-within a dose level, or at different dose levels, only the first occurrence within each dose level was counted in the analyses.

Thus Amgen would like to propose that the currently proposed “AMG 334 through open-label extension pool” will adequately address the request to provide information on subjects who have had > 6 month continuous exposure.

Meeting Discussion:

The sponsor clarified that the “majority” of patients in this pool will have 6 months of data. Based on this response, the Division stated that the proposal not to add a separate pool for patients exposed for >6 months is acceptable. However, the BLA should specify how many patients in the long term pool were not exposed for >6 months.

- b. An integrated, detailed analysis of the safety findings of the phase 1 studies is not required. However, please note that in addition to the integrated analyses of phase 2 and 3 trials, the ISS should include a summary of safety results of all the phase 1 studies.

Amgen Response: We will summarize as part of the SCS.

Meeting Discussion: None.

- c. As per page 20 of the SAP there was adjudication of cardiovascular events but the procedures were different in each study. Please provide a summary of the SOP for adjudication of cardiovascular events with highlights regarding the differences among studies.

Amgen Response: To clarify, the process of adjudication of cardiovascular events did not differ for each study. The only difference amongst the studies was whether events were adjudicated prospectively or retrospectively. By the time the CEC was established some studies were ongoing and thus for events occurring prior to this time, retrospective adjudication was conducted. Otherwise events were flagged as they occurred and sent to the CEC per the guidelines established in the charter (Attachment 2).

Meeting Discussion: None.

- d. The ISS will include an analysis of concomitant acute headache medications. Please also include analyses of concomitant cardiovascular medications at baseline, as well as new or increased dose of cardiovascular medications (e.g. antianginal, antihypertensive, antiarrhythmics) during treatment for each pool.

Amgen Response: [REDACTED] (b) (4)

[REDACTED] -There is a high potential for confounding interpretability because many cardiovascular medications are also used for migraine prophylaxis (e.g. Beta blockers, calcium channel blockers, ACE-inhibitors). Because of these confounders, does the agency agree that providing [REDACTED] (b) (4) is acceptable?

Meeting Discussion:

Use of these medications could confound both efficacy and safety results. The Division did not agree [REDACTED] (b) (4) is acceptable, and instead requested an analysis of concomitant cardiovascular medications with a discussion of the findings to be included.

- e. Lab assessments: Hematology assessments described in the SAP of August 2016 refer only to red cell values. Please include platelets and WBC analyses.

Amgen Response: These will be provided as requested as part of the ISS.

Meeting Discussion: None.

- f. [REDACTED] (b) (4)

Amgen Response: [REDACTED] (b) (4)

Meeting Discussion:

(b) (4)

The Division noted that on page 182 in module 5.3.5.3, the sponsor indicated that the ISE will only contain the episodic migraine (EM) studies. As mentioned in the Type C meeting from September 15, 2016, the ISE should contain a synthesis of all of the relevant evidence supporting efficacy, which includes the chronic migraine (CM) studies.

Amgen Response: This was an oversight in the TOC. The ISE will include information on the four adequately powered and designed studies to support the indication. The long term open label safety study (255) is still on going.

Meeting Discussion: None.

In the briefing package, you describe the results of an *ex vivo* study in human coronary artery, but it was not included in the list of nonclinical studies to be submitted in the BLA (Appendix 1). The study should be included in the BLA.

Amgen Response: Study 121150, entitled, “AMG 334: Human Isolated Coronary Artery Study” is included under Module 4, Section 4.2.3.7.7. Is this location acceptable to the Division?

Meeting Discussion: None.

Question 13.

(b) (4)
(b) (4)

FDA Response:

(b) (4)

Amgen Response: Amgen acknowledges the feedback, no further discussion is needed.

Meeting Discussion: None.

Question 14. Amgen submitted a revised initial pediatric study plan (PSP) on 08 December 2016 (SN 209). Does the FDA agree that the pre-filing pediatric requirements have been met (Section 8.5)?

FDA Response:

No. Although we acknowledge the receipt of your revised iPSP in December 2016, we note that it is currently under review. An Agreed iPSP is required at the time of filing.

Amgen Response: Amgen appreciates the Division's continued support in finalizing the elements of the pediatric study program. Does the Division have an update on when Amgen can expect an update?

Meeting Discussion:

The iPSP is currently under review, and the Division plans to provide feedback sometime in mid-to-late February.

(b) (4)



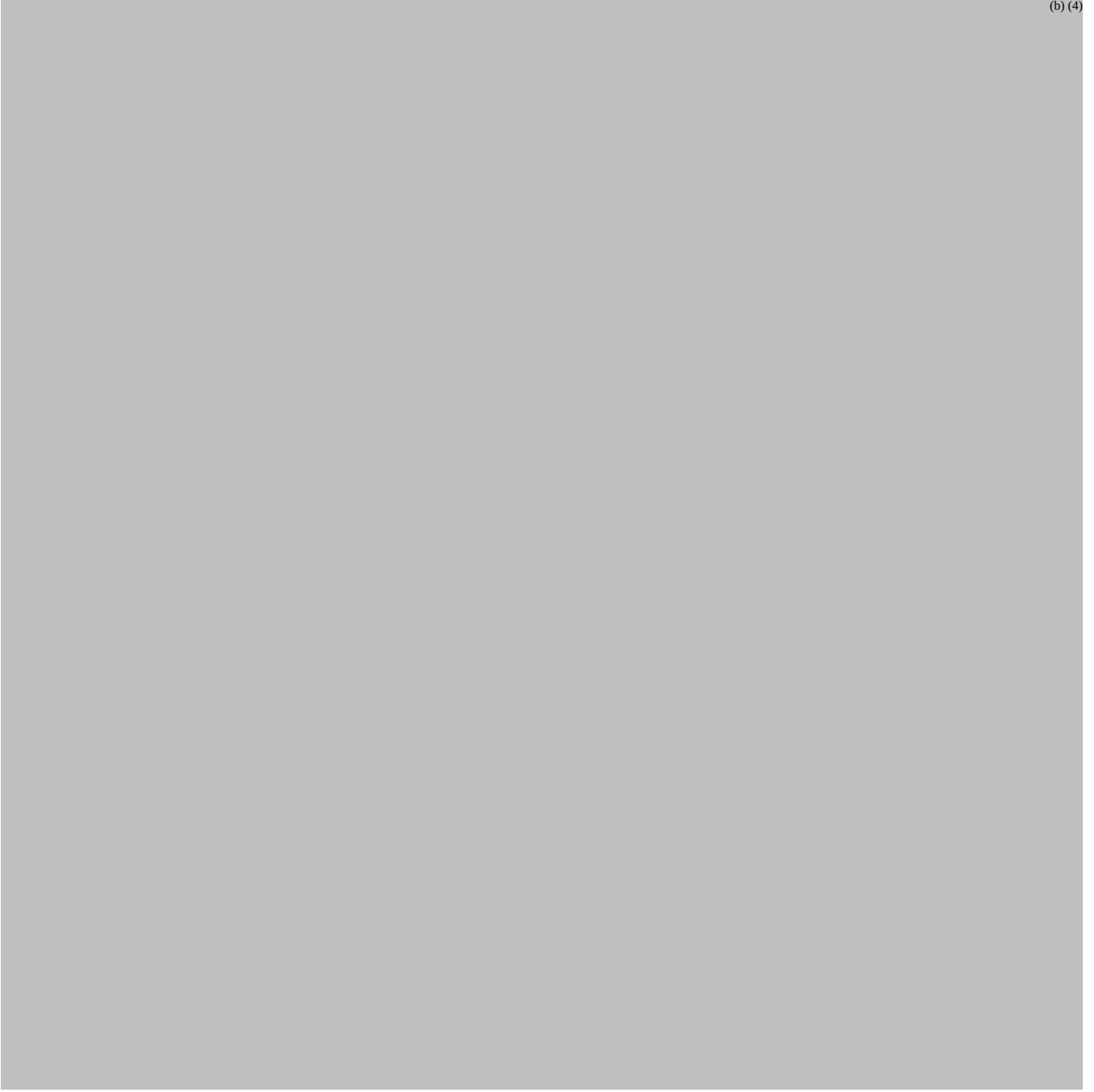
FDA Response:

On face, this plan seems acceptable.

Amgen Response: Amgen appreciates the response, no further discussion is needed.

Meeting Discussion: None.

(b) (4)



FDA Response:

(b) (4)



Amgen Response: Amgen appreciates FDA response, no further discussion is needed.

(b) (4)



(b) (4)



Amgen Response: Amgen appreciates the response, no further discussion is needed.

Meeting Discussion: None.

Structure Format

Question 16. Amgen plans to provide bookmarked and hyperlinked electronic case report forms (eCRFs) for subjects who died during the studies (including the safety follow-up periods) or discontinued from investigational product (IP) due to adverse events. eCRFs will be provided from the phase 2 Studies 20120295, 20130255, and 20120178, and the phase 3 Studies 20120296 and 20120297. The eCRFs will be referenced in the study tagging file of the study to which they belong, organized by site, and tagged per specification. Amgen proposes to submit the subject safety narratives for adverse events leading to discontinuation of IP, serious adverse events, deaths, pregnancies, and cardiovascular events of interest. Amgen intends to provide a fully hyperlinked table of subject safety narratives and CRFs as part of the Reviewer's Guide in Module 1. An example is provided in this Briefing Document, which discusses the eCRFs and safety narratives in further detail. Does the FDA agree with this proposal (Section 9.1)?

FDA Response:

Provide safety narratives as detailed above for adverse events that occurred in the phase 1 studies.

We suggest that you modify the format of your proposed table (referred to as Table 45 in section 9.1 of the briefing package) to include links to the patient narratives rather than to the eCRF. Each narrative should then have a link to the CRF and the IND safety report.

Amgen Response: Amgen would like to clarify the Division's request to hyperlink to the IND safety report, as we are not able to make cross application links (from the BLA to the IND). Is the Division requesting us to reference the SN within the IND application or for us to submit the IND safety reports as part of our BLA?

Meeting Discussion: The sponsor cannot crosslink from the BLA to the IND. The sponsor stated that they would provide serial numbers and dates to identify the patient narratives.

Question 17. Amgen received Written Responses Only from the FDA on 15 September 2016 regarding the structure and format of the BLA. Based on FDA recommendations, Amgen is providing additional clarification on our plans, including an updated Submission Data Standardization Plan (Appendix 7). Does the FDA require any additional clarification or have any additional advice regarding our proposed plans (Section 9.2, Appendix 5)?

FDA Response:

Your approach is acceptable. Please also see our response to Question 12.

Amgen Response: Amgen appreciates the response.

Meeting Discussion: None.

Additional Comments

1. We note that a death was reported to the IND in a suspect adverse reaction report (SUSAR) on [REDACTED] (b) (6) in a 44 year old male (patient # [REDACTED] (b) (6) in trial 20120296). We are unable to locate information about this patient in the current preBLA package. Provide information about this patient in your BLA submission.

Amgen Response: The fatal case referenced was not included the preBLA package due to the data cut off for studies referenced in the pre-BLA briefing book. This case will however be included in the BLA submission.

Meeting Discussion: None.

2. We note a death occurred in study 20120178 and is described on page 90 of your preBLA meeting package. We have been unable to locate the corresponding IND safety report in the IND. Please direct us to where the report is located in the IND and if it has not been submitted, please submit this report to the IND.

Amgen Response: Per the Amgen process and in accordance with the FDA guidance on IND safety reporting, this case was not submitted as a SUSAR as company causality was 'not related'. However per the FDA request a Medwatch for this case will be submitted to the IND within a week.

Meeting Discussion: None.

Request for Additional Clarification

Amgen is requesting clarification the following items provided as part the preliminary responses, beginning on page 11.

ATTACHMENT 2. SUBMITTING BIORESEARCH MONITORING (BIMO) CLINICAL DATA IN ECTD FORMAT

Amgen Response: Yes, we will deliver the BIMO data. We will deliver subject listings with the exception of the ECG data. The ECG data is provided by the ECG vendor who centrally reads the ECGs and is not at the clinical site. Amgen proposes to not include ECG data in the BIMO subject listing since the purpose of including the data is for FDA inspectors to compare the data we have against the source data.

Meeting Discussion: None.

ATTACHMENT 2. DNP PRE-NDA/PRE-BLA MEETINGS GENERAL CLINICAL SAFETY REQUESTS

Other requests:

1. Submit individual patient profiles containing all laboratory and other study results in a single place for each patient. Provide this information for patients who died, had a serious adverse event, discontinued from the trial due to an adverse event, or had a medically significant event for which a narrative is submitted. Include all the information recorded for that patient, including but not limited to:

- Age
- Sex
- Dates of screening, randomization and starting therapy
- Whether the patient completed or did not complete the study, with dates and reason for withdrawal
- Adverse events (reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
- Prior medications and concomitant medications with dates of start and end
- Vital signs and laboratories, sorted by date, with reference ranges *
- Full reports for radiologic studies, ECG, MRI, pathology results, and special studies with dates and reference ranges *

Amgen Response: These data are included in the safety narratives, hyperlinked to the eCRFs. We provide SDTM data, eCRFs with protocol specified data, and narratives, per the guidance. Does this adequately address your request?

Meeting Discussion:

The Division stated that the requested information in attachment two will facilitate the review of the safety data in the application but the absence of the information in the format suggested will not be a filing issue. If the sponsor does not provide this information with the initial application but plans to provide some of the requested information later, the Division requested that the sponsor note which items will be submitted after filing when they submit their application.

The Division stated that they prefer that the narratives include all adverse events for a single subject in a single narrative, rather than in separate narratives. Concomitant medications should be listed with exact start and end dates, as well as, all pertinent laboratory data (positive, negative or normal) to confirm that all relevant labs were done. In the Division's experience, patient profiles greatly expedite the reviewer's work and when these are submitted earlier in the review cycle they are most helpful .

Additional comments received in email 1/30

In addition to the preliminary comments regarding AMG334 sent on January 27, 2017, we have the following comments regarding the proposed safety analysis:

1. ECG analyses: In addition to the proposed analyses please include standard analyses of QTc changes.

Amgen response: Please clarify what is meant by standard analyses of QTc changes.

Meeting Discussion: The Division requested that the sponsor provide any QT data that they collected since a thorough QT study was not required. The following measurements would be most informative: mean and median changes in QTc, changes from baseline to C max, and an outliers analysis.

Post meeting note: Please include similar analyses of the PR and QRS interval as well.

2. We request that you submit a sample integrated summary of safety datasets (with data definition file) for Division comments prior to submitting the BLA. This process could help to identify and resolve any potential issues of navigability or interpretability that could impact the review of your application.

Amgen response: As this was not raised in our structure format meeting, we would like to further discuss at the pre-BLA meeting.

Meeting Discussion:

The Division suggested that the sponsor provide samples of their datasets, so that reviewers can assess whether the datasets are compatible with the tools used for review. The Division suggested that the sponsor provide an informal reviewer orientation for FDA reviewers.

3. We also request that you submit for Division comments an example narrative from a patient who had more than one serious adverse event and participated in the controlled and extension studies (e.g. a patient in group f. of the response to Q.1) prior to submitting the BLA.

Amgen response:

Narratives are typically presented by subject/event combo i.e. 1 narrative per event rather than multiple events in a single narrative. All the narratives (by type, eg SAE, AE leading to discon, etc) will be organized by subject ID and then chronological order of events for that subject. For example, if subject 1 had 3 SAEs with start dates of 01 January, 01 February, and 01 March, there will be 3 narratives in the following order:

- Subject 1, SAE with onset of 01 January
- Subject 1, SAE with onset of 01 February
- Subject 1, SAE with onset of 01 March
- Then subject 2, then subject 3, etc

Attachment 3 of this response contains sample narratives for a subject who experienced an event in the double blind period of a study and another event in the open label extension period.

Meeting Discussion: We prefer that all SAEs for a single subject be presented in a single narrative.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The Division stated that, on face, data from trials 20120296, 20120297, 20120178, 20120295 and 20130255 provide an adequate basis to support a BLA submission for migraine prophylaxis in adults if the safety database provided is consistent with what was described in Table 36 of your briefing package.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- The need for a REMS was not addressed at this meeting. Whether a REMS will be required is a matter of review.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the items listed in Attachment 2 could be submitted after filing provided that the sponsor identify at the time of filing which items will be provided at a later date. We agreed to accept preliminary data from the treadmill study at the time of filing and the complete study report at the 120-day update with the caveat that the study contains the data as described by the sponsor at this meeting (see question 6 for details).

Prominently identify each submission containing your late component with the following wording in bold capital letters at the top of the first page of the submission:

BLA NUMBER: LATE COMPONENT - CLINICAL

In addition, we note that a chemistry pre-submission meeting was scheduled for November 30, 2016. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

ATTACHMENTS AND HANDOUTS

Attachment 1: Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

Attachment 2: DNP Pre-NDA/Pre-BLA Meetings: General Clinical Safety Requests

Attachment 3: Sponsor Study design and Treatment Schemas

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017**, the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

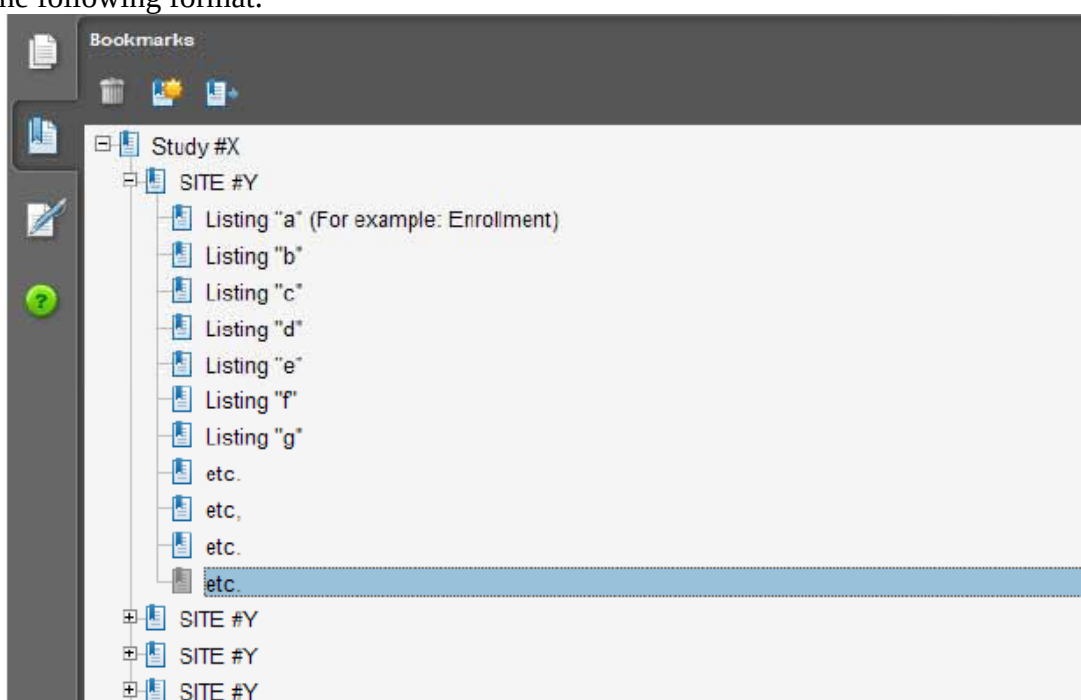
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates

- g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

Attachment 2

DNP Pre-NDA/Pre-BLA Meetings
General Clinical Safety Requests

General Submission Contents:

1. Provide DSMB meeting minutes (including any data/slides presented). For those meetings that were cancelled or meetings where no minutes were taken, please include a place holder for that meeting noting such and signed by a member of the clinical team. Please also ensure that these packages come with a table of contents and are bookmarked by date.
2. Include information regarding important regulatory actions in other countries and foreign labeling (translated, if applicable).
3. Submit an annotated version of the pre-BLA meeting minutes that include hyperlinks, when applicable, to the analysis and/or documents requested.
4. Include a copy of each clinical study protocol as well as each amended protocol. Provide a list of the inclusion and exclusion criteria for each of the studies, including those introduced as part of protocol amendments. Please submit all versions of the protocols (and Statistical Analysis Plan) and the date when changes were implemented. Please ensure that a Summary of Changes for each version is included.
5. Include active hyperlinks from the lists of references to the referenced article.
6. Follow the requirements noted in 21CFR 314.50 (d)(5)(vi), Summary of Safety Information and the [Guideline for the Format and Content of the Clinical and Statistical Sections of an Application](#)
7. Provide an assessment of safety as per the [FDA Guidance for Industry: Premarketing Risk Assessment](#)
8. In addition to the comprehensive analyses performed for the pivotal trials, the ISS should also comprehensively integrate safety analyses for all other study group pools for treatment-emergent adverse events (TEAEs), deaths, serious adverse events, discontinuations for TEAEs, TEAEs of special interest, subgroups, and vital sign/laboratory/ECG measurements.
9. Submit a table detailing all of the tables and figures featured in the clinical efficacy and safety sections of the application. The table should contain the following:
 - a. Title of the table or figure in the application
 - b. A hyperlink to the location of the table or figure with page number
 - c. A hyperlink to the SAS code used to create the table or figure (including information regarding the datasets that were used)
10. Format the tables of the ISS according to examples in FDA's [Reviewer Guidance – Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review](#)

Adverse events:

1. Follow the coding rules for MedDRA in the ICH-endorsed “MedDRA Term Selection: Points to Consider” document.
2. For each of the studies, the submitted datasets should contain both the verbatim terms and the MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event,

MedDRA coding should be provided for the primary MedDRA path as well as the alternative MedDRA coding paths.

3. Provide a summary table of the original AE coding dictionaries that were used in each of the trials.
4. Ensure that all adverse events are presented, and not only events deemed “drug-related.”
5. Provide a table of treatment-emergent adverse events reported in $\geq 2\%$ of subjects (after rounding) in any drug treated dose group (and greater than placebo) sorted by MedDRA SOC (in alphabetical order) and then by MedDRA Preferred Term.
6. Provide a table which summarizes the outcomes of all pregnancies. Provide a table which summarizes all known adverse events in subject offspring.

Narratives and Case Report Forms (CRFs):

1. Provide narratives and case report forms for deaths, all discontinuations, SAEs, pregnancies, and AEs of special interest. You should be prepared to supply any additional CRFs or narratives with a rapid turnaround upon request.
2. Include a word file (and excel spreadsheet) that indicates those subjects for whom you submitted a case report form and/or narrative. This file should include an indicator for whether each item was submitted and the reason why it was submitted along with hyperlinks to the case report form and/or narrative.
3. Provide reports for any autopsies conducted during any of the studies.
4. Provide a line listing, narrative, and case report form for all subjects who fit the Hy’s Law lab criteria.
5. Note that CRFs should include all clinical documents collected about the patient regardless of whether you label them “CRFs”, e.g., Medwatch/CIOMS forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.
6. Provide both narratives and CRFs for all discontinuations (including Lost to follow-up, Other, Physician/investigator decision, Patient decision, Withdrew consent). Provide a tabular listing of all subjects with discontinuations, sorted by reason. The table should include columns for study number, treatment group, unique subject ID, primary reason for discontinuation; for reasons including Lost to follow-up, Other, Physician/investigator decision, Withdrew consent, and Patient decision, provide more specific information regarding the discontinuation.
7. Narrative summaries should provide a complete synthesis of all available clinical data and an informed discussion of the case. The narratives should be comprehensive enough for the reader to come to a reasonable conclusion regarding the subject and the adverse event. The following items should be included (but not limited to):
 - Patient age and gender
 - Adverse event onset and stop dates (presented as relative Study Day number)
 - Signs and symptoms related to the adverse event being discussed
 - An assessment of the relationship of exposure duration to the development of the adverse event
 - Pertinent medical history
 - Concomitant medications with start dates relative to the adverse event

- Pertinent physical exam findings
- Any abnormal vital sign measurements
- Pertinent test results (e.g., lab data, ECG data, biopsy data, autopsy results)
- Discussion of the diagnosis as supported by available clinical data
- For events without a definitive diagnosis, a list of the differential diagnoses
- Treatment provided
- Re-challenge results (if performed)
- Outcomes and follow-up information

Laboratory and Vital Sign Measurements:

1. Refer to the following FDA webpage for the CDER position on use of SI units for lab tests:
[SI Units](#)
2. Provide the normal reference ranges for every laboratory value.
3. Clearly list the normal values, as well as the thresholds for analysis of outliers, for outlier analyses of laboratory data, vital signs data and ECG data.
4. When possible, use the latest version of the National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) for toxicity grades and shift analyses.
5. Report the number and percentage of subjects with at least one post-treatment vital sign measurement meeting any of these criteria:
 - Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mmHg
 - Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg
 - Pulse Rate: <60 bpm, >100 bpm
 - Body Weight: decrease of $\geq 7\%$ from baseline and increase of $\geq 7\%$ from baseline
 - Temperature: >38.0 °C, <36.0 °C
 - Respiratory rate: <12 breaths/min, > 20 breaths/min
6. Summarize the protocols for collecting ECG data. Summarize the frequency of post-treatment QTc >450 ms, >480 ms, and >500 ms.

Other requests:

1. Submit individual patient profiles containing all laboratory and other study results in a single place for each patient. Provide this information for patients who died, had a serious adverse event, discontinued from the trial due to an adverse event, or had a medically significant event for which a narrative is submitted. Include all the information recorded for that patient, including but not limited to:
 - Age
 - Sex
 - Dates of screening, randomization and starting therapy
 - Whether the patient completed or did not complete the study, with dates and reason for withdrawal
 - Adverse events (reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
 - Prior medications and concomitant medications with dates of start and end

- Vital signs and laboratories, sorted by date, with reference ranges *
- Full reports for radiologic studies, ECG, MRI, pathology results, and special studies with dates and reference ranges *
- Autopsy reports for all deaths. (If an autopsy report is not available, explicitly state this.)

* Provide relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, in each patient file. Also include baseline study results.

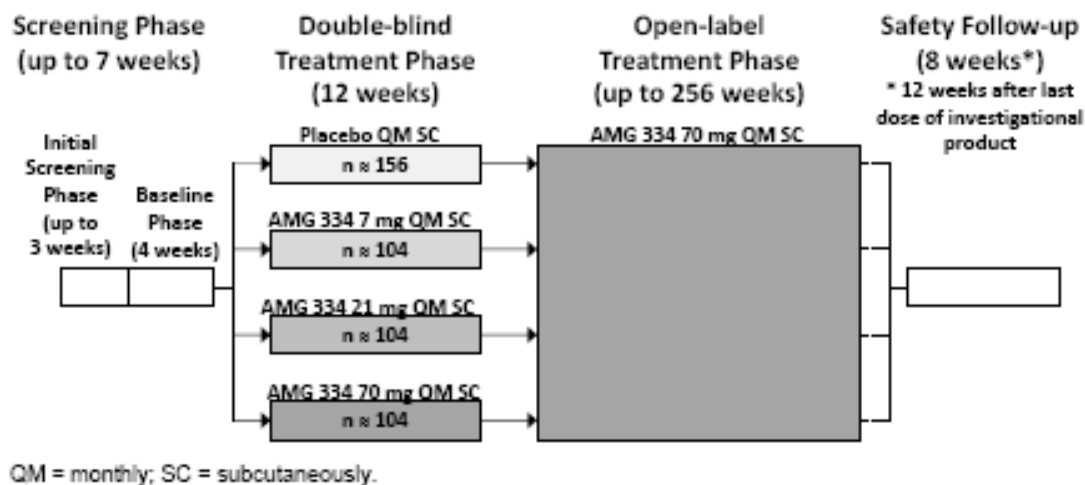
For patients who had IND safety report(s), include dates when the initial and follow up safety reports were submitted to IND 116098.

Create a PDF file for each patient and a table of contents with links to each assessment for each patient.

Attachment 3: Study Design and Treatment Schemas

Study 20120178 : A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of AMG 334 in Migraine Prevention

Figure 8-1. Study Schema



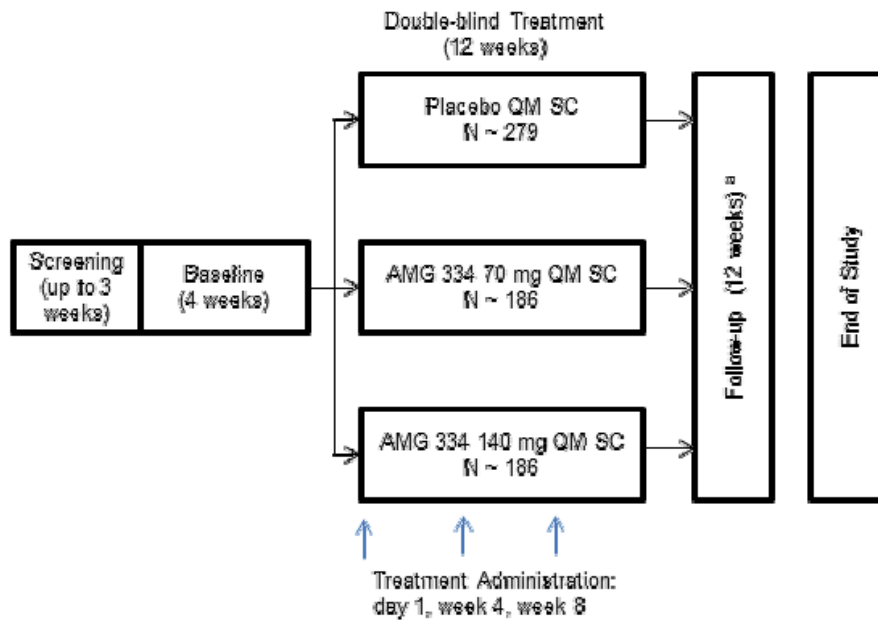
Study 20130255: An Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of AMG 334

Study Design and Treatment Schema



Study 20120295: A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of AMG 334 in Chronic Migraine Prevention

Figure 8-1. Study Design and Treatment Schema

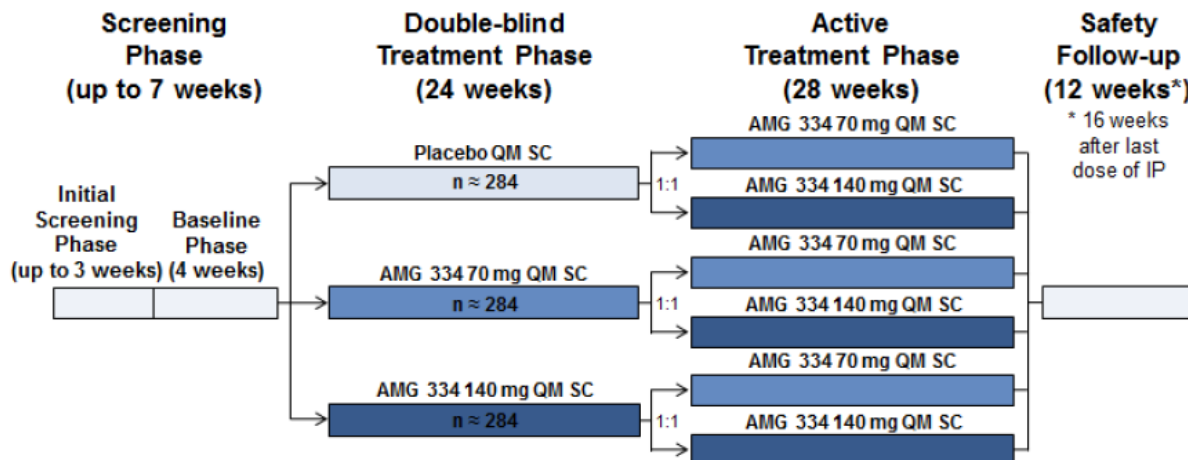


QM = monthly (every 4 weeks); SC = subcutaneous.

^a 16 weeks after last dose of investigational product

Study 20120296: A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of AMG 334 in Migraine Prevention

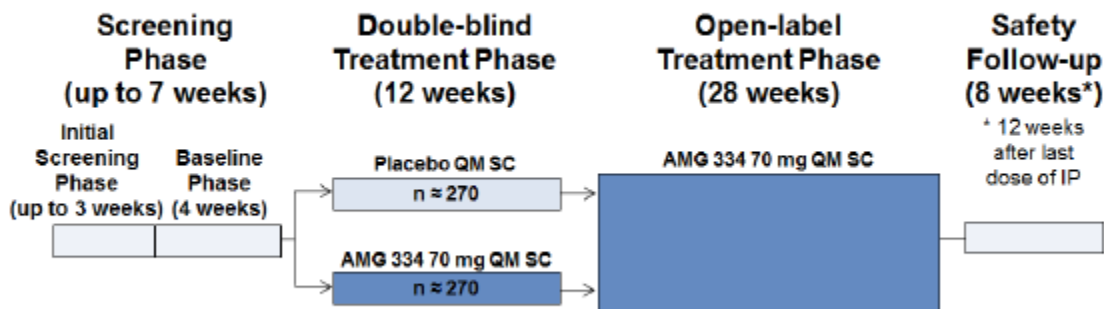
Study Design and Treatment Schema



IP = investigational product; QM = monthly; SC = subcutaneous

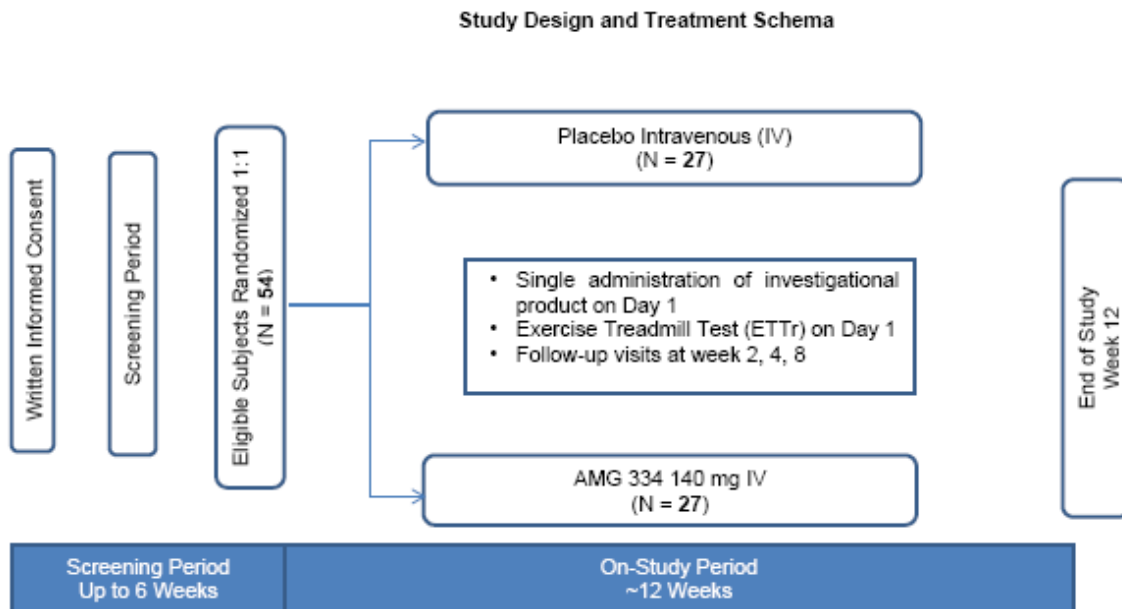
Study 20120297: A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of AMG 334 in Migraine Prevention

Study Design and Treatment Schema



IP = investigational product; QM = monthly; SC = subcutaneous

Study 20140254: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effect of AMG 334 on Exercise Time During a Treadmill Test in Subjects With Stable Angina



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

/s/

ERIC P BASTINGS
02/28/2017



IND 116,098

MEETING MINUTES

Amgen, Inc.
Attention: Vanessa Shurn
9201 Corporate Blvd, Suite 400
Rockville, MD 20850

Dear Ms. Shurn:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AMG 334.

We also refer to the meeting between representatives of your firm and the FDA on March 4, 2015. The purpose of the meeting was to discuss your development program.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Lana Chen, Regulatory Project Manager at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Eric Bastings, M.D.
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: March 4, 2015
Meeting Location: FDA White Oak

Application Number: IND 116,098
Product Name: AMG 334
Indication: Migraine Prophylaxis
Sponsor/Applicant Name: Amgen

Meeting Chair: Billy Dunn, MD, Director, DNP
Meeting Recorder: Lana Chen, RPh, Project Manager

FDA ATTENDEES

Division of Neurology Products

Billy Dunn, MD, Director
Eric Bastings, MD, Deputy Director
Suhail Kasim, MD, Clinical Reviewer
Kun Jin, PhD, Statistical Team Leader
Junshan Qiu, PhD, Statistical Reviewer
Angela Men, PhD, Clinical Pharmacology Team Leader
Michael Bewernitz, PhD, Clinical Pharmacology Reviewer
Lana Chen, RPh, Project Manager

Sarrit Kovacs, PhD, Study Endpoints Reviewer
Bindi Nikhar, MD, Associate Clinical Director, Office of Combination Products
Ethan Hausman, MD, Clinical Reviewer, Division of Pediatric and Maternal Health

Division of Medication Error Prevention and Analysis (DMEPA)

Lolita White, PharmD, Safety Evaluator
Danielle Harris, PharmD, BCPS, Team Leader
Irene Chan, PharmD, BCPS, Associate Director

Via Phone:

Chana Fuchs Ph.D., Product Quality Team Leader, Office of Biotechnology Products

SPONSOR ATTENDEES

Mark Taisey, Vice President, Global Regulatory Affairs
Drew Badger, Director, Global Regulatory Leader
Lisa Mathis Bollinger, Executive Director, Global Regulatory Affairs
Chris Walker, Executive Director, Global Regulatory Affairs
Robert Lenz, Executive Medical Director, Global Development
Hong Sun, Medical Director, Global Development
Suzanne Kiani, Director, Regulatory Affairs, Device
Ganesh Balasubramanian, Director, Toxicology
Vanessa Shurn, Senior Manager, US Regulatory Leader
Arline Nakanishi, Executive Director, Biostatistics
Yun Chon, Director, Biostatistics
Marie-Louise Trotman, Director, Biostatistics
Ed Lee, Senior Manager, Clinical Pharmacology
Javier Waksman, Medical Director, Global Safety
Thuy Craveiro, Senior Scientist, Clinical Pharmacology Modeling and Simulation
Nina Cauchon, Senior Manager, Regulatory Affairs

DISCUSSION

Question 1 – Phase 3 Studies

Does the Agency agree that the proposed global, randomized, double-blind, placebo controlled, pivotal, phase 3 studies (Studies 20120296 and 20120297) are sufficient to support product registration for prophylaxis of episodic migraine headache in adults? In particular, Amgen seeks Agency feedback regarding the following:

FDA Response:

On face, the proposed phase 3 studies (Studies 20120296 and 20120297) appear adequate to support product registration for prophylaxis of episodic migraine headache in adults. However, we note that your completed study in episodic migraineurs (Study 20120178) has many of the characteristics of an adequate and well-controlled pivotal efficacy trial. We are open to an argument that the results of that study could also support a marketing application for your product.

Amgen Draft Response:

Amgen agrees that Study 20120178 has characteristics of an adequate and well-controlled pivotal study. There were two data review groups/committees who reviewed unblinded safety and efficacy data during the trial. The trial included a Data Review Team, which is an internal group of Amgen employees who assess the unblinded safety data of the ongoing double-blind portion of the study. This team comprised two clinicians and one statistician who were independent from the clinical study team. Appropriate firewalls were established between them and the team and a charter was drafted and followed. No unblinded data was shared with the study team and no modifications to the study were made based on the review of the safety data. There was a second group of internal Amgen employees and an external statistician who served on an Interim Analysis Steering Committee. This group was composed on the Global

Development Lead, the VP of the Development therapeutic area, two internal statisticians, and an independent, external statistician. None of these members had study responsibilities, and appropriate firewalls were put in place and the processes were captured in a formal charter. No data was shared with the study team and no actions were planned or taken based on reviews of the efficacy data. Amgen considers that, due to the appropriate firewalls put in place as well as the lack of any modification to the trial, Study 20120178 could serve as an adequate and well-controlled pivotal study. Does FDA agree?

Discussion at Meeting:

Amgen provided further clarification to their response to DNP preliminary comments regarding their unblinded review of the data from the completed phase 2b EM study (Study 20120178), which may be used as a pivotal trial. Amgen confirmed that all protocol amendments were submitted to the IND and procedures associated with interim data evaluations were well documented. Amgen was informed to submit a justification supporting utility of Study 20120178 as a pivotal study to the IND, including a description of the Data Review Team Charter and any changes to the study protocol and SAP during or after the study associated with interim data reviews.

- a. Study duration: Does the Agency agree with the proposed study durations to demonstrate safety and efficacy?

FDA Response:

A 24-week double-blind treatment phase is acceptable, and exceeds the minimum required duration of a pivotal study for that indication (i.e., 3 months).

Discussion at Meeting:

None. Amgen acknowledges FDA's feedback.

- b. Study Population: Does the Agency agree with the selected study population as defined by the inclusion and exclusion criteria described in the phase 3 protocols ([Appendix 5](#) and [Appendix 6](#))?

FDA Response:

Yes, the selected study population, as defined by the inclusion and exclusion criteria described in the phase 3 protocols, is acceptable.

You state that elderly patients will be excluded from the pivotal phase 3 trials due to the potential for misdiagnosis (which may confound efficacy). You also indicate that, according to the EMA guidance regarding special populations for the treatment of migraine, pharmacokinetic data and safety data may be sufficient in elderly patients suffering from migraine for many years. We agree, but recommend you include a sufficient number of patients ≥ 65 years in your open label safety studies to characterize the safety profile in that population. Your proposal to characterize the pharmacokinetics in the elderly subpopulation using pharmacokinetic data obtained from 25 patients age ≥ 65 years in the exercise treadmill Study 20140254 is acceptable.

Amgen Draft Response:

Amgen would like to clarify that patient's ≥ 65 years are not eligible to participate in the open label portion of the currently proposed phase 3 trials since this is a continuation of the double-blind study that excludes patients ≥ 65 years. It is expected that many patients >65 years will not meet study entry criteria based on not fulfilling the diagnostic criteria for migraine. Therefore, removing the upper age limit is unlikely to result in meaningful numbers of patients with migraine aged > 65 years. Therefore at the time of registration, safety and pharmacokinetic data will be available from approximately 25 patients age ≥ 65 years from the exercise treadmill Study 20140254. Amgen would like to confirm that this amount of data is acceptable to support registration and a product label that allows use in patient's ≥ 65 years.

Discussion at Meeting:

In order to support information for labeling in patients ≥ 65 years of age, it was communicated that Amgen should include AMG 334 exposure data on as many patients ≥ 65 years as possible, but that this issue would not impact product approvability.

- c. Dosing Rationale: Does the Agency agree that the results of the phase 2 study primary analysis (Study 20120178) support the proposed dose selection for phase 3?

FDA Response: We agree that 70 mg is a reasonable dose to study, but we recommend evaluating a higher dose as well (e.g., 140 mg). In addition, your simulations show that with a fixed dose of 70 mg, patients with a higher body mass are expected to experience a smaller reduction in migraine days, and you therefore may want to consider weight-based dosing. Topline results from the ongoing study in chronic migraineurs (Study 20120295) should additionally guide your selection of the appropriate dose(s) prior to initiation of the proposed phase 3 pivotal studies in patients with episodic migraine.

(b) (4)

(b) (4)

However, an alternate approach would be to include a 140 mg arm into the proposed phase 3 trials.

Amgen Draft Response:

Amgen appreciates the Agency response, and seeks further discussion of dose selection and filing scenarios during the EOP2 meeting. Although PK-PD simulations suggest patients in the upper quartile of body weight (>85 kg) have smaller reductions in steady-state migraine days with fixed-dosing relative to weight-based dosing, the distributions of predicted responses for these 2 weight groupings largely overlap. The mean change in migraine days for the upper quartile body weights was only 8% different from that in subjects with body weights in the interquartile body weight range ($63.3\text{kg} < \text{Wt} < 85.4\text{kg}$). This difference is not expected to be clinically meaningful since it is much smaller than the magnitude of the overall variability in migraine response in subjects with bodyweights in the interquartile range ($\text{CV}=100\%$). Thus, the PK, and efficacy data support fixed doses in the phase 3 trials.

Discussion at Meeting:

Amgen clarified their position on the doses selected, and were informed that a dose of 70 mg AMG 334 vs. placebo in the proposed Phase 3 studies in EM would support registration, if found to be safe and effective.

Amgen further discussed the FDA recommendation to evaluate a higher dose in addition to the proposed 70 mg dose (e.g., 140 mg). Amgen stated that their exposure response modeling predicts that the 140 mg dose will not produce a meaningfully improved clinical benefit relative to 70 mg dose. The results of ongoing Phase 2b CM study (Study 20120295), which evaluates AMG 334 doses of 70 mg and 140 mg, will be available in early 2016. At that time, if results of the Phase 2b CM study indicate that a 140 mg dose of AMG 334 has a clinically meaningful improved benefit relative to 70 mg, Amgen would consider conducting a single pivotal trial in EM with AMG 334 70 mg, AMG 334 140 mg, and placebo. FDA confirmed that an additional single EM trial that includes AMG 334 70 mg and AMG 334 140 mg vs. placebo could provide sufficient evidence for approval of AMG 334 140 mg when combined with the data from the Phase 2b CM study that included evaluation of AMG 334 140 mg dose.

(b) (4)

- d. Endpoints: Does the agency agree with the proposed primary and secondary endpoints?

FDA Response:

Primary endpoint: The change from baseline in mean monthly migraine days is an acceptable primary endpoint.

Secondary endpoints:

The following secondary endpoints in each of the pivotal phase 3 studies appear acceptable; however, their inclusion in labeling requires demonstration of statistically significant results after controlling for multiple comparisons:

- 50% responder rate: defined as the proportion of subjects with 50% reduction in number of migraine days over months 4, 5 and 6 in the double-blind treatment phase
- Mean monthly migraine-specific medication days: defined as change from baseline in monthly use days of migraine-specific medication for acute treatment (e.g., triptans, ergotamine) over months 4, 5 and 6 in the double-blind treatment phase
- Mean monthly migraine hours: defined as change from baseline in monthly migraine hours over months 4, 5 and 6 in the double-blind treatment phase

In addition, you proposed the following patient-reported outcomes (PROs) as secondary endpoints:

- Physical impairment: change (reduction) from baseline in physical impairment of the last 3 months (months 4, 5, and 6) of the double-blind treatment phase as measured by the Migraine Physical Function Impact Diary (MPFID)
- Everyday activities: change (reduction in impact) from baseline in everyday activities of the last 3 months (months 4, 5, and 6) of the double-blind treatment phase as measured by the MPFID

Assessing migraine impact on patients' physical impairment and everyday activities appears important and meaningful to patients. However, we do not have enough information in order to review the MPFID's content validity. We do not have the instrument evidence dossier. Please provide the following items for our review:

1. Patient interview transcripts and saturation grid.
2. A conceptual framework that includes the MPFID items and whether or not each of them relate to a domain.
3. A copy of the final revised instrument used in your pivotal phase 3 clinical trials. For example, during the June 18, 2014, meeting, the Agency recommended that you consider revising the instrument's instructions so that patients are not forced to attribute their symptoms to migraine and you agreed to work on revising the instructions.
4. MPFID user manual, including the screen shots and patient instructions for the diary, as well as any patient, investigator, and site training materials

We recommend you request a separate meeting for a focused discussion of these PROs in the presence of additional data.

Amgen Draft Response:

Amgen appreciates the Agency's response and indicated that we plan on requesting a separate PRO Type C Meeting in the coming months.

Discussion at Meeting:

None.

Question 2 – Phase 3 Statistical Testing Strategy

(b) (4)

FDA Response:

(b) (4)
we have some preliminary comments on the protocols as below.

In addition to specifying the interim analysis at the time of 80% of the patients randomized, the subset of the randomized population used for variance estimation should be specified in the protocol.

The generalized estimation equation (GEE) procedure implements the inverse probability weighted method to account for dropouts under the missing at random (MAR) assumption. Sensitivity analyses based on missing not at random (MNAR) need to be proposed to check the robustness of the primary results. In addition, please provide details of the IPW method such as missing mechanism models and a strategy for handling non-convergence issues.

Amgen Draft Response:

(b) (4)

Discussion at Meeting:

None.

Question 3 - Indication

- a. Does the Agency agree that positive data from the ongoing study in subjects with chronic migraine (Study 20120295) along with positive data from the 2 pivotal phase 3 studies in episodic migraine (Studies 20120296 and 20120297) are sufficient to support registration for the indication “prophylaxis of episodic and chronic migraine headaches in adults”?

FDA Response:

On face, your approach appears acceptable to support registration for the indication “prophylaxis of migraine headaches in adults” based on results from the proposed episodic migraine (Studies 20120296 and 20120297) and the chronic migraine study (Study 20120295). As previously discussed with you during the Type C meeting on March 12, 2013, positive trial results from single adequate and well-controlled studies in each population (episodic and chronic migraine) would be sufficient to support a global prophylaxis claim, for the dose(s) demonstrated to be effective in these (initially submitted) registration studies. In addition, please see our responses to Question 1-c and Question 3-b regarding evaluating additional doses.

Amgen Draft Response:

Amgen appreciates the Agency’s response, no further discussion is needed.

Discussion at Meeting:

None.

b.



FDA Response:

This is possible, but would be a matter of review. As discussed above, we recommend including the additional 140 mg dose in your proposed phase 3 episodic migraine studies (Studies 20120296 and 20120297). Please see our response to Question 5 regarding the safety database to support registration of the 140 mg dose.

Amgen Draft Response:

Amgen appreciates the Agency’s response and any further questions will be addressed during discussion of responses to Question 1.

Discussion at Meeting:

This item was addressed during discussion with Question 1c.

Question 4 – Clinical Pharmacology

Does the Agency agree that the planned clinical pharmacology program is sufficient to support product registration? Does the Agency agree with the proposal not to conduct dedicated renal and hepatic impairment studies?

FDA Response:

- Topiramate/Sumatriptan Interactions:

In Study 20120298, you should measure the trough level of topiramate to assess the effect of topiramate on AMG 334 pharmacokinetics as well as the effect of AMG 334 on topiramate pharmacokinetics.

Amgen Draft Response:

We would like to clarify that study 20120298 is a head to head Ph3b tolerability study comparing AMG 334 to topiramate. AMG 334 and topiramate will be not co-administered and thus collecting PK will not provide information on the effect of AMG 334 on topiramate pharmacokinetics..

Discussion at Meeting: The Sponsor was asked if they intended AMG 334 to be used concomitantly with topiramate. The Sponsor replied that they are not intending for topiramate to be used concomitantly with AMG 334. The Division responded that in this case, an in-vivo drug interaction study (as per the “2nd pathway” in Figure 7 of the current drug interaction guidance) will not be required.

In the proposed sumatriptan interaction study (Study 20140255), you should assess sumatriptan pharmacokinetics. In addition, you should assess the effect of AMG-334 on sumatriptan pharmacokinetics as well as the effect of sumatriptan on AMG 334 pharmacokinetics. Also, you should prohibit the use of MAO-A inhibitors in Study 20140255 trial, as concomitant use with sumatriptan is contraindicated (according to the current Imitrex label).

Amgen Draft Response:

Study 20140255 is a pharmacodynamic interaction study designed to evaluate the effect on blood pressure when AMG 334 is co-administered with sumatriptan relative to sumatriptan alone. This study is not designed to assess pharmacokinetic interactions as we feel such an assessment is not warranted because AMG 334 and sumatriptan are cleared via different pathways, i.e., target mediate clearance/protein catabolism and monoamine oxidase type A, respectively. Additionally, there are no reports of monoclonal antibody drugs affecting monoamine oxidase type A expression or small molecule drugs affecting the catabolism of monoclonal antibody

drugs. Thus, we feel additional PK sampling in this pharmacodynamic study is unnecessary.

Discussion at Meeting: FDA clarified that, per the current DDI guidance, if sumatriptan is to be co-administered with AMG-334, a pharmacokinetic drug interaction needs to be evaluated. The Division acknowledged that there is no mechanistic basis to suggest that sumatriptan will alter the biotransformation of a monoclonal antibody such as AMG 334. In addition, FDA acknowledged that AMG 334 is not expected to be co-administered with sumatriptan chronically, as sumatriptan is only used to treat acute migraine. Therefore, an in-vivo pharmacokinetic drug interaction study is not necessary.

- Specific Populations: The proposal to not conduct renal impairment and hepatic impairment studies is acceptable.

Amgen Draft Response:

Amgen appreciates the Agency's response and no further discussion is needed.

Discussion at Meeting:

None.

- Immunogenicity Assessments: The immunogenicity assessments in the proposed phase 3 trials occur only during the 24-week double-blind phase. However, this medication is intended for use beyond 24-weeks. For patients that demonstrate a positive immune response during the double-blind phase, you should continue assessing immunogenicity into the open-label phase.

Amgen Draft Response:

Amgen would like to clarify that immunogenicity assessments will also be performed during the open label treatment phase. The timepoints for assessment during the open label phase are weeks 28, 36 and 52 (page 443 of the briefing book). For subjects who test positive for neutralizing antibodies to the investigational product at the final scheduled study visit or following unblinding will be asked to return for additional follow-up testing. This testing is to occur approximately every 3 months starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable, or (2) the subject has been followed for a period of at least 1 year ($\pm$ 4 weeks) after the last dose of investigational product.

Discussion at Meeting:

The Agency confirmed that Amgen's strategy for immunogenicity sampling was acceptable.

Question 5- Safety Database

Does the Agency consider the size of the overall safety database and the duration of exposure at the time of submission of the initial marketing application sufficient to support approval for the proposed indication of prophylaxis of episodic and chronic migraine?

FDA Response:

Even though any decisions regarding adequacy of the safety data is a matter of review, your proposal appears acceptable based on the exposures proposed in Table 3 of your submission that will support registration of 70 mg AMG 334 for episodic and chronic migraine prophylaxis. Your safety database should include AMG 334 exposures with monthly injections at the maximal recommended dose proposed for registration in at least 150 subjects for 6 months, and at least 50 subjects for one year.

Your safety database planned at the time of the marketing application for the 140 mg dose will include a total of approximately 500 subjects who will be exposed to AMG 334 at 140 mg, and approximately 100 of these subjects will be exposed at 140 mg for ≥ 1 year, which would be acceptable.

Amgen Draft Response:

Amgen appreciates the Agency's response, no further discussion is needed.

Discussion at Meeting:

None.

Question 6- Cardiovascular-Related Safety

Does the Agency agree with Amgen's plan of not conducting a thorough QT study and with the ECG monitoring plan for the proposed phase 3 studies?

FDA Response:

Yes.

Amgen Draft Response:

Amgen appreciates the Agency's response, no further discussion is needed.

Discussion at Meeting:

None.

Question 7- Systemic Blood Pressure

Does the Agency agree that the studies completed to date in combination with monitoring plans described in planned studies will adequately characterize the theoretical risk of increasing blood pressure associated with the mechanism of action of AMG 334?

FDA Response:

On face your proposal appears acceptable. However, the acceptability of your database addressing increase in blood pressure will be a matter of review.

Amgen Draft Response:

Amgen appreciates the Agency's response, no further discussion is needed.

Discussion at Meeting:

None.

Question 8 – Characterization of Putative Cardiovascular Risks

Based on available preclinical and clinical data with CGRP antagonists and cumulative data from completed, ongoing, and planned clinical studies with AMG 334, does the agency agree that the theoretical cardiovascular risks associated with the mechanism of action of AMG 334 are characterized adequately?

FDA Response:

The acceptability of your database to address the theoretical cardiovascular risks associated with the mechanism of action of AMG 334 will be a matter of review. On face, your proposal appears acceptable.

Amgen Draft Response:

Amgen appreciates the Agency's response, no further discussion is needed.

Discussion at Meeting:

None.

Question 9 – Evaluation of Abuse Liability

Given the low potential for central nervous system (CNS) penetration with AMG 334, and the lack of evidence for abuse liability from the preclinical/clinical studies to date, Amgen is not planning to conduct preclinical or clinical abuse liability studies. Does the Agency agree?

FDA Response:

We will provide our response in our final meeting minutes.

Discussion at Meeting:

This question was not discussed at the meeting. Response will be provided in the final meeting minutes.

Post- Meeting Response:

In determining if a drug needs to be studied for its abuse potential, CSS relies on the principles described in the draft *Guidance for Industry: Assessment of Abuse Potential of Drugs* (2010) for general guidance (e.g. description of binding studies typically conducted for CNS active drugs) <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>). As stated in this draft guidance the abuse potential of a drug needs to be assessed if the drug has a central nervous system effect, or is pharmacologically similar in activity to other drugs with known abuse potential, or produces psychoactive effects such as sedation, euphoria, and mood changes.

While AMG 334 has a mode of action in the CNS *per se*, it does not appear to be chemically or pharmacologically similar to any other drug with known abuse potential. AMG 334 interacts with the extracellular domains of the CGRP receptor and blocks the action of CGRP. The CGRP receptor is made up of a G-protein-coupled calcitonin-like receptor (CLR) and a single transmembrane domain protein receptor-activity-modifying protein (RAMP1). Nonclinical

studies with AMG 334 revealed that it binds and antagonizes both human and monkey CGRP receptors and doesn't bind or binds to the CGRP receptor in other species, including rat, dog, and rabbit. We ask, as part of your safety analysis, you continue to monitor for abuse-related adverse events in all Phases of development. If proposed, we will provide comments on any future protocol(s) relating to the abuse potential of AMG 334. It does warrant noting that some endogenous peptides, such as insulin or transferrin, undergo receptor-mediated transport (RMT) across the BBB *in vivo* (Pardridge, 2007). "Molecular Trojan horses" may be formulated with fusion protein technology, avidin-biotin technology, or Trojan horse liposomes for targeted delivery across the BBB with virtually any large molecule pharmaceutical (Pardridge, 2007).

NOTE: Formal drug discrimination, conditioned place preference, and self-administration studies are not necessary at this point.

Question 10 – Nonclinical Data Package

Does the Agency agree that the proposed nonclinical data package (pharmacology, pharmacokinetics, and toxicology) is sufficient to support the phase 3 clinical trials and product registration?

FDA Response:

The proposed nonclinical program is sufficient to support Phase 3 clinical trials. The adequacy of the studies will be a matter of review. To support your carcinogenicity study waiver request, you should submit a waiver request, with justification, and all supportive data, to the IND for review.

If clinical trials are to be conducted in pediatric patients <12 years of age, you will need to conduct a juvenile animal toxicology study in one species (typically, rat). (See ADDITIONAL CLINICAL COMMENTS: Pediatric Studies.)

Amgen Draft Response:

Amgen appreciates the Agency's response, no further discussion is needed.

Discussion at Meeting:

This question was not discussed at the meeting. Amgen indicated that it would be requesting a Type C meeting with the Agency later in the year to discuss the PSP based on Day 60 comments.

Post Meeting Request for Further Agency Clarification

As discussed at the EOP2 meeting, Amgen will conduct an enhanced pre/postnatal developmental toxicity study in female cynomolgus monkeys consistent with ICH M3[R2] and ICH S6[R1], 2011 guidance. In this study, pregnant females will be dosed from gestation day 20 to 22 through parturition. The infants will be evaluated for skeletal and morphologic endpoints after birth and then followed for 6 months for assessment of various postnatal development endpoints. Amgen would like to confirm the acceptability of submitting an audited interim report that includes 1-month post-partum evaluations at the time of initial BLA filing to support product registration. The final report will also be submitted to the IND subsequent to the initial BLA filing.

FDA Post Meeting Response:

A final study report for the enhanced pre- and postnatal developmental toxicity study in female cynomolgus monkeys should be included in the initial BLA submission.

Question 11 - Device

- a. Does the Agency agree that the proposed bioequivalence study (Study 20140477) as proposed will allow adequate bioequivalence assessment of the prefilled syringe presentation and autoinjector presentation to support approval of the prefilled syringe and autoinjector at initial market launch?

FDA Response:

The proposed approach to assess whether the pre-filled syringe is bioequivalent to the pre-filled syringe with an autoinjector is, on face, acceptable.

However, Study 20140477 will assess bioequivalence based on abdomen injections, yet the proposed phase 3 trials will allow injections into the abdomen, upper leg, and upper arm. Please provide information on whether the bioavailability for each of the 3 injection sites is comparable.

Amgen Draft Response:

Published data indicate that monoclonal antibody drugs have similar bioavailability across these 3 injection sites (Xu et al, J Clin Pharmacol 2010;50:276-284). Abdomen was the only injection site chosen by patients in Ph2. PK samples and injection site will be collected in the Ph3 and a population PK analysis will be conducted to confirm injection site is not a significant pharmacokinetic covariate..

Discussion at Meeting: The Division asked what injection sites will be selected for each patient and each successive AMG 334 administration. The Sponsor stated that the injection site will be selected based on patient preference. For an individual subject, once the injection site is selected, the Sponsor intends to use only that injection site for each administration for the whole duration of the trial.

FDA stated that use of a population PK approach to assess the comparability of the injection sites is acceptable. This approach is appropriate for the proposed plan under which each patient will receive AMG 334 injections in a site of their choice, and within that same site throughout the trial.

(b) (4)

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Additional Device comments

You have provided minimal information regarding the design of the device constituent parts of the proposed pre-filled autoinjector and pre-filled syringe combination products. Within future investigational or marketing applications, the Agency expects that you will provide all necessary information to support the safety and functionality of the constituent parts. You are advised to consult the following guidance documents and consensus standards prior to future investigational or marketing applications:

- Guidance Document: Technical considerations for Pen, jet, and Related Injectors Intended for Use with Drug and Biological Products.
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147095.pdf>
- Draft Guidance Document: Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM346181.pdf>
- FDA Draft Guidance for Industry and Food and Drug Administration Staff (2012): Design Considerations for Devices Intended for Home Use
<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm331681.pdf>
- ISO 11040-4 Prefilled Syringes-Part 4: Glass barrels for injectables.
- ISO 11040-5 Prefilled Syringes-Part 5: Plunger stoppers for injectables.
- ISO 11608-1:2012: Needle-based injection systems for medical use – Requirements and test methods-Part 1: Needle-based injection systems, Part 2: Needles and Part 3: Finished Containers.

If either device will consist of a Sharps Injury prevention feature:

- Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features.
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071663.htm>
- ISO 23908:2011: Sharps injury protection -- Requirements and test methods – Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling.

Question 12 – Target Product Label

Amgen has developed a target product label (TPL) for the Agency's consideration to ensure the overall AMG 334 development program supports our labeling goals (Appendix 1). Amgen

intends to include the target labeling concepts presented in the TPL in the US package insert, as appropriate. Does the Agency agree with the proposed labeling concepts as provided in the TPL?

FDA Response:

The precise text that will be used to describe the results of the clinical studies in the product label will be a matter for further discussion once the results of those studies are available and reviewed. You should consider all comments that follow in this context.

Amgen Draft Response:

Amgen appreciates the Agency's response, no further discussion is needed.

Discussion at Meeting:

None.

- a. Amgen is including several secondary endpoints in pivotal trials in hopes that one or more of them are deemed appropriate for inclusion in Section 14 of the product label. Does the agency agree that all of these secondary endpoints are appropriate for inclusion in the product label assuming they demonstrate statistical significance based on the statistical testing strategy described in Section 2.9.1.2? Is there a maximum number of secondary endpoints that would be appropriate for inclusion in the product label to complement the primary endpoint data?

FDA Response:

The secondary endpoints appear appropriate for inclusion in section 14 of the product label, assuming the patient reported outcome measures are validated and that they demonstrate statistical significance. In addition, please see response to Question 1-d.

Amgen Draft Response:

Amgen appreciates the Agency's response, no further discussion is needed.

Discussion at Meeting:

None.

- b. Prior Prophylactic Treatment: In the phase 3 pivotal studies, each subject's prior prophylactic treatment information will be collected during the screening phase.

(b) (4)

Does the Agency agree?

FDA Response:

Yes.

Amgen Draft Response:

Amgen appreciates the Agency's response, no further discussion is needed.

Discussion at Meeting:

None.

- c. Patient Reported Outcomes: Assuming there is a statistically significant and meaningful reduction in physical impairment and impact on everyday activities caused by migraines, does the Agency agree with plans for the location and proposed labeling concepts to reflect the PRO data in the product labeling (TPL Section 14.1, Appendix 1)?

FDA Response:

Your proposed label includes the following in Section 14:

(b) (4)

It is premature to comment on the labeling claims at this time given that there is inadequate evidence to conduct a review of the MPFID as we do not have the final instrument evidence dossier. (b) (4)

We can review proposed labeling claims if there is adequate evidence establishing the content validity, acceptable psychometric properties (including reliability, construct validity, and ability to detect change), and clinical meaningfulness of any statistical significant findings for the MPFID.

Amgen Draft Response:

Amgen acknowledges the Agency's feedback on this topic. (b) (4)

(b) (4)

Discussion at Meeting:

None. Amgen plans to request a Type C Meeting to discuss Patient Reported Outcomes.

- d. Cardiovascular Class Labeling: Amgen acknowledges the recently released draft FDA Guidance for Industry entitled, "Migraine: Developing Drugs for Acute Treatment." Under labeling considerations, it is mentioned that new drugs of other classes (ie, non-triptan) that also have the potential for vasoconstrictive effects probably would be subject to similar class labeling. It is conceivable that these labeling considerations would apply to both acute and prophylaxis migraine treatments. Unlike triptans, which are agonists that intrinsically constrict blood vessels, AMG 334 has no intrinsic vasoconstrictive property. It is an antagonist to the CGRP receptor and only reverses CGRP-induced vasodilation, returning the dilated vessels to their normal tone. In the absence of observing relevant safety signals from completed, ongoing, and proposed studies, does

the Agency agree that the pharmacologic activities of AMG 334 do not warrant class labeling similar to triptans?

FDA Response:

This is a matter of review. However, in the absence of safety signals from completed, ongoing, and proposed studies, AMG 334 may not warrant class labeling similar to triptans.

Cardiovascular Safety Assessment

The acceptability of data and the inclusion of information to support use of AMG 334 in patients with risk factors for, or history of, pre-existing coronary artery disease and at the same time the degree of cardiovascular restriction in labeling will be a NDA review issue. The data submitted from non-clinical, controlled clinical and long-term safety studies will be considered when deciding inclusion of such information in labeling, and the evidence submitted must be concordant. The data from non-clinical studies must be very convincing, since the clinical data will not have sufficient assay sensitivity because of the large number of patient exposures required to assess that risk.

In your development program you should plan to include at least 20% patients with pre-existing cardiovascular disease (with approximately 40-50 patients in the 1-year long term safety data), and include additional patients with risk factors for coronary artery disease in the 1-year long term safety data. We encourage you to include as many patients with risk factors as possible, as ultimately the acceptability of the package will be a review issue. You should also account for patient drop-outs, especially among the patients with coronary artery disease while planning the safety database.

It is acceptable to include in clinical studies patients with ischemic stroke or previous cerebrovascular disease and peripheral vascular disease who have no documented coronary disease. For purposes of safety evaluation, these patients should be included in the group considered to have pre-existing cardiovascular disease.

Amgen Draft Response:

Amgen appreciates the Agency's response. Amgen would like to understand the agency's thinking on what constitutes "convincing" non-clinical data to avoid restrictive product labeling in patients with risk factors for, or history of, pre-existing coronary artery disease. Specifically, what data gaps exist, if any, beyond those studies conducted with AMG 334 and the broader class of CGRP antagonists as described in the briefing book (Sections 2.9.3 and 2.9.5.1)?

Amgen would like to clarify the recommendations around inclusion of subjects with cardiovascular disease versus those with risk factors for cardiovascular disease. FDA proposes to include "at least 20% with preexisting cardiovascular disease". Would patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidemia, diabetes, etc) contribute to the 20%? The prevalence of cardiovascular disease in patients of the proposed and expected age group in the pivotal trials is relatively low. In a published clinical trial of 1677 patients with migraine evaluating the acute effects of an

oral CGRP receptor antagonist, telcagepant, 10.6% of the patients had a secondary diagnosis of a vascular disorder and 0.6% of patients had a diagnosis of cerebral infarction, cerebrovascular accident, transient ischemic attack, or myocardial infarction (Ho et al. Cephalalgia 30(12), 1443-1457). Based on these prevalence data, phase 3 studies are unlikely to include at least 20% of patients with preexisting cardiovascular disease. If similar prevalence rates are observed in the AMG 334 clinical program, would this allow adequate assessment of the cardiovascular safety profile to support a product label devoid of triptan class labeling?.

Discussion at Meeting:

Amgen communicated that there was no non-clinical evidence of a class effect similar to triptans and that triptan class labeling did not appear to be warranted for AMG 334. Any additional information in order to address additional non-clinical data will be provided as post-meeting comments.

The Agency confirmed that the lack of meaningful inclusion of patients with cardiovascular disease in the pivotal trials would not be an approvability issue. The Agency recommends Amgen actively enrolls patients with cardiovascular disease, and noted that even small numbers of these patients in clinical trials could meaningfully enrich the long-term safety database. The Agency indicated that it was premature to have explicit labeling discussions in the absence of the complete submission package. However, the Agency did indicate that in the absence of specific non-clinical or clinical findings indicative of cardiovascular concerns, it is unlikely that AMG 334 would have a product label similar to triptans. Moreover, if risks associated with the mechanism of action remain theoretical, this would be most likely be conveyed in the warnings and precautions section of the product label.

Post-Meeting Comments: FDA recommends that Amgen provide in vitro (e.g., isolated coronary artery preparation) or in vivo nonclinical studies to assess the potential for AMG 344 to cause coronary artery constriction or reduced coronary blood flow. These studies should include appropriate negative and positive (e.g., triptan) controls. If you believe that such studies are not feasible or are not necessary, you should provide a justification (with supportive data) to the IND to support that position.

e.

(b) (4)

Amgen Draft Response:

Amgen appreciates the Agency's response, no further discussion is needed.

Discussion at Meeting:

None.

Question 13 – Data Standards

Pursuant to Agency guidance regarding standardized study data (February 2014), Amgen has created and is currently following a study data standardized plan and proposes to provide clinical study data compliant with Clinical Data Interchange Standards Consortium (CDISC) data standards.

- a. Amgen proposes to submit study data tabulation model (SDTM) datasets for tabulation data compliant with CDISC SDTM Version 1.3 (SDTM Implementation Guide [IG] Version 3.1.3) for all phase 2 and 3 studies.

FDA Response:

Yes, this is acceptable. Please refer to [Study Data Technical Conformance Guide \(December 2014\)](#) on how to submit standardized electronic study data.

Discussion at Meeting:

None.

- b. Amgen proposes to submit analysis data model (ADaM) datasets for analysis data based on CDISC ADaM Version 2.1 (ADaMIG Version 1.1) for all phase 2 and 3 studies.

FDA Response: Yes, this is acceptable.

Discussion at Meeting:

None.

- c. Amgen would like to request a single point of contact with FDA for any follow-up questions or issues related with CDISC.

FDA Response: You may contact edata@fda.hhs.gov

Discussion at Meeting:
None.

ADDITIONAL CLINICAL COMMENTS

Pediatric Studies

You submitted an initial Pediatric Study Plan (iPSP) on 27 June 2014 (SN 0057), and responded with revisions and edits (email correspondence 19 November 2014) to the Agency feedback which was sent on 24 September 2014. Please additionally see most recent FDA communication sent to you on February 4, 2015 to your non-agreed iPSP including proposed studies and timelines for the evaluation of AMG 334 in adolescents 12 to < 18 years of age with episodic or chronic migraine.

(b) (4)
information from a National Institutes of Health (U01NS076788) sponsored study suggests that it may be possible to conduct studies in pediatric patients >6 years old with episodic migraine¹. Therefore, this issue will need to be revisited.

(b) (4)

Additional comments:

Your proposed drug product, i.e. AMG 334 for migraine prophylaxis, meant to be used with a prefilled syringe/autoinjector is a combination product and as such is subject to 21 CFR Part 4 - Current Good Manufacturing Practice Requirements for Combination Products accessible at: <https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products>.

Amgen Action Items

- 1) Amgen to submit a justification to support the utility of the completed phase 2 EM study to support product registration (details on protocol changes, charter)
- 2) Amgen to submit the results of the final formative human factor study for Agency review prior to conducting the Clinical Home Use study.

¹ Hershey AD et al. Childhood and Adolescent Migraine Prevention (CHAMP) study: a double-blinded, placebo-controlled, comparative effectiveness study of amitriptyline, topiramate, and placebo in the prevention of childhood and adolescent migraine. *Headache*. 2013 May;53(5):799-816.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S.

conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm) (<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>).

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

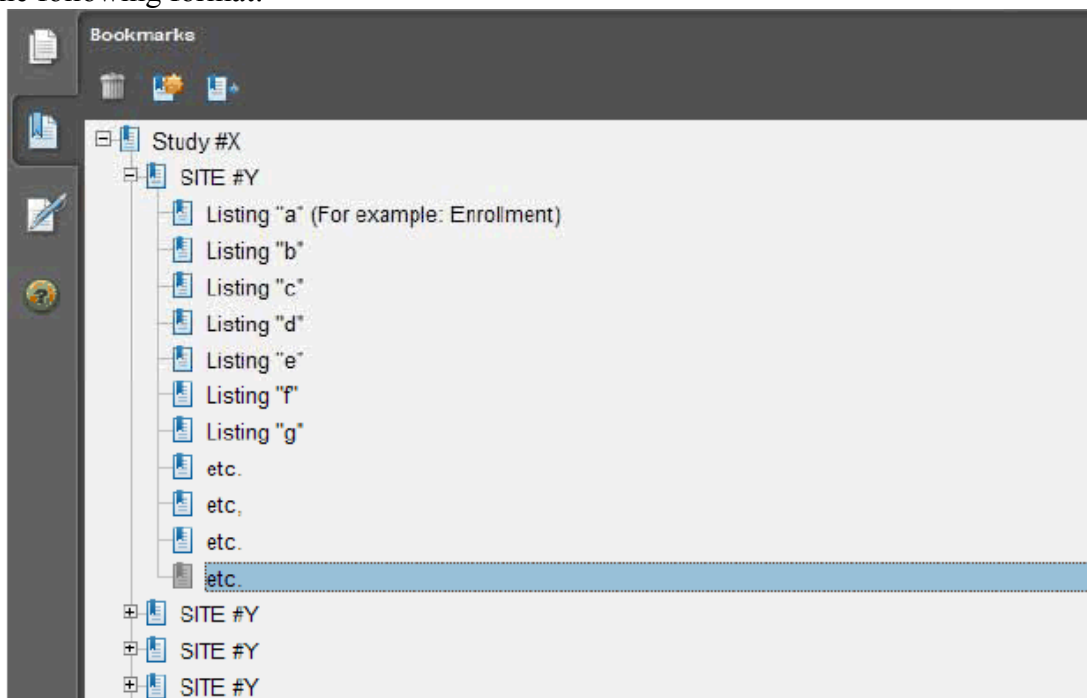
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator

- c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)

- c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing

Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ²	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

² Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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/s/

ERIC P BASTINGS
04/02/2015