CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761063Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 111295

MEETING MINUTES

Eli Lilly and Company
Attention: Thomas J. Konechnik, R Ph
Lilly Corporate Center
Indianapolis, IN 46285

Dear Mr. Konechnik:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LY2951742 (galcanezumab).

We also refer to the meeting between representatives of your firm and the FDA on July 18, 2017. The purpose of the meeting was to discuss the contents and associated topics of your planned Biologics License Application (BLA) for LY2951742.

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, contact E. Andrew Papanastasiou, Regulatory Project Manager, via email at emilios.papanastasiou@fda.hhs.gov, or by phone at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
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 and Time: Thursday, July 18, 2017 from 2:00 to 3:00 EST
Meeting Location: 10903 New Hampshire Avenue
Silver Spring, MD 20903

Application Number: 111295
Product Name: LY2951742 (galcanezumab)
Indication: Migraine prevention
Sponsor/Applicant Name: Eli Lilly and Company

FDA ATTENDEES

Division of Neurology Products

Billy Dunn, MD	Director, Division of Neurology Products
Eric Bastings, MD	Deputy Director, Division of Neurology Products
Heather Fitter, MD	Clinical Team Leader
Sally Jo Yasuda, MD	Safety Team Leader
Suhail Kasim, MD	Clinical Reviewer
Lois Freed, PhD	Supervisory Pharmacologist
Edmund Nesti, PhD	Nonclinical Reviewer
Jacqueline Ware. PharmD	Chief Project Management Staff
E. Andrew Papanastasiou, PharmD, MS	Regulatory Project Manager

Office of Clinical Pharmacology

Huixia Zhang, PhD	Clinical Pharmacology Reviewer
Kevin Krudys, PhD	Team Leader, Pharmacometrics

Office of Biostatistics

Kun Jin, PhD	Biostatistics, Team Leader
Jinnan Liu, PhD	Reviewer, Biostatistics

Office of Pharmaceutical Quality

Lakshmi Narasimhan, PhD	Reviewer, Division of Microbiology Assessment
Maxwell Van Tassel, PhD	Reviewer, Division of Microbiology Assessment

Office of Surveillance and Epidemiology

Laura Zendel, PharmD	Reviewer, Division of Risk Management

SPONSOR ATTENDEES

Brian Millen, PhD	Senior Research Advisor, Statistics
Melissa Veenhuizen, DVM	Senior Medical Director, Patient Safety
Robert Conley, MD	Distinguished Scholar, GBD leader Pain Team
Thomas J. Konechnik, RPh	Director, Global Regulatory Affairs
Robin Wojciesik	Senior Director, Global Regulatory Affairs
James Martinez, MD	Medical Fellow, Pain Team
Jyun-Yan Yang	Senior Medical Director, Clinical Pain Team
William Kielbasa, PhD	Research Advisor, PK/PD & Pharmacometrics
Lisa Churgay	Consultant, Global Regulatory Affairs
Michael Hodsdon, PhD	Medical Fellow, Laboratory for Experimental Medicine
Allison Kennington	Senior Director, Global Regulatory CMC

1.0 BACKGROUND

On July 18, 2017, a Pre-NDA meeting was held between the Agency and representatives from Eli Lilly and company to discuss the planned submission of a Biologics License Application (BLA) for galcanezumab for the prophylaxis of migraine.

FDA sent Preliminary Comments to Eli Lilly on July 17, 2017.

2. DISCUSSION

Question 1a: Does FDA agree that the planned content for the galcanezumab BLA provides a complete application in support of the proposed indication?

FDA Response to Question 1a:
At the time of BLA submission, your application should include complete study reports for all studies required to support approval. If the data from the long term extension trial to study CGAI is necessary to support approval, it should be included with the original BLA submission. Please also see the responses to Question 3a regarding your approach to the 4-month safety update. A final determination of the adequacy of the contents of the BLA

submission will be determined at the time of filing review.

In addition, we have the following requests/comments about your proposed content of your BLA described in this meeting package:

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

Meeting Discussion:
The sponsor provided a handout at the meeting which included a schematic of the Phase 2 and 3 study designs and duration. They stated that they believe the double blind treatment phase of the two episodic studies (CGAC and CGAH) and the chronic migraine study (CGI) along with the 1 year long-term open-label safety study (CGAJ) provided the pivotal data package for the BLA submission. DNP asked that the sponsor populate the row in Table A with the number of patients that received galcanezumab/placebo for other indications so that overall exposure was represented in the table. The sponsor stated that the schematic, along with explanatory comments and number of patients enrolled by treatment group will be included in the BLA submission.

2. Please clarify the exposure in your safety database using the exposure tables below. Table B should include data for the patients with repeated galcanezumab exposure administered monthly. For the data regarding exposure for 6 months and for 1 year, please provide information 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. On face, it appears you have adequate exposure to fulfill ICH requirements, but review of the requested information will further clarify whether that is the case.

Table A: Safety Population, Size and Denominators		
Safety Database for the Study Drug[1] Individuals exposed to the study drug in this development program for the indication under review N= (N is the sum of all available numbers from the columns below)		
Clinical Trial Groups	**Galcanezumab (n=)**	**Placebo (n=)**
Normal Volunteers		
Controlled trials conducted for this indication[2]		
All other than controlled trials conducted for this indication[3]		
Controlled trials conducted for other indications[4]		

[1] study drug means the drug being considered for approval; do not include comparator arm drugs, placebo, or vehicle control in this table
[2] to be used in product's labeling
[3] if placebo arm patients switch to study drug in open label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm
[4] include n in this column only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review. Consider n=0 in this column if no patients treated for other indication(s) were included in this safety database.

Table B. Duration of Exposure				
	Number of patients exposed to the study drug			
	>=3 months	>=6 months	>=12 months	>=18 months
Any Dose				
120 mg maintenance dose				
240 mg maintenance dose				

Meeting Discussion:
The sponsor provided a handout with preliminary drafts of the recommended exposure tables above. DNP stated that Table B should be populated with the actual dose rather than the

modal dose. The modal dose is appropriate for use in AE analyses to identify the dose that an AE occurred, for categorization purposes. The sponsor clarified that most patients received fixed doses of either 120 mg (with a 240 mg loading dose) or 240 mg except for the open label extension period of CGAI, in which a variable dose may have been administered. There were few exceptions in which patients did not receive their correct dose. The sponsor will clarify these numbers in their BLA submission and will provide, in addition, a report of dose by visit. DNP stated that they cannot confirm that the database is adequate until we review these updated numbers, but on face, it appears that there is adequate exposure for the 120 mg dose.

3. We note that you describe the proposed pools in Table 3.1 in your briefing package.

Table 3.1. Summary of Integrated Safety Analysis Sets

Integrated Analysis Set	Studies to Include	Study Periods
A. Primary placebo-controlled Phase 3 integrated analysis set for migraine prevention	CGAG, CGAH, and CGAI	Placebo-controlled double-blind treatment phase
B. Placebo-controlled Phase 2 and Phase 3 integrated analysis set for migraine prevention	ART-01, CGAB, CGAG, CGAH, and CGAI	Placebo-controlled double-blind treatment phase
C. Post-treatment phase directly following placebo-controlled phase integrated analysis set for migraine prevention	CGAG and CGAH	Post-treatment phase
D. Post-treatment phase integrated analysis set for migraine prevention	CGAG, CGAH, CGAI, and CGAJ	Post-treatment phase with galcanezumab-treated patients only
E. Overall galcanezumab exposure integrated analyses set for migraine prevention	ART-01, CGAB, CGAG, CGAH, CGAI, and CGAJ	All phases on or after galcanezumab treatment

Source: [Lilly] Eli Lilly and Company. April 2017. Program Safety Analysis Plan for Galcanezumab (LY2951742).

We agree with the inclusion of pools A, B and E, but recommend three additional pools for : 1) the chronic migraine study CGAI (3-months controlled data) , 2) the chronic migraine 3 month controlled data in addition to the long term extension data for this trial, and 3) the 12 month long term extension trial (CGAJ). The pools should evaluate adverse events by dose (120 mg, 240 mg and all treated). Provide details in the BLA about how you plan to identify a dose that an adverse event occurred at for the patients that received multiple doses. We request for patients that received more than one dose, that you present safety data by assigned dose (randomization group), but also by modal dose (the most frequent dose used by a given patient). Please clarify what you intend to demonstrate in Pools C and D.

Meeting Discussion:

DNP asked that the sponsor include analyses for the individual studies, CGAI and CGAJ, to the other pools stated in Table 3.1 above in the integrated summary of safety. DNP wants to confirm that safety in the overall populations is consistent in the Episodic Migraine, Chronic Migraine and Long Term Extension trial populations. The sponsor agreed to provide information requested regarding the additional pools with appropriate analyses as part of the ISS. These pools will be compared to the other defined analysis sets (or pools) in the ISS in order to evaluate adverse events by dose. The sponsor clarified that analysis sets C and D

allow for the assessment of withdrawal, rebound, and immunogenicity during the post-exposure washout up to 5 half-lives after the last dose of drug.

The sponsor clarified that the pivotal Phase 3 studies as well as the Phase 2 studies were all fixed-dose studies, with the lone exception of the open-label extension period of CGAI. For these studies (excluding the CGAI open-label period), there are very few cases (out of more than 3,000 patients) where modal treatment and assigned treatment differ. There is one case where this occurred due to a dosing error. In addition, there are approximately 25 cases (patients) where this occurs due to early discontinuation. For example, a patient randomized to the 120mg dose regimen drops out of the study having only received the 240mg loading dose. In such cases, the modal treatment would be the 240mg treatment. The sponsor further clarified that analyses for the ISS are presented in terms of modal treatment; however, both modal and assigned treatment for each patient will be available in the data sets as well as specified listings to allow a full inspection of the impact of those cases. For the open-label treatment period of CGAI, all patients are assigned to galcanezumab as a single arm. The ISS analyses will include single arm analyses (assigned treatment), along with analyses by modal treatment, whenever the CGAI open-label period is incorporated.

4. Detailed analyses of the safety findings of the Phase 1 trials is not required in the ISS. However, in addition to the integrated analyses of Phase 2 and 3 trials, the summary of clinical safety should include a summary of the safety results of all of the Phase 1 trials. We also request datasets and clinical study reports for the Phase 1 trials. Narratives for deaths, SAEs and discontinuations due to AEs for Phase 1 trials should also be included.

5. In regard to section 4.1 of your briefing document for the Phase 3 trials, you report that you will submit integrated safety datasets. We request that you provide individual study datasets for the Phase 3 trials in SDTM. In addition, this section states that you will provide some blinded safety data for the cluster headache trials. We request that you provide blinded information on all deaths, SAEs and adverse dropouts, in addition to any significant cardiovascular or hepatic related adverse events or abnormal hepatic laboratory values including elevated liver transaminases >3x ULN, and >5xULN. This can be provided in a summary table. If you have other ongoing trials with your product, we request that you provide this data for those trials as well.

6. Include an analysis of concomitant cardiovascular medications at baseline, as well as new or increased doses of cardiovascular medications (e.g. antianginal, antihypertensive, antiarrhythmics) during treatment for each pool and a discussion of the findings related to concomitant cardiovascular medications use.

Meeting Discussion

DNP clarified that an evaluation of cardiovascular medication changes during the treatment of galcanezumab may provide additional useful information to the standard evaluations of BP change, ECG or cardiovascular AEs. For example, there may be cases where a patient has no report of changes in the blood pressure, ECG, etc., but instead had a change in his/her

cardiovascular medication during the treatment of galcanezumab compared to baseline. The sponsor asked if DNP had a list of medications to include and DNP stated that the sponsor should use their judgement on appropriate categories. The sponsor indicated that they already have analyses for antihypertensive medications and agreed to provide additional analyses of other cardiovascular concomitant medications.

7. Provide orthostatic data, if available, in your analysis of vital signs in the BLA.

Meeting Discussion
The sponsor clarified that orthostatic assessment was conducted in early Phase 1 studies and in the arthritis study, that was stopped, and that they would provide the information they have on orthostatic assessments in the BLA submission.

8. Please provide an epoch variable in the SDTM AE dataset. Clarify how a patient who participates in both the controlled and extension studies will be identified in the SDTM dataset.

9. Include a treatment emergent AE Flag variable in the SDTM AE dataset.

Meeting Discussion
The sponsor indicated that the treatment emergent AE flag was a derived variable included in the ADAM datasets. DNP requested that the flag be included in the SDTM dataset and indicated that they would follow-up with specific direction in a post-meeting follow-up.

Post Meeting Follow-up from FDA
In response to the pre-BLA meeting discussion regarding item #9 in the response to Question 1a in the preliminary meeting comments, we are confirming that you should include a treatment emergent AE Flag variable (AETRTEM) in the SDTM dataset. This variable should be put into SUPPAE.

10. Please refer to responses provided at the Type C meeting from February 2017 and to Attachment 1 of the document that includes the current requests from the Division of Neurology Products for submission of data.

Meeting Discussion:
The sponsor acknowledged receipt of the document described above and expressed appreciation and their plan to ensure alignment of their proposed BLA submission with the division's expectations described in this document.

Quality comments in regard to module 3:

1. Based on the nomenclature shorthand used, it is not clear what some of the items are and therefore, we cannot fully address your question.

2. You propose to market two drug product presentations, a prefilled syringe and an autoinjector. The drug product section should be spilt into specific nodes for each of

these, as relevant. This is not apparent in the draft Table of Contents provided in Appendix 2.

3. RS stability/requalification protocol(s) are not identified in the sections on reference standards or materials or in the regional information. Include the protocol for RS stability/requalification in 3.2.S.5 and/or 3.2.P.6, as appropriate. It is not clear what is included in 32s72-post appr-stab vs. 32r4-comp-protocol-ds-shelf-life–ext. Stability protocols that would be used for the purpose of extension of DS or DP shelf life should be included in 3.2.S.7.2 and 3.2.P.8.2. In Module 5: Include an Integrated Summary of Immunogenicity in eCTD section 2.7.2.4- Special Studies, or Section 5.3.5.3 -Reports of Analysis of Data from More than One Study.

4. This Integrated Summary of Immunogenicity should provide:
   a) An immunogenicity risk assessment specific to your product

   b) Details on the tiered immunogenicity strategy that you followed in your clinical program, and validation summaries for the various immunogenicity assay methods you developed in your program

   c) Links to method development and validation reports for the immunogenicity assays used in your clinical studies, particularly those used to test immunogenicity samples from your pivotal clinical study(ies)

   d) Immunogenicity sampling plan(s) for all clinical studies that had immunogenicity assessment performed

   e) Summary results of immunogenicity analysis for all clinical studies having immunogenicity component, including the results of your correlation analysis between anti-drug antibody status and titers with PK/PD/efficacy/safety (adverse-events) data

   f) Traceability of drug product lots used in all your clinical studies

Meeting Discussion:
With regard to item e), the sponsor indicated that the focus of the immunogenicity assessment (PK/PD/efficacy/safety) will be on the Phase 3 program, which contains the largest volume of exposures and includes the commercial formulation and doses.

***Question 1b*:** Does FDA agree with Lilly's plan to provide efficacy data in the SCE and to waive the requirement for an ISE?

FDA Response to Question 1b:
We recommend that you include an ISE in your BLA because the ISE adds additional value and content that may not be included in the SCE. We strongly encourage you to create your ISE in accordance with the Guidance for Industry, "Integrated Summary of Effectiveness.

(October, 2015)"

The ISE is a detailed analysis that comprehensively examines the effectiveness data derived from the individual clinical studies and describes additional information as it relates to effectiveness, such as dose response, effects in population subsets or timing of a response. Therefore, this section allows for a thoughtful synthesis of the evidence supporting efficacy based on the totality of the evidence provided from the various individual trials presented. In contrast, the SCE is a compact summary of the critical findings reported in the ISE, including individual trial reports and the overall evidence of effectiveness. The SCE should not contain any information or data not discussed or explained in the ISE. We acknowledge that in certain cases the SCE can serve as the ISE if appropriate data can be included within the space limitations of the SCE, but we request that you submit an ISE for the reasons detailed above.

Meeting Discussion:
There was no further discussion.

Question 1c: Does FDA have any preliminary comments on Lilly's approach regarding potential postmarketing risk management actions, including the plan not to submit a REMS?

FDA Response to Question 1c:
Until we review the safety data in its entirety, we cannot agree prospectively that no risk mitigation measures would be needed.

Meeting Discussion:
There was no further discussion.

Question 2a: Does FDA have any preliminary comment regarding Lilly's proposed approach to address dose in labeling?

FDA Response to Question 2a:
(b) (4)
(b) (4) Also, the Division recommends that injection site be assessed as a covariate in your population PK analysis, to determine whether injection site has an effect on galcanezumab pharmacokinetics.

Please refer to these additional comments regarding submission of datasets and codes for PK/PD analysis.

The following are our general expectations for submission of data/codes from Population

PK/PD analyses:

1. 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.

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

3. The codes should be submitted under "module5/datasets/poppk/analysis/programs/" folder (such as run1.ctl.txt, run1.lst.txt, plot1.R.txt) with a define.pdf file to explain the role of each file and with a revieweraid.pdf file to explain the flow of running the code if necessary. The datasets should be submitted under "module5/datasets/poppk/analysis/datasets/" folder (such as poppk.xpt, pkpd.xpt) with a define.pdf file to explain the variables within each data file.

Meeting Discussion:

(b) (4)

Question 2b: Does FDA have any comment regarding Lilly's proposal to use the word "prevention" rather than "prophylaxis" in its indication statement?

FDA Response to Question 2b:
We recommend language that is consistent with previously approved migraine products and therefore prefer the use of "prophylaxis" in the indication statement.

Meeting Discussion:
There was no further discussion.

Question 2c: Does FDA have any preliminary comment on Lilly's proposed approach regarding the inclusion of immunogenicity data in labeling?

FDA Response to Question 2c:
Inclusion of specific immunogenicity data in labeling is a matter of review.

Meeting Discussion:
There was no further discussion.

Question 3a: Does FDA agree with the proposed approach to the 4-month safety update?

FDA Response to Question 3a:
We recommend that you include information from the post-treatment follow up period from the Phase 3 episodic migraine studies (CGAG and CGAH), and the long-term, open-label safety study (CGAJ) during your initial BLA submission. Please see additional discussion to Question 1a.

Table 6.1. Estimated Data to be Available for 4-Month Safety Update

Study	Status at 4-Month Safety Update	Data to be included in 4-Month Safety Update (est.)
CGAG	Study will be complete. All patients will have completed or discontinued the remaining post-treatment follow-up period of the study.	Remaining safety data, as well as ADA, PK, and CGRP, from the post-treatment follow-up phase after the submission data cutoff
CGAH	Study will be complete. All patients will have completed or discontinued the remaining post-treatment follow-up period of the study.	Remaining safety data, as well as ADA, PK, and CGRP, from the post-treatment follow-up phase after the submission data cutoff
CGAI	The open-label treatment phase will be ongoing.	Additional cut of open-label safety data and post-treatment follow-up data, as well as ADA, PK, and CGRP, after the submission data cutoff
CGAJ	All patients will have completed or discontinued the remaining post-treatment follow-up period of the study.	Remaining safety data, as well as ADA, PK, and CGRP, from the post-treatment follow-up phase after the submission data cutoff

Abbreviations: ADA = anti-drug antibody; CGRP = calcitonin gene-related peptide; est. = estimated; n = number of patients within each specific category; PK = pharmacokinetic.

We note that at the time of the proposed BLA submission, the open label phase of CGAI will be ongoing and the post treatment follow up data for several of the trials will not be submitted since they will not have been collected yet. If this data is necessary to support approval, the completed study reports should be included with the original BLA submission rather than as a 120 day safety update. In addition, please clarify the method for adjudicating adverse events to the treatment doses when flexible dosing was permitted based on the investigators judgment in the ongoing 9-month open-label phase of the chronic migraine Study CGAI.

The 120 day safety update should include an updated ISS along with pertinent datasets to support analysis.

Meeting Discussion:
The sponsor clarified that the post-treatment follow-up phase (non-drug exposure) for each study was a post-exposure assessment to allow for the evaluation of withdrawal, rebound, and immunogenicity during 5 half-lives of galcanezumab washout.

The 9-month open-label extension phase of chronic migraine study CGAI along with the

completed Phase 2 studies provides additional supportive efficacy and safety data. Any available data from the follow-up period from these studies and the 9-month open-label extension from chronic migraine study CGAI will be provided at the time of submission and updated in the 4-month safety update. The sponsor reiterated that they consider the data package they plan to submit at the time of BLA submission, which will include the double-blind treatment phase of the two episodic migraine studies (CGAG and CGAH) and the chronic migraine study (CGAI) along with the treatment phase of the 1-year long-term open-label safety study (CGAJ), to be a complete pivotal data package. The Division stated that the information provided at the time of BLA submission should be sufficient to support a full review. If data provided in the 4 month safety update are necessary for approval, then this may be problematic.

Question 3b: Does FDA have any comment on Lilly's plan to submit clinical study report addenda to the IND and not to the BLA?

FDA Response to Question 3b:
You should submit any information necessary for the review of galcanezumab for migraine prophylaxis to the BLA.

Meeting Discussion:
There was no further discussion.

Question 4a: Does FDA have any comment on Lilly's proposal to include updated immunogenicity incidence data as an appendix in the 4-month safety update?

FDA Response to Question 4a:
An immunogenicity update should be part of the 4-month safety update. Data should be submitted to the BLA and should be in the same format as the original immunogenicity data to enable a comprehensive review of the immunogenicity progression for each subject.

Meeting Discussion:
There was no further discussion.

Question 4b: Does FDA have any comment on Lilly's plan to provide initial post-study follow-up (return to baseline) immunogenicity data in the submission, an update of that data at the 4- month safety update, and final data summary as addenda submitted to the IND upon completion of patient assessment?

FDA Response to Question 4b:
See response to Question 1a, 3a, 3b and 4a regarding information required for BLA review.

Meeting Discussion:
There was no further discussion.

Question 5: Does FDA have any comment regarding Lilly's proposed safety topics of interest and the proposed criteria for providing patient narratives in the BLA?

FDA Response to Question 5:
In addition to the proposed safety topics of interest, we recommend that you additionally address hepatic safety during development and the potential risks associated with CGRP antagonists as additional safety topics of interest.

1. adverse events related to injection sites
2. potential hypersensitivity events
3. upper respiratory tract infections
4. cardiovascular safety
5. suicidal ideation and behavior

In addition to the patients narrative you plan to submit, we also request that you provide narratives on adverse events of special interest related to cardiovascular safety and to hepatotoxicity.

Meeting Discussion:
There was no further discussion.

Question 6: Does FDA agree with Lilly's proposal (b) (4)

FDA Response to Question 6:
No, we do not agree. (b) (4)

Meeting Discussion:
There was no further discussion.

ADDITIONAL NONCLINICAL COMMENT
To aid in our evaluation of the cardiovascular safety of galcanezumab, we ask that you provide, in the BLA, all information and data available to you regarding the potential for antagonism of CGRP by galcanezumab to cause coronary artery vasospasm in humans.

Meeting Discussion:
The sponsor asked for clarification on the type of information and data the Division was requesting to address the potential for galcanezumab to cause coronary artery vasospasm in humans. The Division stated that a summary of the relevant information available to the

sponsor should be provided to address this issue, e.g., published literature on the mechanism of action of galcanezumab specifically related to the potential for cardiovascular risk in humans. The sponsor's evaluation should be submitted to the BLA in Module 4.

Post-meeting note: We ask that copies of the published literature references be provided in the BLA, in Module 4.

3.0 ADDITIONAL INFORMATION

Discussion of the Content of a Complete Application

- 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.

- A preliminary discussion on the need for a REMS was held and it was concluded that until we review the safety data in its entirety, we cannot agree prospectively that no risk mitigation measures would be needed.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission.

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. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** 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.

Secure Email Communications

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

Manufacturing Facilities

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

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

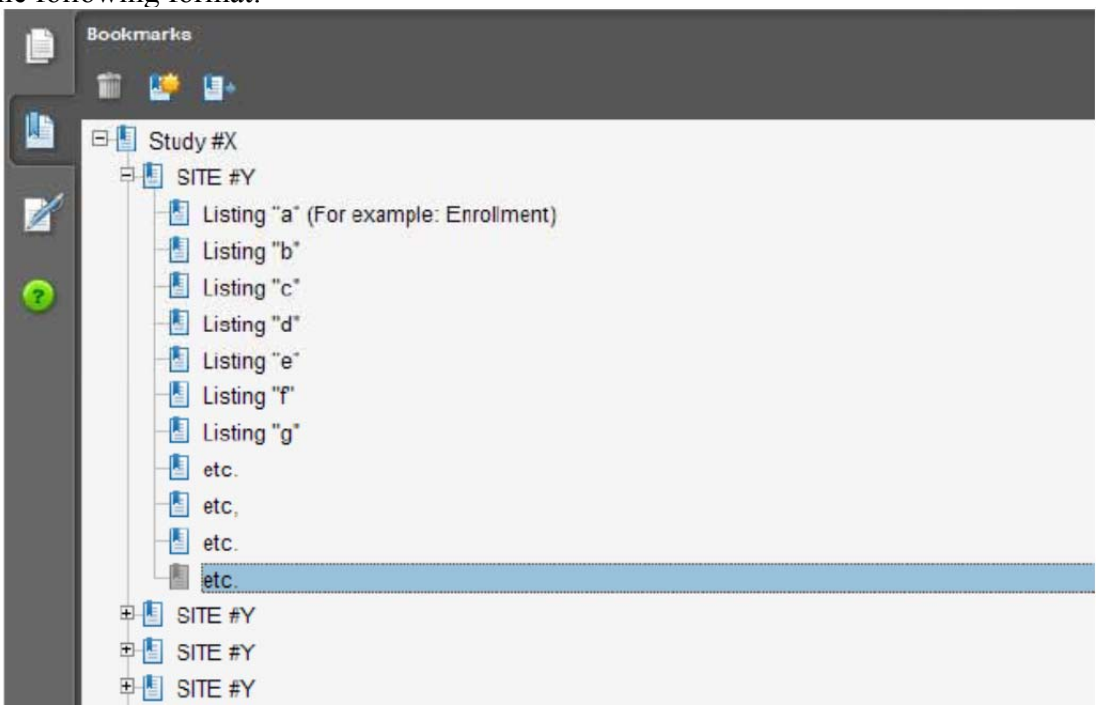
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, 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.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

The handout used at the meeting is attached.

Phase	Study	Treatment and Post-Treatment Phase (N)	Purpose
Phase 2	ART-01	3-month DB; 3-month follow-up	Phase 2 proof-of-concept
Phase 2	CGAB	3-month DB; 3-month follow-up	Phase 2 dose-ranging
Phase 3	CGAG (episodic)	6-month DB (703); 4-month follow-up (355)	Phase 3 efficacy
Phase 3	CGAH (episodic)	6-month DB (785); 4-month follow-up (278)	Phase 3 efficacy
Phase 3	CGAI (chronic)	3-month DB (1,037); 9-month flex-dose open-label (85); 4-month follow-up (36)	Phase 3 efficacy and supplemental open-label exposure
Phase 3	CGAJ (episodic/ chronic)	12-month fixed-dose open-label safety (210); 4-month follow-up (45)	Phase 3 open-label long-term safety
		0 3 6 9 12 Months	

Pivotal data for submission (G/H/I DB phase efficacy data; J long-term safety for long-term exposure requirements)

Follow-up data

Supplemental data

N represents both galcanezumab-treated and placebo-treated patients who have completed the noted phase at the time of submission database lock.

Table A. Safety Population, Size and Denominators

Safety Database for the Study Drug[1] Individuals exposed to the study drug in this development program for the indication under review: N=3006		
Clinical Trial Group	**Galcanezumab (n=3006)**	**Placebo (n=1726)**
Normal volunteers	**419**	**27**
Controlled trials conducted for this indication[2]	**1434**	**1452**
All other than controlled trials conducted for this indication[3]	**1153**	**247**
Controlled trials conducted for other indications[4] Trials conducted for other indications[4]	**0**	**0**

[1]Study drug means the drug being considered for approval; do not include comparator arm drugs, placebo, or vehicle control in this table.

[2]To be used in product's labeling [Includes Studies I5Q-MC-CGAG, I5Q-MC-CGAH, and I5Q-MC-CGAI].

[3]If placebo arm patients switch to study drug in open label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm [Includes Studies I5Q-AR-ART1, I5Q-MC-CGAB, I5Q-MC-CGAJ, and CGAI (only patients who switched from placebo to galcanezumab in the open-label treatment phase)].

[4]Include in this column only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review. Consider n=0 in this column if no patients treated for other indication(s) were included in this safety database.

Note: For Study I5Q-MC-CGAF (N=151, osteoarthritis), Lilly will provide deaths, serious adverse events, and discontinuations due to an AE in the TOSNP, the completed study report, and all data sets in Module 5; however, this data is not included in the integrated safety database.

Table B. Duration of Exposure in Analysis Set E[1] at Time of Submission

	Number of patients exposed to the study drug			
	≥3 Monthly Doses	≥6 Monthly Doses	≥12 Monthly Doses	≥18 Monthly Doses[2]
Any dose	2379[3]	1644	279	NA
120 mg maintenance dose	945	720	112	NA
240 mg maintenance dose	1144	924	167	NA

[1]Includes Migraine Studies ART-01, CGAB, CGAG, CGAH, CGAI, and CGAJ.

[2]Duration of Exposure will not exceed 12 Monthly Doses.

[3]This includes all doses available in these studies: 5 mg, 50 mg, 120 mg, 240 mg, and 300 mg.

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
08/16/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 111,295

MEETING MINUTES

Eli Lilly and Company
Attention: Thomas J. Konechnik, R. Ph.
Lilly Corporate Center
Indianapolis, IN 46285

Dear Mr. Konechnik:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LY2951742.

We also refer to the meeting between representatives of your firm and the FDA on September 10, 2015. The purpose of the meeting was to discuss your Phase 3 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:	**September 10, 2015**
Meeting Location:	**FDA White Oak**
Application Number:	**111,295**
Product Name:	**LY2951742**
Indication:	**Migraine Prophylaxis**
Sponsor/Applicant Name:	**Eli Lilly**
Meeting Chair:	**Eric Bastings, M.D.**
Meeting Recorder:	**Lana Chen, R.Ph.**

FDA ATTENDEES

Division of Neurology Products
Eric Bastings, MD, Deputy Director
Heather Fitter, MD, Clinical Team Leader
Ramesh Raman, MD, Clinical Reviewer
Suhail Kasim, MD, Clinical Reviewer
Lois Freed, PhD, Supervisory Pharmacologist
Donald Charles Thompson, PhD, Pharmacology Reviewer
Kun Jin, PhD, Statistical Team Leader
Angela Men, PhD, Clinical Pharmacology Team Leader
Hristina Dimova, PhD, Clinical Pharmacology Reviewer
Lana Chen, RPh, Project Manager

Office of Biotechnology Products
Chana Fuchs Ph.D., Product Quality Team Leader
Yan Wang, PhD, Product Quality Reviewer
Frederick Mills, PhD, Product Quality Reviewer (via phone)

Clinical Outcome Assessments (formerly SEALD)
Sarrit Kovacs, PhD, Clinical Outcome Assessments Reviewer
Ashley Slagle, M.S., Ph.D., Clinical Outcome Assessments Reviewer

Division of Medication Error Prevention and Analysis (DMEPA)
Deborah Myers, RPh, MBA Safety Evaluator,

Danielle Harris, PharmD, BCPS, Team Leader
Martin Rusinowitz, MD, Clinical Reviewer, Controlled Substances Staff
Janice L. Polacek, RN, BSN, CRNI, Nurse Consultant, CDRH/DAGRID

SPONSOR ATTENDEES

Lilly:
Jeff Yang, M.D., Sr. Medical Director, Clinical Pain Team
Vlad Skljarevski, M.D., Medical Fellow, Clinical Pain Team
Holly Detke, Ph.D., Principle Research Scientist, Clinical Pain Team
Brian Millen, Ph.D., Sr. Research Advisor, Statistics-Neuroscience
Yoko Tanaka, Ph.D., Research Advisor, Statistics-Neuroscience
Bill Kielbasa, Ph.D., Research Advisor, PK/PD and Pharmacometrics
(b) (4) Consultant Scientist, Health Outcomes
Talia Muram, M.D., Medical Advisor, Immunogenicity
John K Towns, Ph.D., Sr. Research Fellow, Regulatory- Devices
JR Dobbins, Principle Research Scientist, CMC Biotechnology
Tom Konechnik, R.Ph., Director, Regulatory
(b) (4) Consultant, Regulatory
Carl Garner, Ph.D., Sr. Director, Regulatory
Aaron Schacht, Global Business Development Leader, Pain Team

DISCUSSION

FDA sent Preliminary Comments to Lilly on September 8, 2015, followed by an addendum on September 9, 2015.

FDA Preliminary Response--General Clinical Comments:

We note that your questions related to the future development of LY 2951742 substantially relies on results from Study I5Q-MC-CGAB that you state is ongoing, and that the submitted results are interim in nature. You further state the following- "*This interim report includes data from the planned interim analysis (database lock: 03 June 2015) following the conclusion of the treatment phase. The report does not include a comprehensive interpretation of the data. A final study report that includes post-treatment data as well as a comprehensive interpretation of all phases of the study will be created once the complete data are available after the final data lock*". Please note that our comments are based on the currently submitted information (interim results) from Study I5Q-MC-CGAB**.**

Question 1: Does FDA agree with Lilly's selection of 2 dose regimens (120 mg/month with a 240 mg loading dose and 240 mg/month) to be tested in the Phase 3 studies (b) (4)

FDA Preliminary Response:
In general, the two dose regimens (120 mg/month with a 240 mg loading dose and 240 mg/month) selected for the Phase 3 studies based on the results of the dose-ranging study and PK/PD analyses appear reasonable.

Meeting Discussion:
There was no further discussion.

Question 2a: Does FDA agree with the proposed definition of migraine headache days that includes both migraine and probable migraine headaches?

FDA Preliminary Response:
Yes.

Meeting Discussion:
There was no further discussion.

Question 2b: Does FDA agree with a ≥30 minutes duration as a defining criterion for migraine headache for study inclusion and primary objective analysis?

FDA Preliminary Response:
Yes.

Meeting Discussion:
There was no further discussion.

Question 2c: Does FDA agree with the proposed 30-day dosing period to enable monthly administration in the label?

FDA Preliminary Response:
Yes.

Meeting Discussion:
There was no further discussion.

Question 2d: Does FDA have any comment on the allowance of continued use of stable doses of topiramate or propranolol in the chronic migraine study (Study CGAI), with a limitation of no more than one-third of the study population?

FDA Preliminary Response:
Yes, as long as concomitant medication use is limited to no more than one third of the study population.

Meeting Discussion:
There was no further discussion.

Question 2e: Does FDA have any comment on the 6-month double-blind treatment duration for the episodic migraine studies (Study I5Q-MC-CGAG [CGAG] and Study I5Q-MC-CGAH [CGAH]) or the 3-month double-blind treatment duration for the chronic migraine study (Study CGAI) to support registration?

FDA Preliminary Response:
The proposed double-blind duration for the referenced studies appears reasonable.

Meeting Discussion:
The sponsor sought further clarification on the Agency's current thinking regarding treatment durations in migraine prevention studies. The Agency stated that while a 3-month treatment duration is the minimum study duration that is acceptable, a 6-month treatment duration is preferable, as it allows for better evaluation on sustained effect of treatment.

Question 2f: Does FDA have any other comments on the overall clinical design and safety monitoring plan for the proposed Phase 3 registration studies?

FDA Preliminary Response:
The safety monitoring and PK sampling plan in the phase 3 studies appear reasonable.

We will provide additional comments about the overall design at the meeting.

Meeting Discussion:

The Agency indicated that at a minimum, two adequate and well-controlled studies in migraine prevention were needed for registration.

The Agency stated that the proposed primary analysis based on the average of months 5 and 6 could be acceptable, but the preferred primary analysis would include an assessment of the entire treatment duration. Also, if the primary analysis only considers the average of months 5 and 6, a sensitivity analysis should assess the entire post-randomization period. The Sponsor agreed with the Agency's recommendation to change the primary endpoint to the average over the entire treatment period

The Agency recommended that administration of abortive migraine treatments (triptans and ergots) on a given day should count as a migraine headache day. The Sponsor clarified that the proposed chronic study included this method, but the episodic study did not. The sponsor agreed to consider aligning the episodic and chronic studies by having a consistent definition in both studies or by providing a sensitivity analysis for both methods of counting migraine headache days.

The Agency asked the sponsor what they would do if patients were to exceed the established limit of acute abortive treatments in the episodic study. The sponsor indicated that such patients

would remain in the study but would be considered protocol violations. The sponsor will consider removing such limits from the proposed protocol.

Statistics

Question 3a: Does FDA agree with the statistical analysis approach of the primary efficacy endpoint for the episodic or chronic migraine studies?

FDA Preliminary Response:
Yes, assuming that the assumptions of the MMRM are justified (e.g., normality). You need to justify that the assumptions of the MMRM are appropriate for the migraine rate data and plan a backup analysis in case they are not justified. You should also do a sensitivity analysis which tests the treatment effect over the entire double blind treatment period since that has been the usual approach in this disease area.

Meeting Discussion:
The sponsor stated that there were significant treatment and visits interactions in the Phase 2 trial data and asked for the Agency's opinion. The Agency commented that this renders the results of MMRM model difficult to interpret. The Sponsor agreed with the Agency's recommendation to change the primary endpoint to the average over the entire treatment period. Thus the MMRM comment is no longer applicable. The sponsor plans to propose a new primary analysis method.

Question 3b: Does FDA agree that the use of sample-size re-estimation, as proposed, is acceptable for Study CGAI, including the plan for reporting estimates and p-values at study completion if the sample size is increased?

FDA Preliminary Response:
You mention the CHW method for sample size re-estimation when around 525 randomized patients have had the chance to complete 3 months of double-blind treatment. Your plan for reporting estimates in the event of sample size re-estimation is not clear. Insufficient details are provided for the Brannath reference cited for determining a median unbiased estimate in the event of sample size re-estimation. Such references usually may describe various scenarios and so may need slight modifications to be directly applicable to the specifics of your trial. Please address any possible ambiguity in the details of how the cited method will be applied to this specific trial.

Meeting Discussion:
The Agency will focus on the *p*-value under the null hypothesis. The Agency cannot agree with the proposed adjustment for the treatment effect. (b) (4) . The Agency will defer the discussion to the time when the NDA is under review.

Question 3c: Does FDA have any comment on the overall statistical approach to control for multiplicity for the key secondary endpoints?

FDA Preliminary Response:
The statistical approach appears acceptable.

Meeting Discussion:
The sponsor asked about the acceptability of including response rates in the label. The Agency stated that in certain cases response rates can be included in labeling. The sponsor asked if these response rates need statistical control for multiplicity. The Agency stated that although this would be a matter of review, description of response rates may not need statistical control for multiplicity since they are based on the primary outcome analysis which controlled for multiplicity. The Agency commented that (b) (4) and therefore would not be described in labeling. Secondary endpoints such as decrease in acute abortive medication use would likely be considered for labeling.

(b) (4)

Clinical: Patient Reported Outcomes

Question 3e: Does FDA agree with the proposed (b) (4)

(b) (4)

   f. Please submit, for Agency review, screen shots of the electronic version of the MSQ v.2.1 (including the patient instructions and questions) exactly how patients will see them in the trials. Please also submit the instrument user manual and patient/investigator training materials.

2. We agree with your decision to ask patients regarding their symptoms (e.g., nausea, vomiting, sensitivity to light and sound, etc.) regardless of whether or not the patients reported experiencing a headache/migraine that day.
3. We note that you have proposed two patient global rating scales, the PGI-I (Patient Global Impression of Improvement) and PGI-S (Patient Global Impression of Severity) scales. We recommend using the patient global rating scales as anchors to help interpret a clinically meaningful change in the MSQ v.2.1 dimension score. No single anchor measure is preferable on its own, but including a number of anchor measures may provide an accumulation of evidence.
   a. We suggest that you assess the PGI-S, not only at baseline, but also at monthly post-baseline visits during the treatment phase. This would allow inclusion of the PGI-S as an anchor measure in anchor-based analyses for defining a responder for the MSQ v.2.1 endpoint.
   b. Rather than a PGI-I scale, we suggest that you consider using a patient global impression of change scale that would include not only improvement, but also no change and worsening.
   c. Please provide, for Agency review, copies of both patient global scales in addition to any other scales you plan to include in both the episodic and chronic migraine trials.
4. If you plan to conduct your trials multi-nationally, we recommend providing evidence of both translation and cultural validation of the MSQ v.2.1 (including instructions, items/domains, and response options). This includes conducting qualitative work on the instrument within all languages and cultures in which the instrument is to be assessed. You may refer to the ISPOR principles for the translation and cultural validation process.[1]

[1] Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P; ISPOR Task Force for

Translation and cultural validation of outcome assessments can affect efficacy findings and it is important to ensure that efficacy assessments are standardized across sites.

Meeting Discussion:
The sponsor is now proposing to use the Role Function-Restrictive domain of the MSQ v2.1 as the key secondary endpoint for functioning for potential inclusion in labeling. The Agency reiterated the acceptability of physical functioning as a key secondary endpoint but emphasized the importance of keeping the measure focused on what is most relevant and meaningful to the patient. The sponsor agreed to provide additional literature evidence supporting the Role Function-Restrictive domain in a regulatory response, specifically addressing the points in the FDA's written comments. The sponsor clarified that the full MSQ v.2.1 will be administered to patients. The Agency agreed that the full scale should be administered despite the decision to use only the Role Function-Restrictive domain for the key secondary endpoint. The sponsor also agreed to submit copies of all of scales used in the episodic and chronic registration studies at the time of final protocol submission.

Chemistry, Manufacturing and Controls

Question 4a: Does FDA agree the proposed analytical comparability plan, coupled with the proposed PK bridging study (Bridging Study 1), is appropriate for bridging from the lyophilized formulation to a solution formulation supplied in a prefilled syringe?

FDA Preliminary Response:
There is no information provided for this analytical comparability in the current meeting package. (b) (4)

(b) (4)

For additional clinical pharmacology feedback, please refer to the response to question 4c below.

In reference to the PK/PD comparability studies, the prefilled syringe appears comparable to the commercially available disposable syringe in form and function and is appropriate for the intended use and will be determined after review of the analytical data. The device would be appropriate for the intended injections sites and route of administration.

Translation and Cultural Adaptation. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health. 2005 Mar-Apr;8(2):94-104.

Meeting Discussion:
The sponsor confirmed that they will incorporate the feedback from the communication referenced above into their comparability studies. Sponsor plans for submission of the comparability assessment in early October.

Question 4b: Does FDA agree that the proposed analytical comparability plan is appropriate for (b) (4)

FDA Preliminary Response:
(b) (4)

Meeting Discussion:
There was no further discussion.

Question 4c: Does FDA agree that the study design, including dose selection, various injection sites, and PK endpoints is sufficient for bridging PK data from the lyophilized formulation to a solution formulation supplied in a prefilled syringe?

FDA Preliminary Response:
It is reasonable to track the injection site locations and injection site reactions as one of the PK parameter endpoints. The statistical analyses for the PK parameters of interest need to include the area under the plasma/serum concentration time curve from zero to the last measurable concentration (AUC_t) of LY2951742 and CGRP. (b) (4)

Meeting Discussion:
(b) (4)

Question 4d: Does FDA have any comment on whether the (b) (4)

(b) (4)

Question 4e: Does FDA have any comment on the plan to gain patient experience with a prefilled syringe and autoinjector in the open-label safety study (Study CGAJ) to support self-administration in labeling?

FDA Preliminary Response:
The prefilled syringe and the auto-injector are two entirely different devices and should be evaluated independent of each other. You have not provided critical performance criteria for the auto-injector such as injection time and dose accuracy. You will also need a plan to track device malfunctions.

Meeting Discussion:
The Sponsor clarified that the open label safety study for migraine prevention will be initiated with the prefilled syringe. Patients will be transitioned to the autoinjector during the study when it becomes available (approximately mid 2016). The Sponsor estimates that there will be data from the autoinjector on 100 patients for 3 months or more, with up to 500 patient exposures total.

Question 5a: Does FDA have any comment regarding the strategy and approach on the validation packages?

FDA Preliminary Response:
The overall strategy and approach used for validation of the immunogenicity screening assay appear appropriate based on our initial assessment.

For the confirmatory (Tier 2) assay and competitive ligand-binding assay for detecting the neutralizing antibodies validations, the assays were only assessed for the cut point. The assay should be fully validated for other relevant parameters. If Lilly has data to support that other parameters, (for example, precision) are the same because the assay formats are similar, this information should be provided in support of not doing a more comprehensive validation study on these assay.
Please see additional responses to Question 5b regarding the validation strategy.

Meeting Discussion:

Regarding validations of the Tier 2 and Tier 4 assays, Lilly stated that the confirmatory and neutralizing assays were performed on the same format as the screening assay and the screening assay was validated, and therefore asked the Agency to clarify why the confirmatory and neutralizing assays need to be fully validated. The Agency emphasized that the confirmatory and neutralizing assays were not identical to the screening assay. One example of a difference was the use of different reagents, so it is not clear that all the parameters of validation would remain the same. Lilly agreed that the data for these assays will be re-evaluated and any data regarding the relevant validated parameters for these assays will be submitted to the Agency for review.

Question 5b: Does FDA have any comment on the anti-drug antibody assay parameters that have been assessed, or are there additional parameters FDA would advise assessing for registration?

FDA Preliminary Response:
From the initial assessment of the assay validation reports submitted in the 14 July 2015 IND amendment we have the following comments and request for additional information: we note that for many parameters (e.g., levels of controls used, etc), no information was provided to support the choices made so that the relevance of these in the validation studies is not clear.
i. Regarding the positive controls:
a. We note that **positive controls** with high, medium and low level of ADA were generated from the pooled normal human sera (NHS) spiked with sera from monkeys hyper-immunized with LY2951742. These positive controls have been used in Tier 1 ADA screening assay, Tier 2 ADA confirmation assay and Tier 4 neutralizing ADA assay. However, it is unclear why and how the levels of ADA in these positive controls were selected. Justifications for the positive controls at the selected levels should be provided.
b. Estimation of the assay rejection rate for the low positive control used in Tier1 ADA screening assay, Tier 2 ADA confirmation assay and Tier 4 neutralizing ADA assay should be provided and the selection of the rejection rate for these assays should also be justified. We recommend that a concentration to be selected as the low positive control should reliably produce a result above the assay cut point but that can result in a 1% assay failure rate (Guidance for Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins).
c. Based on the data in Addendum#2 for evaluation of the robustness of ADA screening assay regarding the low positive control, we roughly estimate that at least 99.7% (Mean±3SD) of the results from the low positive controls used in ADA screening assays (0.189-1.311 OD) will be statistically above the ADA screening cut point at OD 0.166. This indicates that the low positive control in ADA screening assay has the very low rejection rate. The Justification for the appropriateness of your selected rejection rate and cut point should be provided.
ii. To prove the specificity of the ADA screening assay, irrelevant antibody was used (Addendum#2). The information about the irrelevant antibody used and relevance of the irrelevant antibody (e.g., isotype and concentration selection) for the specificity assessment should be provided.
iii. To determine the drug tolerance of the ADA screening assay, 250, 375 and 500 ng/mL control antibodies (anti-LY2951742 polyclonal antibody affinity purified from hyper-immune monkey sera) were used (Addendum#2). We note that the sensitivity of the assay is 15.3 ng/mL. The justification for selection of the control antibody at 250, 375 and 500 ng/mL should be

provided. Please also specify why 250 ng/mL was selected as the lowest level of control antibody used for this assessment.
iv. We notice that 20 µg/mL unlabeled LY2951742 was used in Tier2 ADA confirmation assay to assess the confirmatory cut point (Addendum#1). Provide your justification for selecting 20 µg/mL of unlabeled LY2951742.
v. To establish the neutralizing assay cut point, 0.051 µg/mL CGRP target peptide was used to inhibit the binding of the ADA with LY-2951742 in the AEC assay. The justification of using CGRP target peptide at 0.051µg/mL should be provided to enable assessment of validity of using this concentration.
vi. Verification or normalization of the assay cut points should be performed during implementation of the assay testing. From the reports submitted it appears that NHS was used for the studies rather than patient serum, even though this product has been used in a number of clinical trials. The verification and normalization should be based on the evaluation and comparison of the pre-defined assay cut point from the NHS samples in the assay validation and the assay cut point assessed from the naïve patient samples. The method for the verification and normalization of the assay cut point should be predetermined. Please refer FDA Guidance: Assay Development for Immunogenicity Testing of Therapeutic Proteins. The data comparing assay cut points from NHS samples and the naïve patient samples should be submitted in the BLA in support of the ADA data to be included for the patient population studied.

Meeting Discussion:
The sponsor agreed to provide the additional information as requested by the Agency.

Question 5c: Does FDA agree with the proposed immunogenicity Phase 3 sampling and safety monitoring plans for LY2951742?

FDA Preliminary Response:
The immunogenicity Phase 3 sampling plan seems reasonable.

Meeting Discussion:
There was no further discussion.

Abuse Liability
Question 6a: Does FDA agree with the plan not to conduct any further nonclinical abuse assessment or human abuse liability studies but to monitor for abuse-related adverse event terms during Phase 3 studies?

FDA Preliminary Response:
Yes.

Meeting Discussion:
There was no further discussion.

Clinical

Question 6b: Does FDA agree with the proposed list of adverse event terms to evaluate abuse potential in clinical studies?

FDA Preliminary Response:
You should refer to the 2010 draft Guidance for Industry on the Assessment of Abuse Potential of Drugs on the AE terms. Abuse related AEs should be presented by study, dose, population (patients and normal), etc., as well as appropriate pooling of data.

Meeting Discussion:
There was no further discussion.

Question 7: Does FDA have any initial comments on the draft Pediatric Study Plan?

FDA Preliminary Response:
Your plan to request a waiver for children < 6 years is acceptable. If you plan to request a waiver for patients ages 6-11 years, we suggest that you provide a detailed rationale in your initial Pediatric Study Plan (iPSP). Our current thinking is that trials in episodic migraine are feasible in children ≥ 6 years of age.

Your brief description (Table 7.1, pg. 151) of the proposed juvenile animal toxicology study does not specify an assessment of reproductive function, which should be included. We strongly recommend that you submit a final study protocol for feedback prior to study initiation.

Meeting Discussion:
The sponsor clarified that the pediatric efficacy study would be powered to evaluate adolescents 12-17 years of age. (b) (4)

(b) (4)

Question 8: Does FDA agree with the proposed approach of including a study addendum to Study CGAH to provide additional patients from countries that require local data for registration but cannot recruit a sufficient number of patients during global enrollment?

FDA Preliminary Response:
Your approach and plan appear reasonable.

Meeting Discussion:
There was no further discussion.

Additional CMC Comments
Three of the four proposed phase 3 clinical trials are randomized, double blind, placebo-controlled trials. We could not find, in the CMC section of the IND, any information on the manufacturing and release of the placebo that was used in your previous clinical trials under this IND or that is intended to be used for the phase 3 clinical trials. In support of the proposed phase 3 trials, submit CMC information on the placebo to be used, or a letter of cross-reference to another submission where this information can be found. Additionally, submit to the IND available lot release results for the placebo lots and the LY2951742 lots in prefilled syringe (PFS) and AI, and samples of the placebo and LY2951742 in PFS and AI.

Meeting Discussion:
The sponsor clarified that the (b) (4) placebo (b) (4) by the clinical sites. The sponsor asked the Agency to clarify the requirement of providing the placebo and LY2951742 samples in PFS and AI. The Agency explained that the samples will be evaluated for the ability to maintain blinding in the randomized, double blind placebo controlled clinical trials. If differences, for example in product (b) (4) are apparent, the sponsor should also provide information on how blinding will be maintained despite the apparent difference. The sponsor agreed to submit the CMC information for the placebo in PFS and AI in a CMC amendment in early October. In addition, the sponsor agreed that the placebo and LY2951742 samples in PFS and AI will be provided to the Agency for an evaluation for the purpose of maintaining a blinded placebo controlled trial.

Additional Nonclinical Comments
In the reproductive and developmental toxicology studies conducted in rat (#902585, # (b) (4) 353311) and rabbit ((b) (4) -353310), the highest dose tested (100 mg/kg/week) was a NOAEL for maternal and embryofetal toxicity in both species. The maximum plasma exposures achieved in rat and rabbit do not provide a safety margin compared to that in humans at the maximum anticipated clinical dose. In addition, we are not aware of data demonstrating saturation of pharmacodynamic effect in either species. We ask that you submit justification for high dose selection in each species (cf. Guidance for Industry: S6 Addendum to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, ICH, 2012) or specify the location of the relevant information in the IND.

Meeting Discussion:
The sponsor stated that additional information to address this issue will be submitted to the IND for review.

HUMAN FACTORS (DMEPA)

You should conduct a comprehensive use-related risk analysis of your proposed LY2951742 product. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and that all residual risks are acceptable (i.e. not easily reduced further and outweighed by the benefits of the product). The risk analysis will guide you in the design of your human factors summative study protocol that you submit to the Agency for review.

To ensure your approach and methodology are acceptable, you should submit the following to the Agency for review and comment prior to conducting your human factors summative study:

- A summary of your results and analysis from your formative studies
- A discussion of changes made to your product's user interface after the formative study and how changes will be validated
- An updated use-related risk analysis for your product
- Your Human Factors (HF) Summative Study Protocol
- A copy of all labels and labeling (including Instructions for Use) that you intend to test in the HF Summative Study (final to-be-marketed design)
- 3 samples of the to-be-marketed product you intend to test in your HF summative study

Note that DMEPA will need 90 days to review and provide comments under the IND.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management,* available online at: http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm094460.htm .

Note that we have also published three draft guidance documents that while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors and product design:

a. *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* (Draft), available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM259760.pdf

b. *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (Draft), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

c. *Safety Considerations for Product Design to Minimize Medication Errors* (Draft), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf

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 (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. 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 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

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study

Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* 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.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards 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. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.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 the FDA website entitled, Study Data Standards Resources and the

CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.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.

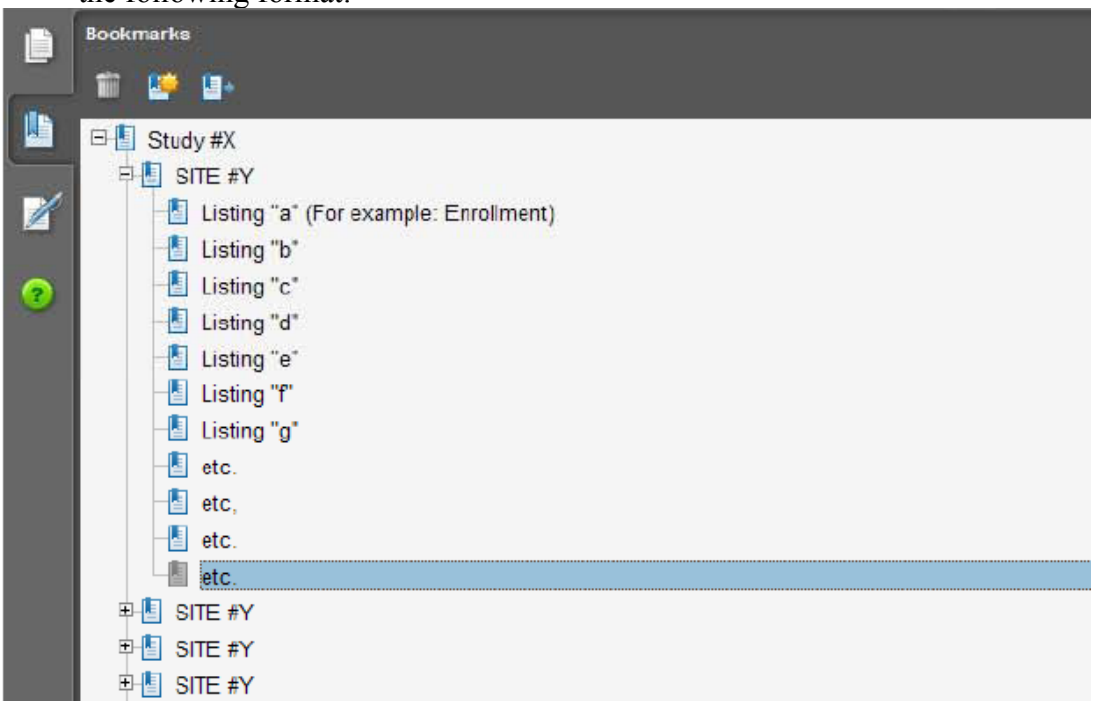
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere 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[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

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

/s/

LAURIE A KELLEY on behalf of LANA Y CHEN
10/09/2015

ERIC P BASTINGS
10/09/2015