CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761089Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 106,533

MEETING MINUTES

Teva Pharmaceuticals
Attention: Khalid Yousif
41 Moores Rd, P.O. Box 4011
Frazer, PA 19355

Dear Dr. Yousif:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for fremanezumab (TEV-48125).

We also refer to the meeting between representatives of your firm and the FDA on August 31, 2017. The purpose of the meeting was to discuss your planned BLA submission.

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:	**Pre-BLA**
Meeting Date:	**August 31, 2017**
Meeting Location:	**FDA White Oak**
Application Number:	**IND 106,533**
Product Name:	**fremanezumab (TEV-48125).**
Indication:	**migraine**
Sponsor Name:	**Teva Pharmaceuticals**
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
Suhail Kasim, MD, Clinical Reviewer
Lois Freed, PhD, Supervisory Pharmacologist
Edmund Nesti, PhD, Pharmacology Reviewer
Kun Jin, PhD, Statistical Team Leader
Mariam Ahmed, PhD, Clinical Pharmacology Reviewer
Sreedharan Sabarinath, PhD, Clinical Pharmacology Team Leader
Lana Chen, RPh, Project Manager

Office of Biotechnology Products
Chana Fuchs, PhD, Product Quality Team Leader
Nina N. Brahme, PhD, MPH, Product Quality Reviewer

Office of Process and Facilities/Division of Microbiology Assessment
Patricia Hughes, PhD, Acting Branch Chief, Branch IV

Office of Combination Products
Maryam Mokhtarzadeh, MD, Senior Medical Officer

Division of Medication Error Prevention and Analysis (DMEPA)
Chad Morris, PharmD, MPH, Safety Evaluator
Ebony Whaley, PharmD, BCPPS
Lolita White, PharmD, Team Leader

Center for Devices & Radiological Health (CDRH)
Matthew Ondeck, Device Lead Reviewer
John McMichael, Combination Product Team Lead
CAPT Alan Stevens, Branch Chief

SPONSOR ATTENDEES
Teva Pharmaceuticals
Douglas Harnish, PhD VP, Regulatory Affairs
Dawn Kelly, PhD Assoc. Director, Regulatory Affairs CMC
Valerie Mulligan, PhD VP, Global Regulatory CMC and Growth Markets RA
Ernesto Aycardi, MD VP, Migraine and Headaches Clinical Development
Paul Yeung, MD, MPH Sr. Director, Migraine and Headaches Clinical Development
Nicola Faulhaber, MD, MBA Director, Global Patient Safety and Pharmacovigilance
Ronghua Yang, PhD Sr. Director, Biostatistics
Mary Ma, MS Assoc Director, Biostatistics
Jason Bock, PhD VP, Global CMC Biologics
Gary Henniger Director R&D
Michele Rasamoelisolo, PhD Director, Biologics, Assays and Technology
Orit Cohen Barak, PhD Director, Clinical Pharmacology & Pharmacometrics
Maya Sokolovsky, MSc Associate Director, Nonclinical Safety
Jana Noeldeke, PhD Sr. Director Project team Leader
Khalid Yousif Sr. Manager, Regulatory Affairs

DISCUSSION

Regulatory

Question 1:
Does the Agency have any comments on the proposed Table of Contents (TOC) or data to be included in the pre-filled syringe (PFS) BLA?

FDA Response:
On face, the layout of your TOC appears adequate.
In addition, please see response to Question 12 regarding recommendations for including an ISE.

Meeting Discussion: None.

Question 2:
Is the proposal to provide the ongoing Phase 3 long-term safety data acceptable to FDA?

FDA Response:
You stated that at the time of submission, the long-term safety study will not be complete. If you are not able to provide a final CSR at the time of BLA submission, you must submit a report of a quality similar to the final report. If the final study report from the long-term extension trial is

necessary to support approval, it should be included with the original BLA. Please provide information on how many patients were exposed to doses of 675 mg quarterly for 6 months and 1 year. Please refer to our response to Question 15b in regard to how you plan to address the safety of product withdrawal, rebound and immunogenicity during the washout period.

Meeting Discussion: None.

Question 3:

a. Does the Agency agree that fremanezumab, Injection, (b) (4)

FDA Response:

(b) (4) please clarify your plan regarding the labeling for the PFS (b) (4)

Company Response to FDA Comments: (b) (4)

Post-meeting FDA comment: (b) (4) In this case, based on the information you have provided, we recommend that you submit a BLA for the PFS (b) (4)

b. Does the Agency agree that the content provided in the PFS BLA (b) (4)

FDA Response:

(b) (4)

c. (b) (4)

Meeting Discussion for Question 3(a-c): None. Please refer to post-meeting comment from FDA following Question 3(a).

Chemistry, Manufacturing, and Controls

Unless otherwise noted, Teva acknowledges FDA's comments on our Chemistry, Manufacturing and Controls Questions. Additionally, Teva acknowledges FDA's Additional Comments #2, #3 and #4. Responses to FDA's comments have been provided for Questions 4, Question 6 and Question 8. Specifically, Teva would like to engage in additional discussion on Question 4 and Question 6.

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(b) (4)

Meeting Discussion:

(b) (4)

Question 5:
Does the Agency agree that the comparability protocol is sufficient to review the alternate site during BLA review. (b) (4)

FDA Response:
We agree that the comparability protocol appears sufficient to permit evaluation during BLA review, but a determination of its appropriateness at this stage is premature. (b) (4)

(b) (4)

Meeting Discussion: None.

Question 6:
Does the Agency agree that the data package that will be provided at the time of the PFS BLA submission, and during the first 30 days after submission, is sufficient to accept the PFS BLA?

FDA Response:
The extent of stability data that will be submitted in the original BLA for the PFS (summarized in Tables 11 and 12 in Appendix C of the meeting package) appears acceptable to file the application. Note that we will accept the minor stability update (identified in Table 11) not later than 30 days after the submission of the original BLA. However, as we communicated in WRO of April 24, 2017, the Agency will request, if necessary, the update of available stability data via information request prior to month 7 for a standard submission or prior to month 4 for a priority submission to assess up-to-date data from ongoing stability studies and assign an appropriate dating period for the drug product.

See the Additional Comments section for product quality microbiology information expected for a complete BLA submission.

It appears that you will not provide stability testing of the PFS device functionality for the PFS combination product up to the proposed expiry of 24 months at the time of submission. This should be submitted within the first 30 days after submission.

As was described in the previous Type C Meeting dated April 24, 2017, stability testing of the PFS device functionality for this combination product should be provided up to the proposed expiry period at the time of submission. Alternatively, you may provide an accelerated aging study, equivalent to the proposed expiry of 24 months, and available real time data at the time of submission. This should also contain the protocol and timeline for the real time stability study of the combination product.

The ability to assign the 24 month shelf life based on stability data from clinical/stability batches manufactured using different manufacturing line and batch size will depend on the comparability between the clinical/stability devices, and on assessment of whether manufacturing of the above clinical/stability batches is fully representative of and simulating the commercial manufacturing process.

Stability testing of the PFS combination product will require demonstration that all of PFS essential performance requirements are maintained to the predetermined specifications, up to the proposed labeled date of expiry to support stability of the combination product. Your proposed documentation does not include:

1. Verification of the device essential performance requirements after shipping. Provide verification documentation for all of the essential performance requirements after shipping testing to show maintenance of device performance in your PFS BLA submission.

2. A risk analysis associated with the final finished PFS combination product. In your PFS BLA submission, provide a risk analysis for the final finished combination product that includes all identified risks, risk control measures and/or mitigation strategies, verification of risk control measures, and the acceptability of any residual risk associated with the device. You should outline the methods in which you identified the risks of the product within your risk analysis documentation (e.g., DFMEA, UFMEA, Fault Tree Analysis, etc.).

Additionally, it is unclear if your specifications are appropriate for the intended use of the product. In particular, we are concerned with your specifications for break, glide, and cap removal force. We recommend that in your risk analysis you compare the noted specifications of the commercial PFS presentation to the clinical/stability PFS batches. Please also see our response about human factors in question 4.

Company Response to FDA Comments:
Teva commits to providing the minor stability updates as indicated in the pre-BLA briefing book, Table 11, no later than 30 days after submission of the BLA.

Reference is made to Teva's Type C meeting request of February 10, 2017, Sequence 0100 seeking FDA feedback on the company's strategy to support the proposed shelf life for fremanezumab pre-filled syringe and the Agency's written responses received on April 24, 2017. Consistent with Teva's correspondence, we confirm that we intend to justify our proposed 24 months shelf-life primarily through the use of accelerated aging study data at 25°C/60%RH with available supportive real-time data at 2-8°C.

Teva can assure the Agency that the specifications for break, glide, and cap removal force are based on ISO or other relevant government/regulatory standards and the specifications have remained unchanged between clinical and proposed commercial products. A justification of specifications will be provided in the BLA.

Teva would like to seek consensus with FDA regarding Human Factors Studies for our PFS. Reference is made to a June 20, 2017 email communication from FDA providing feedback on Teva's proposed Human Factors Studies and Instructions for Use for our pre-filled syringe submitted to FDA on February 21, 2017. FDA indicated that "there are no unique use-related risks identified for the proposed fremanezumab PFS (b) (4)" FDA concluded that "it is not necessary for Teva to conduct a simulated use HF validation study for the fremanezumab PFS (b) (4) Product." FDA's assessment is consistent with Teva's HF studies, one of which was conducted after incorporation of Agency feedback on the IFU, that have concluded there were no unacceptable risks regarding use of the PFS for fremanezumab. Therefore Teva has concluded that no additional HF studies are required as our existing HF studies data are sufficient to support the use of the PFS.

Meeting Discussion: The Division agreed to provide post meeting comments to address the need for HF studies which will incorporate input provided in the sponsor's response above.

Post-meeting FDA comments:
We acknowledge that our communication dated June 20, 2017 indicated that human factor (HF) validation studies were not necessary to support the proposed fremanezumab (b) (4) PFS. However, following additional internal discussion with the fremanezumab review team and further review of the risks associated with the proposed user interfaces and the product characteristics, we conclude that HF validation studies are necessary to support the future BLA (b) (4) to ensure the safe and effective use of the proposed fremanezumab (b) (4) PFS. (b) (4)
(b) (4)
(b) (4) We have reviewed the HF validation study protocols for (b) (4) submitted on February 21, 2017, and have identified several areas of concern. We will provide a review of your HF validation protocols in a separate communication.

Please also refer to the meeting discussion comments under Question 8.

Question 7:
Does the Agency agree (b) (4)

FDA Response:
(b) (4)

Meeting Discussion: None.

Question 8:
Does the Agency agree (b) (4)

FDA Response:
(b) (4)

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(b) (4)

[redacted]

Clinical Pharmacology

Question 9:
Does the Agency agree with the proposed presentation of Phase 1 data in module 5 and the pharmacokinetics summary documents?

FDA Response:
We recommend that you state if the to-be-marketed devices (PFS (b) (4)) were used in your efficacy trials. If they were not used, bridging studies may be necessary to adequately validate the to-be-marketed presentation.

Your proposal appears adequate. The studies that were analyzed using non-validated bioanalytical assay(s) (i.e., studies (b) (4)) are not considered supportive for your application. Information from these studies may not be appropriate for the product label because of the assay reliability issues. (b) (4) If the to-be-marketed product is significantly different from those studied in Phase 3, you should provide acceptable bridging information for these products.

Company Response to FDA Comments:
Teva confirms that the to be marketed PFS was in fact used in our phase 3 efficacy studies so no bridging studies will be provided for the PFS in our upcoming BLA application.

In regards to having data from study LBR-101-011 in the USPI, the absolute bioavailability data from study LBR-101-011 will be based on re-analyzed data using the optimized and validated PK assay. This will be made clear in our BLA documentation.

Meeting Discussion: None.

Clinical

Question 10:
Does the Agency agree that the proposed data package is acceptable for submission and review of the fremanezumab PFS BLA for the proposed indication for the preventive treatment of EM and CM in adult patients?

FDA Response:
On face, your proposed data package appears adequate to support a BLA, but a final decision will be made at the time of filing.

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.

Please note that the exact wording of the indication statement will be determined during the BLA review.

Also, see the response to Question 9.

Company Response to FDA Comments:
Teva confirms that for the BLA submission a clear schematic 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 will be provided.

For the meeting, Teva would like to understand the FDA's approach regarding the appropriate indication language for new preventive migraine products. We want to be able to align our indication language with your expectations for the BLA filing.

Meeting Discussion:
The Division clarified that the exact language describing the indication statement with either "prophylaxis" or "prevention" will be discussed during the time of labeling, along with any information specifically stating the populations studied in the indication statement, i.e., CM or EM. The Division indicated that decisions have not been made yet and that these issues will be discussed with the sponsor during the BLA review.

Question 11: Does the Agency agree with Teva's proposal to license fremanezumab, Injection, for both quarterly and monthly dosing for EM and CM?

FDA Response:
The recommended doses and dosing regimen are a matter of review.

You should provide justification in the BLA (b) (4) The supporting information may include data from the non-clinical, clinical pharmacology and clinical studies.

The results of your PK/PD or exposure-response analyses should provide support for the proposed dosing regimens.

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.

Company Response to FDA Comments:
Is there any specific concern regarding (b) (4)

Meeting Discussion:
The Division clarified that while there were no specific concerns at this time, the Division was (b) (4)

(b) (4)

The Division asked the sponsor to provide data supporting the suggestion that patients may prefer monthly dosing to quarterly dosing, in the event that efficacy of both dosing arms were comparable.

The Division noted similar concerns about the proposed dosing regimen (b) (4) and that if there truly was no difference between quarterly and monthly dosing options, then quarterly dosing may be preferred. The sponsor reiterated that monthly dosing may be preferred by patients and that they wish to preserve that option.

The Division stated that dosing recommendations in the label should be as clear and simple as supported by the data. The Division stated that even though it appears the quarterly dosing option may be preferred (which would mean less office visits for patients (b) (4) The sponsor should submit patient preference data, along with any other information requested to support their proposed dosing regimen in labeling in their BLA submission. Final dosing recommendations (b) (4) would be a review issue.

The sponsor confirmed that there were sufficient exposures with 675mg quarterly to meet ICH requirements.

Question 12:
Does the Agency agree with the proposed presentation of efficacy data in the SCE?

FDA Response:
The presentation of efficacy data in the proposed SCE appears acceptable. However, 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. It is not intended to include only a collection of data tables or a pooling of efficacy data from multiple studies, as you suggest. 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. Therefore, the ISE 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. For example, the ISE provides opportunity to explain further and to provide justification for the treatment choice to be made that offers convenience and flexible treatment options for the patients and physicians with

the proposed fremanezumab dosing regimens for the preventive treatment of EM and CM. 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 recommend that you submit an ISE for the reasons detailed above.

Please provide a cumulative distribution analysis presented as a histogram by dose based on the primary endpoint findings for each of the pivotal efficacy trials. The x axis should represent the change from baseline in the number of monthly migraine days/headache days (the selection of which is displayed on the x-axis depends on whether change in migraine day or change in headache day was the primary endpoint for that particular study). Include both positive and negative values on the x-axis. The y-axis should represent the relative frequency (% of patients in entire trial). Please provide a separate figure for each pivotal trial. It would be useful if the number of patients (n) represented by each bar on the histogram was displayed.

In addition, please provide a cumulative distribution analysis, also presented as a histogram by dose for each pivotal efficacy trial, based on the primary endpoint findings with the x axis displayed as bins of 0 ≤ 25% reduction of migraine days/month from baseline, >25% - ≤50%, >50% - ≤75% and > 75% - ≤ 100%. The y axis would be displayed as % of total patients enrolled. Please include these cumulative distribution plots in the individual study reports of the pivotal trials.

Company Response to FDA Comments:
Teva agrees with the SCE and ISE general requirements provided by the Agency and will provide an ISE document. Teva requested confirmation that they do not need to integrate the data from the controlled studies (i.e., no pooling of the data sets). As mentioned in your response to Question 13, we agree that the pooling of the efficacy data has limited utility. Teva will provide the requested cumulative distribution analyses in the ISE.

Meeting Discussion:
The sponsor confirmed that the ISE will be provided and it was agreed that there was no need to pool efficacy data from Phase 2 and Phase 3 studies in the ISE.

Question 13:
Does the Agency agree that data from all study sites, United States (US) or foreign, can be pooled to support US licensure?

FDA Response:
Please clarify whether your question refers to pooling for the purpose of efficacy evaluations and/or safety evaluations.

Pooling of efficacy data has limited utility and would be considered exploratory.

Company Response to FDA Comments:
The intent of the original question was to confirm that we do not need to include a 1572 for ex-US sites that participated in the studies. Please refer to our briefing package company position regarding the conduct of the global studies.

Meeting Discussion:
During the meeting, the Division confirmed that Form 1572 was not required for sites outside of the US. The principal investigator CV should be included.

Safety

Question 14:
Does the Agency agree with Teva's proposal for providing case report forms and narratives?

FDA Response:
Please see the attached document for additional information regarding format and content of narratives.

In addition to the case report forms and narratives you propose to provide for the Phase 2 and Phase 3 studies, please also provide these for the Phase 1 studies for any SAEs, deaths, and early termination due to adverse events (AEs), adverse events of special interest (AESI), and pregnancies, or clearly indicate if no such events occurred.

We also would like narratives from any ongoing trials with fremanezumab (based on a similar cutoff for the other trials submitted for safety review in this BLA) if an event occurs that meet the regulatory requirements for submitting an expedited safety report.

Meeting Discussion: None.

Question 15:

a. **Does the Agency agree with the proposal to integrate safety data from the 4 placebo-controlled studies?**
   FDA Response:
   We agree that a pool to evaluate safety in all 4 placebo controlled studies is acceptable. We also recommend that you include an additional pool for the controlled portion of the placebo-controlled Phase 3 studies CM-0049 and EM-0050. The pools should evaluate adverse events by dose (225 mg monthly, 675mg loading dose followed by 225mg monthly, 675 mg once every three months and all treated).

   Company Response to FDA Comments:
   We consider that our defined cohorts outlined for the ISS properly characterize the safety profile for fremanezumab. Given the available data, we do not consider the information from the proposed cohort to be critical or material for BLA submission. If deemed

necessary, Teva requested clarification if the Agency would agree to receive this data as soon as it became available or at the time of request by a reviewer.

Meeting Discussion:
The Division clarified that they are looking ahead to the review process, and believe that it may be useful to see the integrated safety analyses of the Phase 3 controlled data, in addition to the integrated safety analyses of the Phase 2 and 3 controlled data. The Division agreed to provide flexibility to submit this additional pool for the Phase 3 efficacy studies within 30 days after the BLA submission, and that the lack of providing this pool at the time of filing will not be a reason for refuse to file.

b. Does the Agency agree with the proposed presentation of long term safety (LTS) data?

FDA Response:
Yes. We agree with the inclusion of pools described for the long-term safety data.

Please clarify if your proposed safety database will include any patients in the post-treatment phase directly following study completion in the double-blind period and after the 12 month long-term extension trial that allows for the assessment of withdrawal, rebound, and immunogenicity during the post-exposure washout up to 5 half-lives after the last dose of drug. If so, please specify how many patients you estimate will be in this safety database.

Provide details in the BLA about how you plan to categorize adverse events in terms of dose in patients that have received multiple doses as part of their dosing regimen. In general, we request that sponsors categorize these events based on modal dose as the primary presentation, but also provide information about these findings for the randomized dose. Since some of the cohorts have a single bolus followed by lower monthly doses, you must clearly identify when an AE corresponded to a patient whose modal dose was 225 mg, but who also received a 675 mg bolus.

You should include analyses for the age groups 18-40, 41-60, and >61year old. If you plan to submit other age ranges, it may be acceptable, but we ask that you provide your rationale. We understand that based on low numbers in particular groups, you may choose to have different cutoffs. As requested in response to Question 13, please also provide safety data by geographic locations.

In addition, we have the following comments:

1. We expect that the data Table 11/12 in Appendix J (pages 401/402) in your briefing book will include patient exposure based on the actual number of months they received dosing. If a patient missed a dose during their participation in the trial, that patient should be accurately categorized in the table. If patients received fewer than the expected number of doses, provide information regarding the time gap between doses. Please note that for patients that received quarterly doses, if a

patient received four doses over the course of the year (did not miss any scheduled doses), then we would consider this to be equivalent to 12 months of dosing, in the Table requested above.

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.

In your BLA submission, please provide updated information shown in Table 5 of the meeting background materials, with data for the controlled trials conducted for other indications. In addition, in Table 5, if the placebo arm patients switched to study drug in the open label extension, the "n" for the all treated group should include their number. Do not count twice the patients who received study drug in the controlled trial and in the extension trial. Please refer to our response to Question 10 in regard to the request for a clear schematic that describes the number of patients enrolled in the Phase 2 and 3 trials, and the long term extension trial.

Table 5: Number of Patients Included in Each of the 6 Integrated Cohorts (Safety Population)

Cohort: studies	Placebo	Fremanezumab					Total
	Monthly	675 mg quarterly	225 mg monthly	675/225 mg monthly	675 mg monthly	900 mg monthly	
1: Studies 021, 022, 30049, and 30050	862	667	385	467	96	86	**2563**
2: Studies 021 and 30049	464	376	--	467	--	86	**1393**
3: Studies 022 and 30050	398	291	385	--	96	--	**1170**
4: Studies 021, 022, 30049, 30050, and 30051	--	1086	550	712	96	86	**2530**
5: Studies 021, 30049, and 30051	--	620	--	712	--	86	**1418**
6: Studies 022, 30050, and 30051	--	469	550	--	96	--	**1115**

Source document: ISS

2. You should provide blinded (unless unblinded narratives were generated) safety data for the ongoing Phase 3 cluster headache trials for 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.

3. Include an analysis of concomitant cardiovascular medication changes during the treatment of fremanezumab from 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 medication use. An evaluation of cardiovascular medication may provide additional useful information to the standard evaluations of BP change, ECG or cardiovascular AEs.

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

5. 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.

6. Include a treatment emergent AE Flag variable (AETRTEM) in the SDTM AE dataset. This variable should be put into SUPPAE.

7. Please see **Attachment 1** of the document that includes the current requests from the Division of Neurology Products for submission of data.

Company Response to FDA Comments:
We concur with the FDA's general requests included within 15b, with the following clarifications:

At the time of the BLA, we will have approximately 60 patients (28 CM, 32 EM) that end study treatment in the pivotal studies and enter the long term safety study only for the ADA follow-up. In addition, we have 16 patients (8 CM, 8 EM) who have completed treatment in the long term safety study and 122 patients who ended treatment in the long-term safety study, for a total of 138 patients in the post exposure wash out will exceed more than 5 half-lives after last dose of drug. Our plan to provide data on rebound and withdraw will be based on spontaneous adverse event reporting. Immunogenicity will be analyzed for all patients after out to more than 5 half-lives after the last fremanezumab injection. There are no patients currently that have completed the washout period.

We acknowledge the discussion included on modal dose. However, in our study design, the modal dose is almost identical to the randomized dose. Therefore, we do not believe that this additional analysis is critical for the BLA submission. If considered necessary, would the agency agree to receive this data as soon as it is available at the time of request by a reviewer?
We consider that our defined ISS analysis properly characterized the cardiovascular safety profile for fremanezumab. With our available data, we do not consider this additional detailed analysis to be critical for the BLA submission. We would like to clarify the purpose of the request. If considered necessary, would the agency agree to receive this data as soon as it is available at the time of request by a reviewer?

Could the Division clarify the rationale for your request for all information (e.g., published literature) and data available regarding the potential for antagonism of CGRP by fremanezumab to cause coronary artery vasospasm in humans? This is not an event that we have observed either non-clinically or clinically.

Meeting Discussion:

Modal dose
The Division clarified that the AE information was requested based on the modal dose since this is a more accurate representation of what the patient received during the trial and may be a better indicator of expected AEs at that dose level. The sponsor confirmed that the modal dose was almost identical to the randomized dose. The Division stated that if the findings of the analysis of AEs using the modal dose, as compared to, the randomized dose truly is the same, then the sponsor could provide the analyses based on the randomized dose, but if these analyses are different, then the Division requests that the sponsor provide both analyses in their BLA submission. It is acceptable to provide this additional analysis within 30 days of submission of the BLA if it is not available at the initial BLA submission.

Cardiovascular Safety
The sponsor asked for clarification of the Division's request for a review of published literature addressing the potential for fremanezumab to cause coronary artery vasospasm in humans. The sponsor also asked if additional studies to address this concern would be needed. The Division stated that additional nonclinical studies would not be needed. However, a review of published literature relevant to the potential for fremanezumab to increase the risk of adverse cardiovascular effects as a result of antagonism of CGRP should be provided. The Division stated that the integrated summary of the published literature should be submitted in either Module 2 or 4 of the BLA and requested that copies of the publications be provided.

The Division explained that the review of information for concomitant cardiovascular medication changes from baseline may provide a more sensitive signal of physiological changes related to cardiovascular function prior to detectable changes in blood pressure, heart rate or the reporting of cardiovascular AEs and therefore, may further characterize whether CGRP antagonists have a cardiovascular target. This data may be provided within 30 days after the BLA submission and does not need to be incorporated into the ISS document but could be provided as a stand-alone response.

c. **Does the Agency agree with the proposed presentation of data from ongoing studies for other indications?**
FDA Response: No. Please see the responses to Questions 14 and 15b.

Meeting Discussion: None

Question 16: Does the Agency agree with the ADA data reporting plan?

FDA Response:
In your BLA submission, include analyses of the effect of ADA status on fremanezumab pharmacokinetics and efficacy. In your 120-day update, immunogenicity data should be in the same format as the original immunogenicity data to enable a comprehensive review of the immunogenicity progression for each subject.

Company Response to FDA Comments:
From the current studies, we observed a low immunogenicity incidence. We are analyzing the impact of immunogenicity on efficacy and pharmacokinetics statistically if the number of positive subjects is sufficient otherwise a descriptive approach of immunogenicity assessment will be conducted.

Meeting Discussion: None.

Statistics
Question 17: Does the Agency Agree or have any advice on the ISS SAP, or the Study Data Standardization Plan that has been provided?

FDA Response:
We ask that you refer to the attached document titled DNP Pre-NDA/Pre-BLA Meetings General Clinical Safety Requests and the Guidances cited therein for the safety analyses and outlier cutoffs expected to be included in the ISS submission.

Meeting Discussion: None.

ADDITIONAL COMMENTS

1. To aid in our evaluation of the cardiovascular safety of fremanezumab, we ask that you provide, in the BLA submission (module 4), all information (e.g. published literature) and data available to you regarding the potential for antagonism of CGRP by fremanezumab to cause coronary artery vasospasm in humans.

2. We are providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your 351(a) BLA submission.

    a. All facilities should be registered with FDA at the time of the 351(a) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for both the drug substance and drug product should be provided in the BLA submission to facilitate the planning of the pre-license inspections during the review cycle. Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

    b. The CMC Drug Substance section of the 351(a) BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The information should include, but not be limited to the following:

(b) (4)

c. The CMC Drug Product section of the 351(a) BLA (Section 3.2.P) should contain validation data summaries to support the (b) (4) operations. For guidance on the type of data and information that should be submitted, refer to the 1994 FDA Guidance for Industry "Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf.

   i. Provide the following information in sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.

(b) (4)

(b) (4)

ii. Provide information and validation data summaries in Section 3.2.P.3.5:

(b) (4)

iii. Provide the following information regarding drug product testing:

- Container closure integrity testing. System integrity (including maintenance of the microbial barrier) should be demonstrated initially and during stability. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns). Container closure integrity testing should be performed in lieu of sterility testing for stability samples every 12 months (annually) until expiry.
- Summary report and results for qualification of the bioburden, sterility and endotoxin test methods performed for in-process intermediates (if applicable) and the drug product, as appropriate. If

compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers.

- Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b).
- Certain formulations have been reported to interfere with endotoxin recoverability in the USP LAL test methods over time. The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of standard endotoxin (CSE or RSE) into undiluted drug product and then testing for recoverable endotoxin over time.

3. For information on where to provide device constituent part information using the eCTD format please see eCTD Technical Conformance Guide: Technical Specifications Document: "Guidance for Industry Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf. (September 2016)

4. Combination products are subject to the current good manufacturing practices (CGMP) requirements applicable to each constituent part (drug, device, biological product) of the combination product. However, as reflected in the final rule on CGMPs for combination products (21 CFR Part 4), manufacturers have the option to demonstrate compliance both with the drug CGMP regulations (21 CFR Parts 210, 211) and with the device quality system (QS) regulation (21 CFR Part 820) through a streamlined approach.

   If utilizing a streamlined approach, you must demonstrate compliance (i) with either the drug CGMP regulations or the QS regulation in their entirety and also (ii) with those provisions specified in Part 4 from the other of these two sets of requirements. Alternatively, you may demonstrate compliance with both the drug CGMPs and QS regulation in their entirety (non-streamlined approach). For further information on 21 CFR Part 4, see Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (Jan. 2017), available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm.

   Information to include in Form 356h: List the manufacturing facilities for the combination product and its constituent parts and identify what activities occur at each site (e.g., assembly, design, filling, sterilization, packaging) involving which constituents parts (e.g., drug only, device only, both drug and device). For facilities that have manufacturing activities for both drug and device constituent parts, you should identify which CGMP operating system is being used at the site for the combination product (streamlined or non-streamlined) and if it is a streamlined system, whether it is a drug-CGMP-based or QS-regulation-based system.

Information to include in your NDA or BLA application: If you are using a drug-CGMP-based operating system, you must demonstrate compliance with the provisions from the QS regulation addressed below. Please provide the information indicated for each requirement unless you are otherwise informed by FDA. Please ensure that the information describes how your firm has applied each applicable regulation in your manufacturing processes, and that it includes descriptions of the specific procedures and activities conducted by your firm and references to the types of protocols used by your firm for each activity. Using the eCTD format, this information should be provided in Section 3.2.P.3 (for further information, see sec. 5 of eCTD Technical Conformance Guide (Sept. 2016), available at https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf).

- **Management Responsibility (21 CFR 820.20)**

  Provide a summary of how your firm's management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4). Also, provide a description of the functions and responsibilities of each facility involved in the manufacturing of the combination product and its constituent parts.

- **Design Control, General (21 CFR 820.30)**

  Explain how you utilized the design control process to develop the combination product under review and provide a description of your design control procedures. Please address how requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file are being satisfied. Provide a copy or a summary of the plan used to design the combination product.

- **Purchasing Controls (21 CFR 820.50)**

Provide a summary of the procedure(s) for purchasing controls. The summary should:

a. Describe your supplier evaluation process and describe how it will determine the type and extent of control you will exercise over suppliers.
b. Explain how you maintain records of acceptable suppliers and how you address the purchasing data approval process.
c. Explain how you will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.

Explain how the procedure(s) will ensure that changes made by contractors/suppliers will not affect the final combination product. Provide a description of how you apply the purchasing controls to the suppliers/contractors used in the manufacturing of the combination product. (e.g., through supplier agreements).

- **Corrective and Preventive Action (21 CFR 820.100)**

Summarize the procedure(s) for your corrective and preventive action (CAPA) system. The CAPA system should require:

a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;
b. Investigation of nonconformities and their causes;
c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and
d. Verification or validation of the actions taken.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our June 21, 2017, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

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.

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 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.

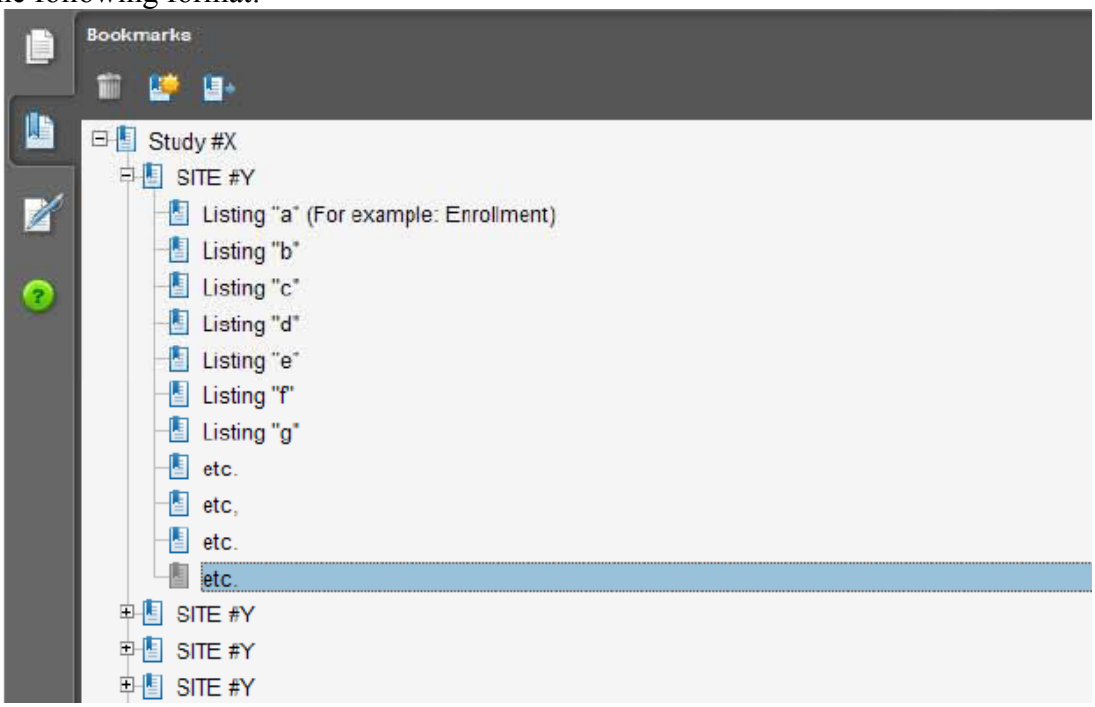
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere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

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

Electronic Regulatory Submission:

1. Follow the guidance documents and specifications regarding Electronic Common Technical Document (eCTD) submissions located at the following FDA webpage: eCTD
2. Refer to the following FDA webpage regarding the electronic submission of regulatory information to CDER: Electronic Regulatory Submission
3. The agency provides a process for submitting an eCTD sample for eCTD validation tests. Further instructions are listed at this FDA webpage: Sample eCTD Submission
4. Send any questions and general information regarding the preparation of submissions in electronic format to esub@fda.hhs.gov

Datasets:

5. Refer to the following FDA webpage on Study Data Standards Resources
6. Follow the following Guidance Documents:
   a. Providing Regulatory Submissions in Electronic Format-Standardized Study Data
   b. Study Data Technical Conformance Guide – Technical Specifications Document
      - As outlined in Section 2.2, include a Study Data Reviewer's Guide in the eCTD Module 5 that describes the use of study data standards and their conformance validation (this is in addition to the Reviewer's Guide in eCTD Module 1 that provides a high level overview of modules 1 through 5 with hyperlinks).
      - As outline in Section 4.1, use SDTM data format specifications for clinical tabulations datasets and ADaM for analysis datasets. Analysis datasets should be traceable to the tabulations datasets.
        - As outlined in Section 4.1.1.2, each individual subject should be assigned a single unique identifier across the entire application (e.g., including open label extensions of the trials).
        - As outlined in Section 4.1.4.5, the data definition file, define.xml, should be included to describe the format and content of the submitted SDTM and ADaM datasets.
      - As outlined in Section 6.3.1, the preparation of the adverse event dataset for the ISS should include MedDRA Preferred Terms from a single version of MedDRA.
      - As outlined in Section 8.3.2, specify whether Legacy data has been converted to SDTM formatting. If this is the case, the rationale, methods, and approach to this conversion process will need to be discussed with our data standards team (eData@fda.hhs.gov). Submit both the original (legacy) and the converted (SDTM) data for these trials. If Legacy data has not been converted to SDTM formatting, provide the rationale.
7. The agency provides a process for submitting sample standardized datasets for validation tests. Further instructions are listed here: Standardized Data Sample Submission
8. Open CDISC is one possible tool to check for conformance to the CDISC standard.
9. Send any questions regarding the submission or structure of datasets to eData@fda.hhs.gov

10. Submit datasets for all Phase 1, Phase 2, Phase 3 studies (including open label extension studies), including the Phase 2 and 3 studies performed for indications other than the one proposed for this application.
11. Submit all SAS codes used to create your analyses for the ISE and ISS. If a SAS code contains a macro, please also include the macro code.

General Submission Contents:

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

Adverse events:

1. Follow the coding rules for MedDRA in the ICH-endorsed "MedDRA Term Selection: Points to Consider" document accessible at MedDRA
2. For each of the studies, the submitted datasets should contain both the verbatim terms and the MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event, MedDRA coding should be provided for the primary MedDRA path as well as the alternative MedDRA coding paths.
3. Provide a summary table of the original AE coding dictionaries that were used in each of the trials.
4. Ensure that all adverse events are presented, and not only events deemed "drug-related."
5. Provide a table of treatment-emergent adverse events reported in ≥ 2% of subjects (after rounding) in any drug treated dose group (and greater than placebo) sorted by MedDRA SOC (in alphabetical order) and then by MedDRA Preferred Term.
6. Provide a table which summarizes the outcomes of all pregnancies. Provide a table which summarizes all known adverse events in subject offspring.

I. **Narratives and Case Report Forms (CRFs):**

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

- An assessment of the relationship of exposure duration to the development of the adverse event
- Pertinent medical history
- Concomitant medications with start dates relative to the adverse event
- Pertinent physical exam findings
- Any abnormal vital sign measurements
- Pertinent test results (e.g., lab data, ECG data, procedures, biopsy data, autopsy results)
- Discussion of the diagnosis as supported by available clinical data
- For events without a definitive diagnosis, a list of the differential diagnoses
- Treatment provided
- Re-challenge results (if performed)
- Outcomes and follow-up information

II. **Laboratory and Vital Sign Measurements:**

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

Other requests:

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

- Whether the patient completed or did not complete the study, with dates and reason for withdrawal
- Adverse events (reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
- Prior medications and concomitant medications with dates of start and end
- Vital signs and laboratories, sorted by date, with reference ranges *
- Autopsy reports for all deaths. (If an autopsy report is not available, explicitly state this.)
- Full reports for radiologic studies, ECG, MRI, pathology results, special studies and procedures with dates and reference ranges *

  * Provide relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, in each patient file. Also include baseline study results.
- For patients who had IND safety report(s), include dates when the initial and follow up safety reports were submitted.

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

2. Please submit for Division comments an example narrative from a patient who had more than one serious adverse event and participated in the controlled and extension studies.

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

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

- 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.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:

    1. An integrated analysis for an additional safety pool, including only the Phase 3 controlled data.
    2. An analysis of AE information based on the modal dose.
    3. An analysis of concomitant cardiovascular medication changes from baseline by treatment group
    4. Minor stability updates as described in Table 11 of the pre-BLA briefing book

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

  BLA 761089: LATE COMPONENT – CLINICAL
  BLA 761089: LATE COMPONENT – QUALITY

ATTACHMENTS AND HANDOUTS
The attached narrative (Attachment III) was provided by Teva with the firm's response to FDA's Preliminary Comments.

2 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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
09/29/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 106,533

MEETING MINUTES

Teva Pharmaceuticals
Attention: Douglas C. Harnish, Ph.D.
41 Moores Rd, P.O. Box 4011
Frazer, PA 19355

Dear Dr. Harnish:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TEV-48125.

We also refer to the meeting between representatives of your firm and the FDA on September 17, 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 17, 2015**
Meeting Location:	**FDA White Oak**
Application Number:	**106,533**
Product Name:	**TEV-48125**
Indication:	**Migraine Prophylaxis**
Sponsor/Applicant Name:	**Teva Pharmaceuticals**
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
Suhail Kasim, MD, Clinical Reviewer
Lois Freed, PhD, Supervisory Pharmacologist
Donald Charles Thompson, PhD, Pharmacology Reviewer
Kun Jin, PhD, Statistical Team Leader
Junshan Qiu, PhD, Statistical Reviewer
Ta-Chen Wu, PhD, Clinical Pharmacology Reviewer
Xiaofeng Wang, PhD, Pharmacometrics Reviewer
Lana Chen, RPh, Project Manager

Office of Biotechnology Products
Michele Dougherty, PhD, Acting Review Chief
Bazarragchaa Damdinsuren, PhD, Chemistry Reviewer

Division of Medication Error Prevention and Analysis (DMEPA)
Deborah Myers, PharmD, Safety Evaluator,
Danielle Harris, PharmD, BCPS, Team Leader

Center for Devices & Radiological Health
Richard Chapman; Chief, General Hospital Devices Branch CDRH/ODE/DAGRID
Ryan McGowan, Reviewer, General Hospital Devices Branch CDRH/ODE/DAGRID
Janice L. Polacek, RN, BSN, CRNI, Nurse Consultant, DAGRID

SPONSOR ATTENDEES

Teva:
Douglas Harnish, PhD Sr. Director, Regulatory Affairs
Susan Franks, M.S. SVP, Global Branded Products Regulatory Affairs
Dawn Kelly, PhD Assoc. Director, Regulatory Affairs CMC
Marcelo Bigal, MD, PhD VP, Migraine and Headaches Clinical Development
Ernesto Aycardi, MD Sr Director, Migraine and Headaches Clinical Development
Nicola Faulhaber, MD, MBA Safety Physician, Global Patient Safety and Pharmacovigilance
Ronghua Yang, PhD Sr Director, Biostatistics
Mary Ma, MS Assoc Director, Biostatistics
Jason Bock, PhD VP, Global CMC Biologics
Dong Geng, PhD Assoc. Director, Global Bioassay and Technology
Orit Cohenbarak, PhD Assoc Director, Phase 1 & Clinical Pharmacology
Maya Sokolovsky, MSc Sr Manager, Nonclinical Safety
Lena Ohannesian, PhD Sr. Director Project team Leader

DISCUSSION

Chemistry, Manufacturing and Controls

Question 1

As part of product development, Teva has made focused process improvements and will be increasing the scale of manufacturing from (b) (4) to (b) (4) To support these changes, Teva has designed a comparability plan consisting of an orthogonal panel of assays to assess the impact of these changes on the quality attributes of the product. In preparation for the (b) (4) clinical runs, the (b) (4) process has been run in a scaled down (b) (4) model and assessed by a comparability panel. This panel is the same as will be run with the (b) (4) material (data to be provided in the IND amendment), and is considered appropriate to support Phase 3 studies. Teva believes that the product quality comparative data at (b) (4) demonstrate that TEV-48125 manufactured by process (b) (4) are comparable, and will be further supported by the comparability data generated from the (b) (4) material. Does the Agency consider this approach acceptable?

FDA Response:

FDA considers the comparability of TEV-48125 manufactured by process (b) (4) to the material manufactured by the (b) (4) process as the required data for the intended purpose, and therefore we are not clear about what limits the use of the (b) (4) data to only being "supportive" data. Our assumption when reviewing the meeting package is that TEV-48125 manufactured by the (b) (4) process will be assessed at least as comprehensively as (b) (4)

product made by the (b) (4) model and that the data will be available when submitting the IND amendment and prior to use in clinical studies.

For comparability of the drug substance (DS) manufactured by process (b) (4) at the (b) (4) scale at Celltrion against the DS manufactured from process (b) (4) at (b) (4) and which has been used in your clinical trials, and for comparability of the drug product (DP) in prefilled syringe (PFS) to be manufactured at (b) (4) against DP (b) (4) manufactured at (b) (4) the following should be incorporated:

a. Comparability assessment should include accelerated/stressed stability assessment of the DS manufactured by process (b) (4) at the (b) (4) scale and by clinical process (b) (4) In section 10.1.1.8 of the meeting package, accelerated conditions are identified at -(b) (4)°C and (b) (4)°C. The comparability assessment should include conditions under which changes in DS would be anticipated to occur so that rates of degradation as well as degradation pathways can be compared.

b. The test panel presented in Table 11 seems adequate for assessment of comparability of the TEV-48125 materials. The meeting package does not include information on acceptance criteria for comparability assessment and therefore, we cannot comment on the acceptability of this part of the comparability plan.

c. It appears from the meeting package that Teva's planned comparability study will include only one lot of DS manufactured by the (b) (4) process against one lot of DS manufactured by the clinical (b) (4) process. To enable an assessment of comparability, especially in case where there is some difference seen in any quality attribute, the IND submission should also include data from all clinical process (b) (4) lots manufactured. For example, some differences apparent in the pilot scale data presented include (b) (4) and (b) (4), and based on the information provided it is not clear whether these are within historical ranges.

d. We note that Table 2, identifying summary comparability results for process (b) (4) pilot scale material only reports a subset of the results. For example, cIEF only reports main peak %, RP-HPLC only reports the % of the (b) (4), HILIC only reports the % of (b) (4). When submitting the comparability results to the IND, all quality attributes identified by these and other assays should be addressed. For differences seen in any quality attributes already identified as non-critical, justification, including the data showing that the quality attribute is not critical, should be included.

e. Relevant comparability data for DP manufactured by processes (b) (4) in the (b) (4) PFS (b) (4) should also be provided.

Meeting Discussion:

The sponsor clarified (b) (4) The drug substance lot manufactured by processes (b) (4) (used in phase II clinical studies) has been fully processed and is no longer available, however the process (b) (4) drug product material, which is used in clinical studies, is available and will be used in comparability assessments, including degradation studies. In addition, FDA recommended that the sponsor provide a risk assessment of suitability of use (b) (4) drug product instead of (b) (4) drug substance used in the comparability assessment.

Since only one lot of drug substance and one lot of drug product was manufactured by (b) (4) process, FDA agreed that acceptance criteria are not required (item "b").

The sponsor clarified that full comparability data will be included in the IND as presented in the background section (item "d").

Regarding item "e", FDA agreed to the sponsor's proposal that the comparability of the drug product may consist of drug product test results against drug product specifications. Teva also confirmed that historical batch analysis and stability data of all lots will be provided in the IND.

Question 2

After Teva took responsibility for product development for TEV-48125 (b) (4) Teva is planning to control histidine and EDTA levels in the (b) (4) process to be consistent with actual values observed in the Phase 1 and 2 clinical lots and update the label and dossier accordingly. Does the Agency concur?

FDA Response:

Yes. To support the proposed change, the following information should be amended in the IND:

a. the results of the histidine and EDTA levels in the clinical lots,
b. information on analytical methods, and
c. information showing that the EDTA addition (b) (4) have no effect on process performance and product quality.

Meeting Discussion:

There was no further discussion.

Question 3

The mechanism of action for TEV-48125 is binding to soluble CGRP thus preventing it from binding to the CGRP receptor. TEV-48125 has been demonstrated to have very weak binding to

FcγRs, which is consistent with it being an IgG2 mAb and having been engineered specifically to reduce effector function. The Sponsor proposes no further characterization or routine testing of FcγR binding for TEV-48125. Does the Agency concur?

FDA Response:

Yes. Please include the results of the FcγR binding characterization studies mentioned in section 10.1.1.4.3 in your IND submission.

Meeting Discussion:

There was no further discussion.

Question 4

As TEV-48125 is an IgG2 mAb and binds to a soluble ligand, Teva believes glycan analysis for TEV-48125 is more suitable for purposes of product characterization and product comparability studies, than for lot release. Does the Agency concur?

FDA Response:

We agree with Teva's proposal to remove glycan analysis for TEV-48125 as a lot release test. However, glycan analysis should continue to be collected from lots manufactured by process (b) (4) in order to have a robust database for the glycan species and levels on TEV-48125 used in the phase 3 clinical studies, and to support establishing acceptance criteria for comparability analysis following future manufacturing changes.

Meeting Discussion:

There was no further discussion.

Question 5

The (b) (4) for host cell protein (HCP) detection was used to release (b) (4) material. Teva will investigate a process specific HCP assay prior to process validation and bridge from the (b) (4) Teva believes the (b) (4) for HCP detection to be suitable for testing TEV-48125 Phase 3 material using the existing acceptance criteria. Does the Agency concur?

FDA Response:

It is not clear how Teva is bridging the HCP assay results from different assays, e.g. whether Teva is going to include testing of retain samples from previously manufactured clinical lots in its assessment of the current HCP assay, and any future HCP assays that will be developed. Teva's proposal to test TEV-48125 phase 3 material for HCP using (b) (4) however, Teva should develop a clear plan for bridging the HCP results using the (b) (4) with any assay proposed to be used for the marketed product so that the

levels and species of HCPs identified can be compared. Teva should bank retain samples from each lot for this purpose.

Meeting Discussion:

There was no further discussion.

Question 6

In support of Phase 3, Teva has developed a new cell based potency assay based on the TEV-48125 mechanism of action for lot release and stability. Upon successful completion of the validation activities for the cell-based assay, including method bridging, Teva is proposing to continue testing TEV-48125 by (b) (4) as part of product characterization and comparability but no longer for lot release and stability. Teva believes the cell based potency assay is sufficient and appropriate for determining TEV-48125 potency for the Phase 3 material at release and while on stability. Does the Agency concur?

FDA Response:

No. We do not have sufficient information to assess whether the cell based potency assay and (b) (4) potency assay are fully interchangeable or if one assay provides better control over potency and product quality than the other. Until sufficient data are developed and assessed, both (b) (4) and cell based assays should be used for lot release and stability testing. The type of data required includes release and stability results of multiple DS and DP lots, as well as TEV-48125 samples that have been stressed by different mechanisms.

Both assays should also be used for characterization of product variants and/or product-related impurities and the data from these can also be used to support the comparison of the two potency assays.

Please note that pending availability of these data and FDA's assessment of the full dataset in the marketing application, both assays should be validated. Validation information for the cell based potency assay should include data to support the variability allowed by the assay; for example, robustness studies should address cell age and plating, options on coating the plate, dilutions of CGRP, etc.

Meeting Discussion:

There was no further discussion.

Question 7

In moving from process (b) (4) to process (b) (4) and as additional development experience has been gained, Teva has updated some test methods and/or acceptance criteria that are used in the release of TEV-48125 drug substance and drug product. Teva believes the proposed changes allow for adequate control of product quality and safety, and are suitable for the duration of Phase 3 studies. Does the Agency concur?

FDA Response:

No. The following should be addressed:

a. No data were provided to enable an assessment of the acceptance criteria that are intended for the duration of Phase 3 studies. Your IND submission should include the release and stability results for the DS and DP lots manufactured to date in support of your acceptance criteria.

b. Please see our response to question 6 regarding use of the potency assays in lot release and stability assessment of TEV-48125.

c. Identity by ELISA and cIEF are acceptable, however, we note that peptide mapping is a powerful tool to assess product quality. Teva should assess whether this method provides information not covered by other assays.

d. Please consider assigning more definitive acceptance criteria for color and a quantitative limit for cIEF basic peak based on release and stability data from lots manufactured to date.

e. The specifications do not appear to include any criteria for assessment of lower molecular mass species (LMMS) and fragments. Include a parameter for LMMS by SE-HPLC in DS and DP specifications for lot release and stability. If another assay is better for separation, capture and quantification of these species, include the appropriate testing as part of your DS and DP specifications for lot release and stability.

f. For the DP in PFS, Teva should start collecting information on breakloose and extrusion forces from the lots released for clinical trials.

It is our understanding that the changes identified will also apply for the stability methods and specifications, as described in the section 3.2.S.7.1. and 3.2.P.8.1. of the IND.

Meeting Discussion:

There was no further discussion.

Question 8

The container closure system for the Phase 3 clinical program will be a 2.25mL prefilled syringe. Teva anticipates making enhancements to the prefilled syringe configuration in support of product commercialization (b) (4) Does the Agency concur?

FDA Response:

Meeting Discussion:

There was no further discussion.

Question 9

There have been no changes to the formulation of TEV-48125 when moving from process (b) (4) (Phase 2) and (b) (4) (Phase 3). (b) (4) In the IND Amendment, Teva is planning to include the following data to support the (b) (4) drug product in syringes:

- 2 year stability data from the (b) (4) process (b) (4)
- 6 month stability data from a (b) (4) pilot scale batch (in syringes)
- 3 months stability data from a (b) (4) pilot scale batch (in syringes)
- Batch release data on the (b) (4) clinical batch (in syringes)

The sponsor believes the drug product stability data that will be generated in support of the (b) (4) process, combined with the comparability assessment, will support that process (b) (4) material may be used in the proposed Phase 3 clinical trials. Does the Agency concur?

FDA Response:

In order to enable use the identified data to initiate a clinical trial using (b) (4) material in PFS, Teva should provide comparability data of the pilot scale material and the (b) (4) clinical batches from the (b) (4) and (b) (4) pilot scale batches to the IND. In addition, your proposed stability specifications should include:

- Potency by ELISA
- pH

- Endotoxin (may be done on an annual basis)

Meeting Discussion:

There was no further discussion.

Nonclinical

Question 10

APPEARS THIS WAY ON ORIGINAL

TEVA conducted a comprehensive non-clinical package, including toxicology and pharmacokinetics studies according to ICH M3(R2), ICH S6 and other relevant guidance. Based on the list of non-clinical studies described in Section **Error! Reference source not found.** does the agency agree that the completed and ongoing non-clinical studies are sufficient for an adequate review: 1) to support phase 3 clinical trials and 2) a forthcoming Biologic License Application (BLA)?

FDA Response:

In addition to the ongoing nonclinical studies intended to support the proposed Phase 3 clinical trial, you will need to submit a pre- and postnatal development study for marketing approval. If the drug substance manufactured by the new process (b) (4) is not found to be comparable to the drug substance used in the completed and ongoing nonclinical studies, additional nonclinical studies may be needed. (Also, see response to Question 11.)

Meeting Discussion:

The sponsor stated that a pre- and postnatal development study will be conducted and asked if it is acceptable to conduct the study in rat. The division indicated that rat is generally an acceptable species for this type of study.

Question 11

In the main phase of the embryo-fetal development (EFD) study in rabbits, the pregnancy rate of the time-mated females was lower in the intermediate and high dose groups when compared to control. The, numbers of rabbits eventually confirmed as pregnant were 17, 17, 14 and 15 for the control, low, mid and high dose groups, respectively.

Based on the Sponsor's position, does the agency accepts the study as valid in spite of the fact that number of litters in the mid and high doses was lower than the minimum requested (i.e., 16 litters per group) as per the ICH S5R2 guideline?

FDA Response:

The number of litters available for evaluation (17, 17, 14, and 14 for control, low, mid, and high doses, respectively) is less than the recommended number (16-20/group) at both the mid and high doses (*cf. ICH S5(R2), November 2005*); therefore, the study will need to be repeated. The repeat study may be conducted concurrently with the proposed Phase 3 trial.

Meeting Discussion:

The sponsor stated that the plan is to add 6 mid-dose and 6 high-dose animals to the ongoing study in order to increase the total number of animals per group. It has been one month since the last dose was administered, but the exact same experimental conditions will be used to test the additional animals. The sponsor confirmed that toxicokinetic data were collected in the original study. The division indicated that the plan was unusual but might be acceptable if a concurrent control group (n = 6) is also added and if toxicokinetic data are collected in the additional animals. The division noted, however, that the study may need to be repeated if there are discrepancies in the findings between the original and additional animals.

Clinical Pharmacology

Question 12

TEV-48125 is a large protein with a molecular weight of 148kDa and thus, unlikely to be eliminated through renal excretory or hepatic mechanisms. Does the Agency agree with the Sponsor's intention not to conduct pharmacokinetic studies in patients with renal and hepatic impairment?

FDA Response:

Yes.

Meeting Discussion:

There was no further discussion.

Question 13

Does the Agency concur with the Applicant's proposal not to conduct drug-drug interaction studies?

FDA Response:

Yes.

Meeting Discussion:

There was no further discussion.

Question 14

Teva is requesting a waiver from the requirement for the conduct of a thorough QT/QTc (TQT) study for TEV-48125. The data to support the request are contained in a position paper that is submitted with the meeting briefing package. Does the Agency agree with the Sponsor's proposal not to conduct a TQT study?

FDA Response:

Yes.

Meeting Discussion:

There was no further discussion.

Clinical

Question 15

a. Teva conducted and analyzed the phase 2 CM study with sufficient rigor to meet phase 3 pivotal study requirements. Does the Agency agree that this CM study could support an indication for the prophylactic treatment of CM with a second positive phase 3 study in CM patients?

FDA Response:

On face, the phase 2 trial in CM could be used as one of your registration studies to support an indication for the prophylactic treatment of CM, but any final determination will require a more thorough review of the trial's study report.

Meeting Discussion:

There was no further discussion.

b. Teva conducted and analyzed the phase 2 EM study with sufficient rigor to meet phase 3 pivotal study requirements. Does the Agency agree that this EM study could support an indication for the prophylactic treatment of EM with a second positive phase 3 study in EM patients?

FDA Response:

On face, the phase 2 trial in EM could be used as one of your registration trials to support an indication for the prophylactic treatment of EM, but any final determination will require a more thorough review of the trial's study report.

Meeting Discussion:

There was no further discussion.

Question 16

Teva believes that the two proposed phase 3 clinical trials (1 in EM and 1 in CM) would be sufficient to support registration for the broad prophylactic treatment of headaches in individuals with EM and CM? Does the Agency agree?

FDA Response:

Yes, in the proposed scenario, positive trial results from single adequate and well-controlled studies in each population (episodic and chronic migraine) would be sufficient to support a global prophylaxis claim.

Meeting Discussion:

There was no further discussion.

Question 17

Phase 3 study protocols for CM and EM are provided in Appendix C. Teva would appreciate feedback on the proposed study design, and has specific questions on the following aspects of the protocols, including:

Please note that in the absence of a full protocol, our response is limited and is generally directed to your proposed overall approach and developmental plan of TEV-48125.

a. Is the proposed targeted CM population acceptable?

FDA Response:

Yes, the inclusion of patients with chronic migraine defined as subjects reporting 15 or more days of headache on most of the recent months, with prospective confirmation in the run-in phase of the study of a frequency of at least 15 days of headache, with 8 days of either migraine, migraine preceded or accompanied by migraine aura, or migraine relieved with the use of triptan or ergot compounds, is acceptable.

We do not recommend allowing patients on two migraine preventive medications to enroll in the trial, whether or not taken for the treatment of another medical condition. We recommend, that if you include patients on preventive medications for CM, such as topiramate or propranolol, you limit a limited proportion of patients, e.g., a maximum of 20 to 30% of subjects in the trial, and stratify by this factor, since the use of concomitant migraine preventive medications may confound the results of the primary analysis, in particular if there is an imbalance in preventive medications between treatment groups.

Meeting Discussion:

There was no further discussion.

b. Teva considers that [redacted] (b) (4) is an appropriate primary endpoint for this CM phase 3 study. Does the Agency concur?

FDA Response:

Although the use of [redacted] (b) (4) may be acceptable, we recommend that you use the primary endpoint "*mean change from baseline in headache days"* in your CM trial. Current IHS guidelines recommend that headache days be counted when the headaches are at least of moderate intensity (Reference: Silberstein S et al. Guidelines for controlled trials of prophylactic treatment of chronic migraine in adults. *Cephalalgia*. 2008 May;28(5):484-95). We would be happy to discuss alternate definitions. You should submit your final proposal for special protocol assessment.

Meeting Discussion:

The sponsor stated that they plan to use the primary endpoint mean change from baseline in number of headache days of at least moderate severity in the CM protocol, using the recommended migraine day definition. The sponsor requested clarification about the plan for analysis of the primary endpoint. FDA stated that the preferred method is to analyze the change over the entire treatment period as compared to baseline, (b) (4) The sponsor asked whether we recommended that they submit a Special Protocol Assessment (SPA) since their impression was that there was alignment on many key issues in the proposed Phase 3 protocol. FDA stated that it was the sponsor's choice whether to submit a request for a SPA, and that if one was submitted FDA would provide input within 45 days.

c. Is the proposed targeted EM population acceptable?

FDA Response:

Yes, the proposed episodic migraine population in the phase 3 study appears acceptable (defined as subjects experiencing 5 to 14 migraine-days/month and ≤14 headache-days/month during the screening over a 3- month period).

Please see our response to Question 17a concerning the inclusion of patients with concomitant migraine preventive medications in the CM trial, as the same comment applies to the proposed EM population.

Meeting Discussion:

There was no further discussion.

d. Does the Agency concur with the proposed primary endpoint of mean change from baseline of monthly migraine days at month 3 for the EM study?

FDA Response:

We concur with your proposed primary endpoint "mean change from baseline of monthly migraine days at month 3" for the EM study.

You proposed definition for the efficacy analysis endorsed a migraine day as when at least 1 of the following situations occur:

1. a calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of a headache meeting criteria for migraine with or without aura
2. a calendar day (0:00 to 23:59) demonstrating at least 4 consecutive hours of a headache meeting criteria for probable migraine, a migraine subtype where only 1 migraine criterion is missing

3. a calendar day (0:00 to 23:59) demonstrating a headache of any duration that was treated with migraine-specific medications (triptans and ergot compounds)
4. (b) (4)

We recommend using a shorter migraine duration to define a migraine day in episodic migraine, e.g., at least 2 hours of headache. Also, we recommend elimination criterion 4.

Meeting Discussion:

There was no further discussion.

e. Does the Agency concur with the proposed dosing schedule including the proposed doses for both phase 3 studies?

FDA Response:

On face, your proposed doses and the dosing regimen appear acceptable.

Meeting Discussion:

There was no further discussion.

f. TEV-48125 is a mAb against CGRP and it is expected to exert its action by blocking CGRP in the peripheral trigeminal terminals and trigeminal ganglia, both of which reside outside of the blood brain barrier in humans. Considering this site of action, as well as the known limited brain penetration properties of mAb, does the Agency agree (b) (4)?

FDA Response:

No. Your product may have indirect effects on the CNS; (b) (4) Please refer to the section of this document with the heading (b) (4) below.

Meeting Discussion:

There was no further discussion.

Additional comments:

1. For Study TV48125-CNS-30049, a treatment difference of 22.8 hours of cumulative headache hours between the treatment and placebo groups and a common standard deviation of 71 days were used in the sample size calculation. With the information provided, we cannot confirm your calculation. Please confirm that the common standard deviation is indeed 71 days and the unit of days was converted hours prior to the sample size calculation.

2. For Study TV48125-CNS-30050, a treatment difference of 1.84 hours of cumulative headache hours between the treatment and placebo groups and a common standard deviation of 6

days were used in the sample size calculation. With the information provided, we cannot confirm your calculation. Please confirm that the common standard deviation is indeed 6 days and the unit of days was converted hours prior to the sample size calculation.

3. Please clearly specify analyses populations.

Meeting Discussion:

Teva provided clarification that there were grammatical errors with the units assigned in the briefing document regarding the sample size calculations. Teva indicated for study TV48125-CNS-30049, a treatment difference of 22.8 hours of cumulative headache hours between the treatment and placebo groups and a common standard deviation of 71 hours (not days) was used in the sample size calculation. For study TV48125-CNS-3050, a treatment difference of 1.84 days (not hours) of cumulative headache hours between the treatment and placebo groups and a common standard deviation of 6 days were used in the sample size calculation.

Question 18

Patients completing either Phase 3 study will be eligible to enroll in a randomized, double blind, long-term safety follow-up study. Teva would appreciate feedback on the proposed study design, and has specific questions on the following aspects of the protocol, including:

a. Is the proposed dose that will be administered to all new patients enrolling into the study or that are rolling over from either the CM or EM study acceptable?

FDA Response: Yes, the proposed dose from the clinical study synopsis of the long-term safety follow-up study TV-48125-CNS-30051 appears acceptable.

Meeting Discussion:

There was no further discussion.

b. Is the proposed 1 year duration follow up acceptable?

FDA Response:

On face, yes.

Meeting Discussion:

There was no further discussion.

Safety

Question 19

Does the Agency agree that the proposed clinical development plan provides sufficient evidence for evaluation of the safety and tolerability of TEV-48125 and that the previous clinical experience combined with the proposed phase 3 studies provide a sufficient safety database for registration?

FDA Response:

On face, your proposal to include at least 300 migraine patients (chronic and/or episodic migraine) with 6 months exposure and at least 100 patients with one year exposure to TEV-48125 is acceptable. A final determination will be a matter of review, based on the safety signals identified during development.

In general, there must be adequate experience (meeting ICH guidelines) for the highest dose proposed for labeling. Your safety database should include TEV-48125 exposures with *monthly injections* at the maximal recommended dose proposed for registration in at least 150 subjects for 6 months, and at least 50 subjects for one year.

Meeting Discussion:

There was no further discussion.

Question 20

Does the agency agree with the proposed immunogenicity assessment strategy provided in the briefing document and that anti-drug antibody (ADA) assays are adequate for characterizing ADA response following TEV-48125 treatment?

FDA Response:

The proposed strategy identified in Figure 4 appears reasonable, pending availability of a neutralizing ADA assay. We understand that Teva is currently encountering problems in their development of a neutralizing assay for this drug. Patient serum should be banked for use until a validated sensitive neutralizing assay is available. Assessment of neutralizing ADAs solely by assessing impact on PK profile and PD markers is not sufficient.

If serum samples analyzed by the (b) (4) ADA assay are available, testing these samples with the Teva ADA assays would enable bridging of the data from the previous clinical trial.

Regarding the assay validation data provided in the meeting package, the Office of Biotechnology Products does not generally review immunogenicity validation reports in the context of meeting packages. A comprehensive assessment is in progress and any further comments on this validation study will be provided in a separate communication.

Meeting Discussion:

The sponsor agreed to develop and validate a neutralizing ADA assay. FDA noted that a ligand binding based format neutralizing ADA assay would be an acceptable assay format for the neutralizing ADA assay with appropriate scientific justification.

The sponsor clarified that the (b) (4) ADA assay was only used for the phase 1 studies in a small number of healthy volunteers, and that the sponsor's ADA assay was used to assess all the Phase 2 samples. The sponsor requested not to perform a re-analysis of Phase 1 samples using their

ADA assay, and FDA agreed. However, both sides agreed that the data generated with the (b) (4) ADA assay would not be included in label claim.

Statistics

Question 21

In regards to the phase 3 CM and EM statistical plan;

a. Does the Agency concur with the proposed analysis for the primary efficacy variable?

FDA Response:

On face, the proposed Mixed Effect Model Repeated Measurement (MMRM) seems acceptable. However, we recommend using the data from the phase 2 trials to justify the assumptions (e.g., normality) imbedded in the MMRM model and planning a backup analysis in case they are not justified. The robustness of the MMRM model should be assessed in the sensitivity analyses. In addition, a sensitivity analysis for testing the treatment effect over the entire double blind period should be planned.

Meeting Discussion:

FDA clarified that the requested backup analysis for MMRM analysis was not a sensitivity analysis but the primary analysis if model assumptions for MMRM do not hold (e.g, normality). FDA suggested that the sponsor use the data from the Phase 2 trials to justify the model assumptions proposed for their Phase 3 studies. FDA also suggested that the sponsor use analysis of covariance (ANCOVA) to evaluate the treatment effect given that the primary endpoint is mean change in monthly migraine days from the baseline in the EM trial during the entire double-blind treatment period as each patient will only have 1 post-baseline value contributed to the analysis. FDA asked the sponsor to maintain data quality and to pay close attention to the diary compliance to prevent diary entry afterwards and reduce the intermittent missing data. Teva responded that a hand device will be used for the headache diary to improve diary compliance.

b. Does the Agency concur with the proposed approach of handling missing data for the primary efficacy variable?

FDA Response:

The proposed plan for handling missing data did not clearly address intermittent missing data issue. In order to assess the seriousness of this potential problem, we recommend that you provide information on missing data, especially on the intermittent missingness from the completed phase 2 trials. If there are many intermittent missing diaries per the data from the phase 2 trials, you should consider improving the quality of trial conduct to reduce this type of missingness. In addition, large amounts of missing data will affect the interpretation of the trial results.

Meeting Discussion: See meeting discussion following Question 21a.

Additional CMC comments:

1. Due to implementation of substantial changes in the manufacturing process, an assessment of the viral clearance by the (b) (4) process should be included in the IND.

2. The characterization results of (b) (4)

Meeting Discussion:

Teva agreed to continue (b) (4) distribution on all drug substance lots. Teva proposed to continue the monitoring as part of product characterization but not as part of the drug substance release specification, and FDA agreed with the proposal.

3. TEV-48125 DS stability assessment (b) (4) Results from these studies should be provided to the IND.

Meeting Discussion:

(The following refers to comment 3 and 6)

(b) (4) The sponsor acknowledged the FDA's recommendation for DS stability.

4. The meeting package identifies that (b) (4) For the purpose of supporting shelf-life determination in your marketing application, sufficient data from multiple lots of DS and DP manufactured by the (b) (4) process placed on stability should be available.

5. For the PFS, characterization of breakloose and extrusion forces for PFS, annually and at end of shelf-life, should be collected.

6. [redacted]

7. Two of three proposed phase 3 clinical trials are randomized, double-blind, placebo-controlled 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 TEV-48125 lots in PFS [redacted] as relevant. Additionally, submit samples of the placebo and TEV-48125 in the PFS [redacted] to the Agency for assessment.

Meeting Discussion:

Regarding the requirement to provide samples of the placebo and the drug in relevant presentations, FDA clarified that the submission of few samples of each of DP and placebo is sufficient and can be done concurrent with the submission of the IND. In addition, samples from batches representative to the clinical batches are acceptable, pending that an FDA review deems them comparable. FDA explained that visual examination of the product and placebo in PFS [redacted] is requested to assess whether potential differences in appearance of the investigational product and placebo are unlikely to result in unblinding of patient's treatment group.

8. At this stage of drug development, Teva should address the agency's comments communicated previously, for example, non-hold comments for the original IND sent on 02/17/2010, including the comments #5, 8, 9, which were to be addressed prior to phase 3.

Meeting Discussion:

The sponsor clarified that in support of the [redacted] process a working cell bank has been generated, thus FDA agreed that comment # 5 has been addressed.

Regarding comments #8 and #9, FDA noted that while methods to determine and/or validation of manufacturing capability of removing process related impurities, [redacted], and methods to determine the impact of [redacted] on the drug product, are developed prior to submission of a BLA, at Phase 3 the sponsor should provide at least a risk assessment on process related impurities detailing the capabilities of the [redacted] process to remove the impurities and to assess the theoretical levels of these impurities. FDA agreed that this theoretical clearance and risk assessment might support justification of specification, if relevant. The sponsor stated that they will submit the requested information to the IND.

Human Factor Studies (DMEPA Comments)

You should conduct a comprehensive use-related risk analysis of your proposed TEV-48125 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.

Prospective Suicidality Assessments in Clinical Protocols

Treatment-emergent suicidality (suicidal ideation and behavior) has been identified in recent years as a concern for a number of drugs and drug classes. FDA-conducted meta-analyses of clinical trial data for both antiepileptic drugs and antidepressants have demonstrated that these drug classes increase the risk of suicidal thoughts and behavior. Spontaneous reports have led to concerns about the risk for suicidality with other drugs as well. These drugs include isotretinoin and other tretinoins, beta blockers, reserpine, smoking cessation drugs, and drugs for weight loss.

Given the heightened concern regarding the potential for treatment-emergent suicidality with certain drugs, particularly those products with central nervous system activity, the Division of Neurology (DNP) has made the determination that prospective assessments for suicidality should be included in clinical trials involving all drugs for neurological indications. There are two

primary reasons for this new requirement pertaining to prospective suicidality assessments. First, such prospective assessments will ensure the collection of more timely, complete, and reliable data pertaining to suicidality than have been collected in the past. This will allow assessment of the risk for suicidality with a given drug and, when the data are collected in a systematic and uniform fashion, will allow for additional analyses to be conducted in the future aggregating findings and comparing findings across drugs and drug classes. Second, such prospective assessments will help ensure that patients who are experiencing suicidal thoughts or behavior are properly recognized and adequately managed. This is important whether or not a particular product is known or suspected to be associated with treatment-emergent suicidality.

All clinical protocols for products developed in DNP for any indication should therefore include a prospective assessment for suicidality. These assessments must be included in every clinical protocol, at every visit, and in every phase of development, with the exception of single-dose trials in healthy volunteers. It is reasonable to omit such assessments from these trials. An acceptable instrument should map to the Columbia Classification Algorithm for Suicide Assessment (C-CASA), directly classifying events of interest into one of 11 categories of suicidal ideation and behavior. The Columbia Suicide Severity Rating Scale (C-SSRS) is an example of an acceptable instrument.

You must obtain DNP's prior approval for any alternative assessment instrument that you wish to use. A request to use an alternative prospective suicidality assessment instrument should include a justification for the use of this instrument, including an explanation of how the alternative instrument would map to the Columbia Classification Algorithm for Suicide Assessment (C-CASA). As discussed above, the ability of an assessment instrument to map to a common scale is important for any analyses conducted in the future.

This new policy is applicable to all new protocols submitted to DNP and to ongoing protocols in which you have an IND residing within DNP. For ongoing protocols, amendments must be submitted to incorporate this assessment. For newly submitted protocols drafted prior to you becoming aware of this new policy, the lack of a prospective assessment for suicidality will not constitute a reason for placing your IND on clinical hold. As with ongoing protocols, an amendment should be submitted to incorporate such assessments. In the future, however, the absence of a plan for prospective suicidality assessments may constitute a reason for placing an IND on clinical hold.

It is reasonable to omit prospective assessments for suicidality, or consider alternative assessments, in trials involving patients with impairment that is so substantial as to interfere with such assessment.

A sponsor considering the omission or alteration of standard suicidality assessments from a particular clinical protocol should discuss this omission with DNP to gain prior agreement. In certain instances, alternative instruments may permit the assessment of suicidality.

Further details pertaining to the prospective assessment of the occurrence of suicidality in clinical trials can be found in the following Draft Guidance for Industry:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225130.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

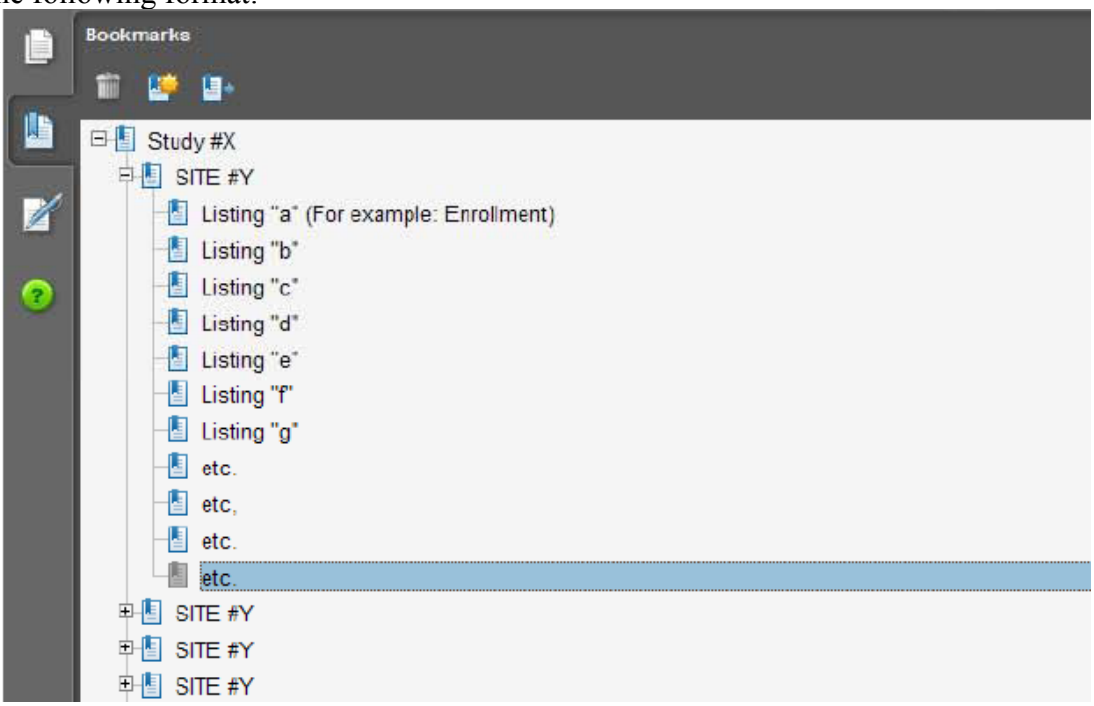
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records,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

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

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
10/16/2015