

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761119Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 114647

MEETING PRELIMINARY COMMENTS

Alder BioPharmaceuticals, Inc.
Attention: John Spoden
Director, Regulatory Affairs, CMC
11804 North Creek Parkway South
Bothell, WA 98011

Dear Mr. Spoden:

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

We also refer to your July 30, 2018 correspondence, received July 30, 2018, requesting a meeting to discuss and obtain the Agency's feedback on Chemistry, Manufacturing and Controls (CMC) data to support your future Biologics License Application (BLA) submission for eptinezumab.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, contact LCDR Oumou Barry, Regulatory Business Process Manager (RBPM) at, 240-402-8257 or via email at, Oumou.Barry@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

LCDR Leslie A. Rivera Rosado
Team Lead
Division of Biotechnology Review and Research IV
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: October 24, 2018, 11:00 AM to 12 PM EST
Meeting Location: FDA White Oak Campus

Application Number: 114647
Product Name: Eptinezumab/ALD403

Indication: For the preventive treatment of migraine in adults
Sponsor Name: Alder BioPharmaceuticals, Inc.

FDA ATTENDEES (tentative)

1. Leslie Rivera Rosado, Ph.D., Team Lead, Office of Biotechnology Products (OBP)/Office of Pharmaceutical Quality (OPQ)/CDER
2. Andrea Franco, Ph.D., Staff Fellow, OBP/OPQ/CDER
3. Oumou Barry, RBPM, Office of Program and Regulatory Operations (OPRO)/OPQ/CDER
4. Lakshmi Narasimhan, Ph.D., Microbiologist, Division of Microbiology Assessment (DMA) Office of Process and Facilities (OPF)/OPQ/CDER
5. Maxwell Van Tassell, Ph.D., Staff Fellow, DMA/OPF/OPQ/CDER
6. Patricia Hughes, Ph.D., Branch Chief, DMA/OPF/OPQ/CDER
7. Steven Fong, Ph.D., Microbiologist, OPF/OPQ/CDER
8. Christopher Downey, Ph.D., Branch Chief, OBP/OPQ/CDER
9. Peter Zhihao Qiu, Ph.D., Branch Chief, OPF/OPQ/CDER

SPONSOR ATTENDEES

1. Patrick Finerty, Jr., Ph.D. – Sr. Scientist, Formulation and Analytical Development
2. Randy Hassler, MS – Executive Vice President, Pharmaceutical Operations
3. Geoff Lee, Ph.D. – Senior Director, Downstream Processing
4. Mary Jo Phoenix, MS – Director, Quality Control
5. Pei Qi, Ph.D. – Senior Director, Formulation and Analytical Development
6. John Spoden – Director, CMC Regulatory Affairs
7. Annette Vahratian – Senior Vice President, Quality
8. Melissa A. Yeager, J.D. – Senior Vice President, Regulatory Affairs

Consultant/Advisor(s) to Alder

9. [REDACTED] (b) (4)



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for October 24, 2018, 11:00 AM to 12: PM EST, FDA White Oak between Alder Biopharmaceuticals and the Office of Pharmaceutical Quality. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting e.g., from face-to-face to teleconference. Contact LCDR Oumou Barry Regulatory Business Project Manager (RBPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

The Purpose of the Type B CMC Pre-BLA Meeting is to discuss and obtain the Agency's feedback on Chemistry, Manufacturing and Controls (CMC) data to support Biologics License Application (BLA) filing for eptinezumab. Eptinezumab (ALD403) is being developed for the prevention of migraine in adult patients. Previous CMC Type C meeting was held in May 2017 for this IND to obtain the Agency's feedback on sponsor approach for evaluating product comparability for new Bulk Drug Substance at (b) (4) and Drug Product at (b) (4). The sponsor intends to submit a BLA via the 351 (a).

FDA feedback is being sought on the following topics:

- Suitability of (b) (4) to support BLA filing and review
- Adequacy of the drug substance and drug product specifications to support the BLA filing and review
- Concurrence with the organization of the eptinezumab comparability data and evaluations within the BLA
- Plan and timing for submission of additional stability data in support of an intended retest and expiry of commercial drug substance and drug product, respectively
- Guidance on facility inspections scheduling in relation to BLA filing timeline

2.0 DISCUSSION

2.1. Chemistry, Manufacturing and Controls

Question 1a: Alder has (b) (4)

FDA Response to Question 1a:

Yes, based on the information provided in the meeting briefing package the proposed Alder's

Question 1b: The eptinezumab BDS and DP specifications are presented for the intended commercial product. The specifications have been established and sufficiently evaluated according to required pharmacopeia standards and regulatory expectation. Does the FDA concur that Alder's analytical methods and associated acceptance criteria for eptinezumab BDS and DP are sufficient to support a BLA filing and review?

FDA Response to Question 1b:

The type of information and data to be provided to support the proposed acceptance criteria for eptinezumab Drug Substance and Drug Product release and stability testing appear adequate for the filing and review of the BLA. However, final determination regarding the acceptability of the proposed commercial DS and DP specifications (test methods and acceptance limits) will require the evaluation of the full characterization of the molecule, assay validation, and manufacturing capabilities which will be made during the review of the BLA.

In addition, we have the following comments regarding your proposed DS and DP specifications:

- *In the current DS and DP specifications, SDS-PAGE test method was replaced by CE-SDS. In the BLA, provide data from bridging studies and scientific justification to support the introduction of any new analytical method.*
- *The BDS and DP (b) (4)*
- *The comments and recommendations provided by the Agency during the Type C meeting held on May 9, 2017 should also be addressed in the BLA.*

Question 2: Alder has aligned its analytical comparability approach for eptinezumab with the recommendations provided by the Agency during discussions at the Type C meeting held on May 9, 2017. Alder's analytical assessment of comparability will include comparisons of data from the pivotal clinical supply manufacturer (b) (4) to data from the proposed commercial manufacturers: (b) (4) for BDS and (b) (4) for DP. Data will be evaluated from the following four general categories: lot release, characterization, GMP stability, and forced

degradation. Does the Agency have any recommendations that will further facilitate its review of Alder's comparability data and evaluation?

FDA Response to Question 2:

The analytical comparability approach presented in the meeting briefing package and the organization of the comparability data you intend to present in the BLA appear acceptable. Final determination on the acceptability of the analytical comparability data will be made during the review of the BLA.

Question 3: Regarding stability data submitted in support of the BLA:

Does the FDA concur with the subsequent submission of the 18-month stability data within 60 calendar days of submitting the BLA for both the eptinezumab BDS and DP?

Based on acceptable 18-month data, does the Agency concur with the proposed (b) (4) retest date for the eptinezumab BDS and 24-month expiry for the eptinezumab DP?

FDA Response to Question 3:

a) *The Agency expects applications to be complete at the time of submission. However, we agree with your proposal to submit a stability update within 60 days from the BLA submission.*

In addition, during the review of the BLA, the Agency may request a "simple stability update" which is defined as stability data and analyses performed under the same conditions and for the same drug product batches in the same container closure system(s) as described in the stability protocol provided in the original submission. This update will use the same tabular presentation as in the original submission as well as the same mathematical or statistical analysis methods (if any) and will not contain any matrix or bracketing approaches which deviate from the stability protocol in the original BLA. Simple stability updates submitted up to month 7 for a standard submission and month 4 for a priority submission will be reviewed and considered in shelf life determinations.

b) *No, the Agency cannot agree at this time with the proposed (b) (4) retest date for the eptinezumab BDS and 24-month expiry for the eptinezumab DP. Generally, DS and DP expiry is established using real time data from lots produced using the commercial manufacturing process and stored in the container closure intended for the commercial product and/or lots representative of the commercial manufacturing process and container closures. Based on the information you have provided, there will be 18 months of stability data for the DS and DP lots manufactured at (b) (4) and (b) (4) respectively, at the time of BLA filing. Due to the change in the scale, manufacturing site, and container closures, the DS and DP lots manufactured at (b) (4) might not be representative of the commercial process at (b) (4) and (b) (4). Refer also to answer to Question 3a.*

Question 4: Can the FDA provide guidance on the impact of the Pre-Approval Inspection for (b) (4) if there is no set schedule for a manufacturing campaign of the drug product after submission of the BLA? How can Alder assist the FDA in this regard?

FDA Response to Question 4:

The need for a pre-licensing inspection of the (b) (4) DP manufacturing facility will be made at the time of BLA submission. If it is determined that an inspection is needed, it would be permissible to demonstrate (b) (4)

The manufacturing process should be similar to that for eptinezumab injection.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our August 10, 2018 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 VI. 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 the Program is available at <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>.

SUBMISSION FORMAT REQUIREMENTS

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

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>.

SECURE EMAIL COMMUNICATIONS

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LESLIE A RIVERA ROSADO
10/15/2018



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114,647

MEETING MINUTES

Alder Biopharmaceuticals
Attention: John K. Spoden
11804 North Creek Parkway South
Bothell, WA 98011

Dear Mr. Spoden:

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

We also refer to the meeting between representatives of your firm and the FDA on September 5, 2018. The purpose of the meeting was to discuss the format and content of your planned BLA for the preventive treatment of migraine in adults.

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 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 and Time: September 5, 2018, 2:00-3:00pm EDT
Meeting Location: FDA White Oak Building 22/ 1315
Application Number: 114,647
Product Name: Eptinezumab (ALD403)
Indication: Migraine
Sponsor/Applicant Name: Alder Biopharmaceuticals
Meeting Chair: Billy Dunn, MD, Director
Meeting Recorder: Lana Chen, RPh, Project Manager

FDA ATTENDEES

Division of Neurology Products

Billy Dunn, MD, Director
Eric Bastings, MD, Deputy Director
Heather Fitter, MD, Clinical Team Leader
Sally Yasuda, MS, PharmD, Clinical Safety Team Leader
Lourdes Villalba, MD, Clinical Reviewer, Safety
Laura Jawidzik, MD, Clinical Reviewer
Lois Freed, PhD, Supervisory Pharmacologist
Edmund Nesti, PhD, Pharmacology Reviewer
Sharon Yan, PhD, Statistical Reviewer
Kun Jin, PhD, Statistical Team Leader
Gopichand Gottipati, PhD, Clinical Pharmacology Reviewer
Sreedharan Sabarinath, PhD, Clinical Pharmacology Team Leader
Susan Pretko, PharmD, MPH, Clinical Outcome Assessments Staff Reviewer
Sarrit Kovacs, PhD, Clinical Outcome Assessments Staff Team Leader
Lana Chen, RPh, Project Manager

SPONSOR ATTENDEES

Alder BioPharmaceuticals

Brent Allan, DO, FAAFP, Vice President, Drug Safety and Pharmacovigilance
Brian Baker, DABT, Senior Director, Toxicology & Clinical Pharmacology
Suman Battacharya, PhD, Vice President, Biometrics
David Biondi, DO, FAAN, Vice President, Clinical Development
Roger Cady, MD, FAHS Vice President, Neurology

Eric Carter, PhD, MD, Chief Medical Officer
Susan Pederson, Senior Director, Bioanalytical
Barbara Schaeffler, MBA, Vice President, Clinical Operations
John Spoden, Director, Regulatory Affairs
Yufan Zhao, PhD, Director of Biostatistics

Consultant to Alder

(b) (4)

Advisor to Alder

(b) (4)

DISCUSSION

Clinical Questions

Question 1: Adequacy of the Clinical Data Package

Does the Agency agree that the clinical package for eptinezumab, including the efficacy and safety data from the two Phase 3 studies in episodic and chronic migraine, PROMISE 1 and PROMISE 2 (ALD403-CLIN-006, and ALD403-CLIN-011, respectively), and an ongoing long-term safety study (ALD403-CLIN-013) along with relevant safety and efficacy data from earlier phase clinical studies, provides a sufficient basis for filing of a BLA for eptinezumab as a preventive treatment of migraine in adults?

FDA Response: On face, the studies appear to have the potential to provide substantial evidence of effectiveness of eptinezumab. However, we are uncertain about the amount of safety data that you will have at the time of your submission. At the time of the initial submission, we expect that you will have at least 300 patients exposed for at least 6 months, and at least 100 patients exposed for one year, with at least 50% exposed to the highest dose proposed for marketing. When you submit your BLA, please populate the tables below with the numbers exposed at the time of submission and provide an updated version of these tables at the time of 120-day safety update. Please also note fileability of an application is a review issue.

Table A: Duration of Exposure

Dosage	N=Number of patients exposed to Eptinezumab in migraine studies (n= exposed who completed 5 half-lives of follow-up)				
	>= 1 dose	>=2 quarterly doses	>=3 quarterly doses	>=4 quarterly doses	>=5 quarterly doses
Any dosage	N= (n=)	N= (n=)	N= (n=)	N= (n=)	N= (n=)
100 mg quarterly	N= (n=)	N= (n=)	N= (n=)	N= (n=)	N= (n=)
300 mg quarterly	N= (n=)	N= (n=)	N= (n=)	N= (n=)	N= (n=)

Table B: Safety Population, Size, and Denominators

Safety Database for the Study Drug ¹ Individuals exposed to any treatment in this development program for the indication under review N= (N is the sum of all available numbers from the columns below)		
Clinical Trial Groups	New Drug (n=)	Placebo (n=)
Healthy volunteers		
Controlled trials conducted for this indication ²		
All other trials conducted for this indication ³		
Controlled trials conducted for other indications ⁴		

¹ Study drug means the drug being considered for approval.

² to be used in product's labeling

³ If placebo arm patients switch to study drug in open label extension, then the sample n should count those patients only once; do not count twice patients who go into extension from randomized study drug arm

⁴ Include n in this row only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review.

Meeting Discussion: There was no meeting discussion.

Question 2: Efficacy Endpoints in the Pivotal Studies

With regard to the endpoints measured in the PROMISE 1 and PROMISE 2 studies:

2a. Does the Agency agree that change from baseline in monthly migraine days (ie, the primary endpoint), and the 75% migraine responder rate [REDACTED] Weeks 1-12 and 50% migraine responder rate Weeks 1-12 (ie, key secondary endpoints) constitute meaningful clinical benefit for patients with migraine and are relevant data to inform clinical decisions of healthcare professionals (HCPs)?

FDA Response: On face, the endpoints you describe above, change from baseline in monthly migraine days, the percentage of patients with a 75% reduction in monthly migraine days over [REDACTED] weeks 1-12, and the percentage of patients with a 50% reduction in monthly migraine days over weeks 1-12 are endpoints that may be considered for labeling if they were pre-specified in the statistical analysis plan and there was a plan in place to control for type 1 error. Please also note that the distribution of change from baseline in monthly migraine days should be displayed in a graph for each pivotal efficacy study in section 14 of labeling.

Meeting Discussion: There was no meeting discussion.

2b. Does the Agency agree that data from the PROMISE 2 study, demonstrating statistically significant improvements in the following endpoints, constitute meaningful clinical benefit for patients with chronic migraine and are relevant data to inform clinical decisions of HCPs?

[REDACTED] (b) (4)

FDA Response: No.

[REDACTED] (b) (4)
The time course of the change from baseline in monthly migraine days should be displayed as a graph in section 14 of labeling.

[REDACTED] (b) (4)

Question 3: Proposed Indication

Based on the totality of data from the Phase 3 studies, PROMISE 1 and PROMISE 2, the Sponsor is proposing an indication of “for the preventive treatment of migraine in adults.” Does the Agency agree with this proposal?

FDA Response: On face, this appears acceptable.

Meeting Discussion: There was no meeting discussion.

Question 4: Proposed Dosing Regimen

The Sponsor is proposing the clinical efficacy and safety data from the Phase 3 PROMISE 1 and PROMISE 2 studies demonstrate adequate evidence to support the 300 mg dose administered by IV infusion every 12 weeks (b) (4)

(b) (4) Does the Agency agree?

FDA Response: The exact dose(s) marketed will be a matter of review, based on the totality of evidence presented in the BLA. (b) (4)

(b) (4) Provide a clear analysis of dose-exposure-response in your proposed BLA submission.

Meeting Discussion: There was no meeting discussion.

Question 5: Adequacy of the Safety Data Package

5a. The Sponsor is proposing the totality of safety data will provide adequate evidence to characterize the safety profile of eptinezumab when used for the preventive treatment of migraine in adults. Does the Agency agree?

FDA Response: This is a matter of review. Please see the response to Question 1.

Meeting Discussion: There was no meeting discussion.

5b. Based on evaluation of treatment-emergent adverse events (TEAEs) throughout the clinical development program and preliminary evaluations of the integrated safety data from the PROMISE 1 and PROMISE 2 studies, the Sponsor is proposing that information in the approved prescribing information will be sufficient to convey the benefits and risks of eptinezumab to physicians and other healthcare professionals and additional Risk Evaluation and Mitigation Strategies (REMS) are not necessary. Does the Agency agree?

FDA Response: At this time, we have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

Meeting Discussion: There was no meeting discussion.

5c. Based on the known mechanism of action of eptinezumab and its lack of safety and behavioral signals for dependence or addiction in nonclinical and clinical studies, the Sponsor is proposing that eptinezumab has no identified abuse potential and therefore a full assessment for proposed scheduling is not required in the BLA. Does the Agency agree?

FDA Response: Yes, we agree. No additional abuse-related studies are needed at this time, and there is no evidence of an abuse potential signal thus far that would warrant inclusion of an extensive abuse potential assessment or proposal for drug scheduling in your BLA submission. We recommend that you describe in your BLA submission, i.e., within the Summary of Clinical Safety, Module 2, the data considered to support your conclusion that eptinezumab does not appear to show any signal of abuse potential based on its mechanism and on the submitted nonclinical and clinical studies.

Meeting Discussion: There was no meeting discussion.

5d. Does the Agency agree that the potential for suicidal ideation and behavior was sufficiently investigated and characterized in the eptinezumab program?

FDA Response: On face, the use of the Columbia-Suicide Severity Rating Scale (C-SSRS) in your clinical trials appears appropriate. Whether suicidal ideation and behavior was sufficiently investigated and characterized is a matter of review.

Meeting Discussion: There was no meeting discussion.

5e. The Sponsor is proposing the 120-day safety update will integrate data from the open-label, long-term safety study ALD403-CLIN-013, which is the only study that will be ongoing at the time of the application filing. Does the Agency agree?

FDA Response: We note that you plan to submit data from 112 additional patients from Study 013 at the time of the 120-day safety update. The 120-day safety update should include an updated SCS, along with the pertinent updated ISS datasets to support the analyses in the updated overall population.

Meeting Discussion: There was no meeting discussion.

Clinical Pharmacology

Question 6: Adequacy of the Clinical Pharmacology Data Package

Does the Agency agree that the proposed clinical pharmacology data package for eptinezumab is adequate to support the submission and filing of a BLA?

Does the Agency agree with the population pharmacokinetic analysis plans for eptinezumab?

FDA Response: Fileability of an application is a review issue. On face, the clinical pharmacology package and the population pharmacokinetic analysis plan seem adequate. As

stated in our response to Question 4, we request that you submit an exposure-response analyses for key efficacy endpoints, as well as safety endpoints.

Meeting Discussion:

FDA clarified that the sponsor should submit their exposure response analysis for efficacy, and not just for safety. In addition, the FDA requested that the sponsor justify the dose selection based on the exposure-response analysis.

Efficacy Data Presentation Questions

Question 7: Presentation of Efficacy Data in Module 2

The proposed analyses for the presentation of efficacy are presented in **Error! Reference source not found.** Does the Agency agree with this approach?

FDA Response: For Study 006, please provide the analyses for up to 24 weeks of treatment, using the same methodology as for the primary and key secondary endpoints.

For the primary endpoint in Studies 006 and 011, please provide a graphical representation of the distribution of responses. Please refer to Figure 2, 4, and 6 in the FDA approved label for AIMOVIG for examples of the preferred way to display this information.

The Sponsor proposes to include a comprehensive Summary of Clinical Efficacy (SCE) in Module 2.7.3 and place all relevant data in Module 5.3.5.3, with hyperlinks from Module 2.7.3 to the data. Does the Agency agree with this approach?

FDA Response: On face, this approach appears acceptable. For further details, please refer to “Final Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (PDF - 98KB)”, located at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>

Meeting Discussion: There was no meeting discussion.

Question 8: Submission of Subject Level Data

The Sponsor intends to submit the case report forms (CRFs) for patients who meet the criteria for a narrative from only pivotal Phase 3 PROMISE 1 and PROMISE 2 studies. The Patients Diary reports (PDRs) for the e-diary daily migraine reporting data will also be provided for randomly selected 5% of subjects from the pivotal Phase 3 PROMISE 1 and PROMISE 2 studies. Does the Agency agree with this proposal?

FDA Response: Consistent with the OSI pre-BLA request, site-specific BIMO data sets should include all subjects' raw e-diary daily migraine data used to generate the derived/calculated endpoint.

You should submit the eCRFs for any patient who meets the criteria for a narrative, not just those patients in the pivotal trials.

Meeting Discussion: The sponsor agreed to submit the requested eCRFs.

Question 9: Submission of Supporting Documentation

Does the Agency agree with the proposed format of the Bioresearch Monitoring (BIMO) clinical investigators list and data sets as described in the Office of Scientific Investigations (OSI) Pre-NDA requests (Addendum 1) in the BLA submission?

FDA Response: The proposed BIMO datasets to be submitted with the BLA appear acceptable. Listing 9 should include all subjects' raw e-diary daily migraine data used to generate the derived/calculated endpoint.

Additionally, for protocols 006 and 011, please describe how the self-reported headache data was handled from the time of entry into the electronic diary device by the subjects until the data reached the study database. Include the roles of the clinical investigator, CRO/vendor (if any), and the sponsor in the process. Please describe the process for making any changes to these data after entry as well as whether audit trails and data clarification forms were in use. In addition, please indicate if and how the self-reported headache data from the electronic diaries were made available to the clinical investigator at their sites throughout the study and after study completion.

Please indicate whether certified CDs of raw e-diary data, with audit trails, are available at each clinical site.

Meeting Discussion: There was no meeting discussion.

Question 10: Submission of SAS® Datasets

The studies performed under the eptinezumab clinical development program and studies for which analysis data and relevant file submissions are planned are summarized in **Error!**

Reference source not found. The Sponsor proposes to submit Study Data Tabulation Model (SDTM) and derived Analysis Data Model (ADaM) SAS® datasets for:

All data sets for safety, efficacy, and pharmacokinetics, with supporting documentation describing the dataset structures along with the annotated CRFs from the studies: ALD403-CLIN-002, ALD403-CLIN-005, ALD403-CLIN-006, ALD403-CLIN-010, ALD403-CLIN-011, ALD403-CLIN-012, ALD403-CLIN-013, ALD403-CLIN-014. A Reviewer's Guide with table of contents will also be provided for each of these studies.

For the Phase1 study ALD403-CLIN-001, the dataset will be provided in legacy format, as agreed in the EOP2 Meeting discussion (13 October 2016).

(b) (4)

All ADaM datasets to support the integrated safety analyses with documentation describing the dataset structures and variables from the SCS. A Reviewer's Guide with table of contents will also be provided.

All datasets as SDTM and ADaM for the SCE and PPK will be provided with supporting documentation along with the Reviewer's Guide describing the dataset structures and variables. A table of contents will also be provided for these studies.

Error! Reference source not found. lists the studies that will be included for the SCE, SCS, the Integrated Summary of Immunogenicity (ISI) and PPK analysis. For SCE, SCS and PPK analysis, eCRT package which consist of define.xml, pooled ADaM datasets, and Reviewer's guide will be submitted.

Table 1: Summary of Efficacy, Safety, Immunogenicity, and Population Pharmacokinetic Analyses

Study	SCS	SCE	ISI	PPK
ALD403-CLIN-001	No	No	No	Yes
ALD403-CLIN-002	Yes	Yes	Yes	Yes
ALD403-CLIN-005	Yes	Yes	Yes	Yes
ALD403-CLIN-006	Yes	Yes	Yes	Yes
ALD403-CLIN-010	No	No	No	Yes
ALD403-CLIN-011	Yes	Yes	Yes	Yes
ALD403-CLIN-012	No	No	No	Yes
ALD403-CLIN-013	Yes	No	Yes	Yes
ALD403-CLIN-014	No	No	No	No

ISI = Integrated Summary of Immunogenicity; PPK = population pharmacokinetics; SCE = Summary of Clinical Efficacy; SCS = Summary of Clinical Safety

The sponsor acknowledges comments received from the Agency on 30 June 2017 and 27 April 2018 and plans to submit the SAS[®] programs for the primary and the key secondary endpoints from the PROMISE 1 and PROMISE 2 studies that will be included in the proposed US prescribing information. Furthermore, the sponsor will provide the SAS[®] program for the proposed data table in the adverse reaction section of the US prescribing information. Other SAS[®] programs will be available as needed.

FDA Response: For each efficacy endpoint, including the primary and all secondary endpoints in the pivotal studies, please provide the dataset name, key variable names and label/descriptions of the variable, and SAS code for the primary and sensitivity analyses in the review guide. The efficacy dataset for analyses of the primary and key secondary endpoints should include corresponding number of days of diary entry (weekly, monthly, or for the period). The raw weekly diary data should also be provided for the pivotal studies.

Proposed SAS® datasets for clinical safety appear acceptable. Please note comments regarding safety datasets for the 120-day SUR.

Meeting Discussion: There was no meeting discussion.

Safety Data Presentation Questions

Question 11: Presentation of Safety Data in Module 2

The proposed analyses for the presentation of safety are presented in **Error! Reference source not found.** Does the Agency agree with this approach?

FDA Response: We recommend that you submit your ISS data analysis plan prior to BLA submission to allow for FDA comments. Please also specify the AEs of special interest. Refer to the attachment “General Clinical Safety Requests” for details on the format and content of the submission related to Clinical Safety. Please also see the response to Question 12.

The Sponsor proposes to include a comprehensive SCS in Module 2.7.4 and place all relevant data in Module 5.3.5.3, with hyperlinks from Module 2.7.4 to the data. Does the Agency agree with this approach?

FDA Response: Yes, this approach appears acceptable. See the response to Question 7b.

Meeting Discussion: There was no meeting discussion.

Question 12: Subject Narratives

The Sponsor intends to include narratives for deaths, other SAEs, pregnancies, discontinuations for any reason, and AEs of special interest (AESI) for subjects receiving eptinezumab. Does the Agency agree?

FDA Response: Please define the AEs of special interest for eptinezumab. Include in your list of AEs of special interest for your product: cardiovascular, hepatic, gastrointestinal, and infusion

related. You should provide narratives for these AESIs as well as for any additional AESIs that you have defined.

Please include the following information regarding cardiovascular safety in your BLA submission:

- A table of baseline CV risk factors

Example

	% Eptinezumab	% Placebo
HTN related	x	x
Diabetes mellitus	x	x
Dyslipidemia	x	x
BMI >30 kg/m ²	x	x
Smoking	x	x
≥ 1 CV risk factor	x	x
Prior history ischemic CV event or procedure	x	x

For HTN related, diabetes mellitus and dyslipidemia, include all relevant PTs (e.g., for hypertension, include blood pressure increased, systolic BP increased, diastolic BP increased, hypertensive crisis, etc.). For prior ischemic CV events, we suggest MI, stroke, angina, TIA, peripheral vascular disease/ Claudication, coronary artery bypass graft. Please provide the % of male and % of patients age ≥40 years as a footnote to the table.

We request that you include in your application an assessment of whether the population in your safety database adequately represents the US migraine population in terms of CV risk.

- A summary table of baseline CV medication.

Conduct analyses of changes (new drug or change in dosing) in concomitant CV meds.

Please see the attachment “General Clinical Safety Requests” for details regarding the content of the proposed narratives and the preferred method for aggregating them.

Meeting Discussion: There was no meeting discussion.

Question 13: Integrated Summary of Immunogenicity

As outlined in **Error! Reference source not found.**, does the Agency agree with the proposed analyses and presentation of data outlined for the Integrated Summary of Immunogenicity (ISI)?

FDA Response:

In addition to the data and information you plan to include in the ISI, you should provide validation summaries for the various immunogenicity assay methods that were developed throughout the program. In addition, this section should provide links to method development and validation reports for all the immunogenicity assays used in the various clinical studies supporting the application, particularly those used to test immunogenicity samples from the pivotal clinical studies.

The proposed plan to assess the effect on immunogenicity on PK/PD of eptinezumab seems acceptable. Please clarify whether there are any data on immunogenicity on re-exposure. If any patients interrupted and reinitiated treatment after missing 1 or 2 doses, please present this information in the proposed BLA.

Meeting Discussion: There was no meeting discussion.

Regulatory Questions

Question 14: Need for Advisory Committee Advice

Does the Agency agree with the assessment that the advice of the Peripheral and Central Nervous System Drugs Advisory Committee will not be needed for this application?

FDA Response: The decision regarding the need for an Advisory Committee meeting will be made after the application is submitted and considered for filing.

Meeting Discussion: There was no meeting discussion.

Question 15: Evaluation of the Pediatric Population

Does the Agency agree with the Sponsor's proposal for studying eptinezumab in the pediatric population?

FDA Response: An agreed iPSP is required at the time of filing. We acknowledge receipt of your revised iPSP. It is currently under review, and we plan to provide feedback in September 2018.

Meeting Discussion: There was no meeting discussion.

Question 16:

(b) (4)

(b) (4)

FDA Response:

(b) (4)

(b) (4)

Meeting Discussion: There was no meeting discussion.

Question 17: Financial Disclosure

The Sponsor proposes to provide in the BLA financial disclosure certification only for the pivotal Phase 3 PROMISE 1 and PROMISE 2 studies as these will serve as the primary basis to support the effectiveness of eptinezumab for the preventive treatment of migraine. Does the Agency agree?

FDA Response: You are required to include financial disclosure information for any clinical study that you or FDA relies on to establish that your product is effective, or any study in which a single investigator makes a significant contribution to the demonstration of safety.

Meeting Discussion: There was no meeting discussion.

Question 18: Applicant Orientation Presentation

Does the Agency agree that the Sponsor can plan to present the key aspects of the eptinezumab BLA during an Applicant Orientation Presentation after submission?

FDA Response: Yes, we agree.

Meeting Discussion: There was no meeting discussion.

ADDITIONAL COMMENTS

We note section 1.3 Dosage Form and Route of Administration of your meeting briefing document states that eptinezumab injection will be presented as 100 mg/mL (1 mL per vial) in a single-use preservative-free solution and administered at a dose of 300 mg every 12 weeks by intravenous infusion. We are concerned that the requirement of three 100 mg/mL vials (1 mL per vial) to achieve one dose may increase the risk of medication error of under dose or contribute to a medication error of wrong technique. It is unclear whether your development plan considered the risk of medication error and under-dosing due to the multiple vials of the proposed 100 mg/mL (1 mL per vial) to achieve one full dose. Provide your plans to mitigate this risk of medication error of under-dosing and wrong technique of administration.

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.
- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

In addition, we note that a chemistry pre-submission meeting is scheduled for October 24, 2018. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

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 Pedsdrugs@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.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your

pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information 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 items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications 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 ORA investigators who conduct those inspections. 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.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for

CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>.

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIC P BASTINGS
10/04/2018



IND 114,647

MEETING MINUTES

Alder Biopharmaceuticals
Attention: Jennifer Wiley
11804 North Creek Parkway South
Bothell, WA 98011

Dear Ms. Wiley:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ALD403.

We also refer to the meeting between representatives of your firm and the FDA on October 13, 2016. The purpose of the meeting was to discuss your Phase 3 development plan.

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes



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

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: October 13, 2016, 11:00 am – 12:00pm EDT
Meeting Location: FDA White Oak

Application Number: IND 114,647
Product Name: ALD403
Indication: Migraine (b) (4)
Sponsor/Applicant Name: Alder Biopharmaceuticals

Meeting Chair: Eric Bastings, M.D.
Meeting Recorder: Lana Chen, R.Ph.

FDA ATTENDEES

Robert Temple, MD, Acting Deputy Director, ODE1
Naomi Lowy, MD, Associate Director for Regulatory Science
Eric Bastings, MD, Deputy Director, Division of Neurology Products (DNP)
Heather Fitter, MD, Clinical Team Leader, DNP
Suhail Kasim, MD, Clinical Reviewer, DNP
Kun Jin, PhD, Statistical Team Leader, Office of Biometrics
Sharon Yan, PhD, Statistical Reviewer, Office of Biometrics
Sreedharan Sabarinath PhD, Team Leader, Division of Clinical Pharmacology I
Xinning Yang, PhD, Reviewer, Division of Clinical Pharmacology I
Michelle Dougherty PhD, Review Chief, Office of Biotechnology Products
Andrea Franco, PhD, Product Quality Reviewer, Office of Biotechnology Products
Lana Chen, RPh, Project Manager, DNP
Susan Tavakoi, Pharmacy Student Intern, DNP

SPONSOR ATTENDEES

Alder Biopharmaceuticals
Brian Baker, DABT, Senior Director, Toxicology
Nancy Boman, MD, PhD, Senior Vice President, Regulatory Affairs and Pharmacovigilance
Roger Cady, MD, Vice President, Neurology
(b) (4)

Susan Pederson, Director, Bioanalytical
Barbara Schaeffler, MBA, Vice President, Clinical Operations
Jeffrey Smith, MD, FRCP, Senior Vice President, Translational Medicine
Tim Whitaker, MD, Chief Medical Officer
Jennifer Wiley, MS, Director, Regulatory Affairs

DISCUSSION

1. Does FDA agree with the dose levels and 12-week dosing interval selected for study in the pivotal trials?
 - ALD403-CLIN-006 (FEM): 30, 100 and 300 mg every 12 weeks
 - ALD403-CLIN-011 (CM): 300 mg every 12 weeks

FDA Preliminary Response:

The Phase 2 CM data you provided suggest possible efficacy over the dose range of 30 to 300 mg; therefore, you may consider also exploring a dose lower than 300 mg in the Phase 3 CM study.

Without sufficient information about the consistency of the treatment response over the 12-week period, it is not possible to comment about your proposed dosing interval. If efficacy is maintained throughout the 12 week period, then the proposed dosing interval may be acceptable. Alternatively, if the treatment response decreases over time during the 12-week dosing period, then a more frequent dosing schedule may be more appropriate.

When you submit the study reports for your pivotal trials, please provide a cumulative distribution function (CDF) plot analysis of the percent change from baseline in the frequency of migraine headache for each treatment group using the following categories: $\geq 0\%$ reduction, $\geq 10\%$ reduction, $\geq 20\%$ reduction, $\geq 30\%$ reduction, $\geq 40\%$ reduction, $\geq 50\%$ reduction, $\geq 60\%$ reduction, $\geq 70\%$ reduction, $\geq 80\%$ reduction (of migraine headache days).

Meeting Discussion: There was no meeting discussion.

2. Alder has proposed a 75% responder rate for Weeks 1-12 as the primary endpoint to FDA and received written feedback on 10APR2014 that the endpoint is acceptable. Alder is proposing to collect and analyze the following key secondary endpoints for the pivotal trials (b) (4)

- Change in migraine days from baseline for Weeks 1-12
- 75% responder rate for Weeks 1-4

Does FDA agree that the secondary endpoint data, if positive and with the planned statistical control, are adequate to demonstrate efficacy [REDACTED] (b) (4)

FDA Preliminary Response:

We agree that the change in migraine days from baseline for Weeks 1-12 is appropriate, and should be described in labeling; in fact, we would prefer it as primary endpoint, although a responder definition is also acceptable.

The 75% responder rate for Weeks 1-4 may be acceptable as secondary endpoint. You must have a plan in place to control for multiple comparisons. We recommend that you realign the sequential testing procedure, taking into account both dose groups and the key secondary endpoints, to control the family-wise type-I error.

You should also include a secondary endpoint that compares the use of acute (rescue) migraine medications between treatment groups.

Meeting Discussion:

The sponsor agreed with FDA's recommendation to use the change in migraine days from baseline for weeks 1-12 as the primary endpoint in their proposed trial and the 75% responder rate as a secondary endpoint.

The Division noted that the planned method for the calculation of the 75% responder rate over 12 weeks was not clear; specifically, the Division requested clarification on how results from 4-week intervals would be combined to produce the 12-week responder rate. The Sponsor stated that they will provide clarification in the revised SAP.

The analysis method of the 75% responder rate was discussed at the meeting. The Division suggested that the Sponsor consider using an analysis on average rate over 12 weeks as the primary analysis. The Division suggested that the Sponsor also perform a sensitivity analysis per 4 week/monthly interval to determine whether the treatment response decreases over time during the 12 week dosing period, in which case a more frequent dosing schedule might be more appropriate.

The Division suggested that the Sponsor present responder rate information using histograms to show outcomes or changes of various sizes for treatment and control groups (e.g., the number or percentage of subjects with worsening symptoms or change in effectiveness measure by 0 to 10 percent, more than 10 to 20 percent, more than 20 to 30 percent, etc., improvement in symptoms or change in effectiveness measure) or by using cumulative distribution curves, showing the effect in all subjects in treatment and control groups. Information from this display, pending review, may be included in the label. Please refer to the following guidance:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079803.pdf>

The Division pointed out that the current proposed multiplicity adjustment would not control for the overall type-1 error in testing the multiple doses and secondary endpoints.

The Sponsor stated that in order to minimize missing data at baseline and to ensure that randomized subjects will likely adhere to eDiary entries, only those patients reporting eDiary entry data for 25 of the 28 days baseline period will be eligible for enrollment in the study. In addition, the Sponsor discussed the high placebo response seen in migraine trials and stated that in general this placebo response extends over several months. A general discussion followed about considering design elements for trials to identify and eliminate placebo responders from the trial.

3. The clinical development program has been designed to achieve the following indication:

[REDACTED] (b) (4)

The target indication will be supported by data from two pivotal trials; one in each of two defined patient populations:

- a. Frequent episodic migraine: During the 28 day screening period, must have ≤ 14 headache days of which at least 4 have to be migraine days (migraine days count as headache days) as documented in the eDiary
- b. Chronic migraine: During the 28 day screening period, must have between 15 and 26 headache days, of which ≥ 8 days were assessed as migraine days (migraine days count as headache days) as documented in the eDiary

Are the two patient populations adequately defined, including definitions of headache days, to support the intended therapeutic indication for ALD403?

FDA Preliminary Response:

On face, your overall plan appears adequate [REDACTED] (b) (4)

[REDACTED] (b) (4) assuming Study ALD403-CLIN-006 and Study ALD403-CLIN-011 have positive results. Efficacy in patients with

[REDACTED] (b) (4)

[REDACTED] . The study population, however, would be described in Section 14 of the label.

Meeting Discussion: There was no meeting discussion.

4. Does FDA agree that the planned trials are adequately designed to characterize the safety profile of ALD403 including the approach for collecting long term data safety (greater than 6 months)?

FDA Preliminary Response:

On face, your proposal appears acceptable. A final determination will be a matter of review, based on the safety signals identified during development.

In addition, there must be sufficient experience with the highest dose/frequency of dosing proposed for labeling. For example, if you propose dosing every 3 months, there should be information on at least 100 patients who have received 2 injections of the highest dose proposed for marketing 10-14 weeks apart, and at least 60 patients treated at the highest dose proposed for marketing with 4 injections 10-14 weeks apart.

Please also refer to our response to Question 6 regarding the final to be marketed product and the acceptability of your planned safety database. If the material used in the pivotal trials is not comparable to the commercial product, safety data from the planned pivotal trials may not be adequate to support marketing.

Meeting Discussion: There was no meeting discussion.

5. Based on FDA's previous agreement that the 75% responder rate for Weeks 1-12 is an acceptable pivotal trial primary endpoint:
 - a. Does FDA agree with the proposed overall statistical testing strategy on the primary and key secondary endpoints (change in migraine days from baseline; 75% responder (Weeks 1-4) in the two pivotal trials)?

FDA Preliminary Response: Please see the response to Question 2.

Meeting Discussion: There was no meeting discussion.

6. Alder plans to conduct two bioequivalence studies to bridge from the non-commercial CMO material used in pivotal trials to use of the commercial CMO material. Does FDA agree with this approach including trial designs and analysis methods?

FDA Preliminary Response:

You state that pivotal clinical studies will use Drug Substance and Drug Product manufactured at (b) (4); however, you plan to apply for licensure of (b) (4) and (b) (4) for commercial drug substance manufacturing and (b) (4) for commercial drug product manufacturing. We generally recommend that major manufacturing changes, such as new manufacturing site and scale up, should be implemented prior to your pivotal clinical studies. We strongly recommend that you request a CMC meeting to discuss your plan to assess comparability for these major manufacturing changes. For more information on comparability studies, refer to ICH guidance Q5E: comparability of biotechnological products subject to changes in their manufacturing process. Please be aware that if

analytical comparability cannot be demonstrated, additional nonclinical and/or clinical studies may be needed.

On face, the design seems acceptable for PK comparison. A final decision will be made when the protocol is received. As to the immunogenicity assessment, the sample size may not be large enough to generate adequate number of subjects with ADA to ensure a meaningful comparison. Whether the plan for immunogenicity comparison is acceptable will be made when more information is available (e.g., immunogenicity from ongoing trials, analytical comparability between the non-commercial and commercial material).

Meeting Discussion: There was no meeting discussion.

7. Does FDA agree [REDACTED] ^{(b) (4)} proposed in the abbreviated Target Product Profile (TPP) as supported by the proposed clinical development program?

FDA Preliminary Response:

Please see responses to Questions 1, 2, and 3.

Meeting Discussion: There was no meeting discussion.

8. Alder has characterized the pharmacokinetics of ALD403 as well as characterized the exposure-response relationship for safety and efficacy to support justification of the ALD403 dosing paradigm. Does FDA agree with the additional following clinical pharmacology development proposals?

- a. Proposal that there is sufficient body of evidence that shows a lack of effect of ALD403 on the QT interval, which supports routine monitoring of ECGs in the pivotal trials, without the need for further clinical trials

FDA Preliminary Response:

On face, this is acceptable, but is subject to review of clinical trial study reports. Please provide more information on the cases with QTc prolongation, including the QT/QTc threshold used. Also provide any information on whether more cases of QTc prolongation events were observed in other clinical studies.

- b. Proposal that evaluations for potential drug-drug interactions may be completed by PPK covariate analysis

FDA Preliminary Response:

We have no objection to this proposal. We recommend that you record the timing and duration of co-medications used during the Phase 3 trials for your population PK analysis.

- c. Proposal that evaluation of ALD403 administration in hepatic and renal impairment populations do not need to be completed

FDA Preliminary Response:

We have no objection to this proposal.

Meeting Discussion: There was no meeting discussion.

- 9. Does FDA agree with Alder's plan to assess the development of human anti-product antibodies?

FDA Preliminary Response:

No, we do not agree. Your proposal (b) (4) is not acceptable. You should evaluate all anti-drug antibody (ADA) confirmed positive samples to assess whether immune responses are directed to the O-linked glycosylation present on the drug.

While your general approach to include screening, confirmatory, titer, specificity assays, as well as a neutralization assay appears to be reasonable, the information you provided in Section 3.2.1.1 on the Electrochemiluminescence (ECL) methods for detection anti-ALD403 antibodies and neutralizing antibodies is not sufficient to determine the adequacy of the method validation.

Refer to the FDA Draft Guidance on Assay Development and Validation for Immunogenicity Testing of Therapeutic Proteins for additional information on method validation.

Regarding your proposed sampling, we generally expect that the testing schedule for an immunogenicity assessment to include the following:

- (1) Testing samples at 7-14 days after the first administration of the drug to detect the IgM type antidrug antibodies
- (2) Testing samples at 4-6 weeks after the first administration of the drug to detect IgG response
- (3) Testing samples at a time when there will be minimal interference from the drug present in the serum
- (4) Testing samples at approximately 30 days or after an appropriate washout period after the last dose
- (5) Patients testing positive for ADA should be monitored until levels return to baseline.

Meeting Discussion:

The Sponsor agreed to follow the Division's recommendations described above.

10. Alder believes that toxicokinetic results obtained from the high-dose group, 150 mg/kg/dose, in the 6-month monkey study are acceptable and sufficient to support a greater than 10-fold exposure multiple over the maximum estimated clinical exposure, 300 mg ALD403, administered by infusion every 12-weeks; however, Alder failed to meet acceptance criteria in the incurred sample reanalysis supporting the study. Does FDA agree with Alder's position that the toxicokinetic results support a 10-fold exposure multiple over the maximum estimated clinical exposure?

FDA Preliminary Response:

Based on the information provided, it appears that plasma exposures in the 6-month monkey study are adequate to justify the highest dose tested; however, a final determination will be made once the data from the reanalysis have been submitted and reviewed.

Meeting Discussion: There was no meeting discussion.

11. Does FDA agree that nonclinical data package (as outlined in **Error! Reference source not found.** and **Error! Reference source not found.**) is adequate to support an approvable BLA for the projected ALD403 indication?

FDA Preliminary Response:

The adequacy of the nonclinical studies to support BLA submission will be a matter of review. If changes in the manufacturing process result in a clinical formulation that is not comparable to the formulation used in the pivotal nonclinical studies, the nonclinical studies may need to be repeated.

Also, see responses to Questions 6 and 10.

Meeting Discussion: There was no meeting discussion.

12. All single-dose and repeat-dose nonclinical toxicology studies supporting ALD403 were initiated prior to December 17, 2016. As such, Alder does not plan to provide nonclinical study data in SEND format for the BLA. All nonclinical data for BLA submission will be in the eCTD standard format. Does FDA agree with this proposal?

FDA Preliminary Response:

Submission of the nonclinical data in eCTD standard format is acceptable.

Meeting Discussion: There was no meeting discussion.

13. Alder will provide SDTM files for all trials that enrolled migraine subjects in the BLA submission. Data for the phase 1 healthy volunteers trials will be submitted but the data files for these trials will not follow SDTM format. Does FDA agree with this proposal?

FDA Preliminary Response:

Yes, we agree.

Meeting Discussion: There was no meeting discussion.

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 (cdcr-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>.

SECURE EMAIL COMMUNICATIONS

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

ABUSE POTENTIAL ASSESSMENT

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

Office of Scientific Investigations (OSI) Requests

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

that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

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

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

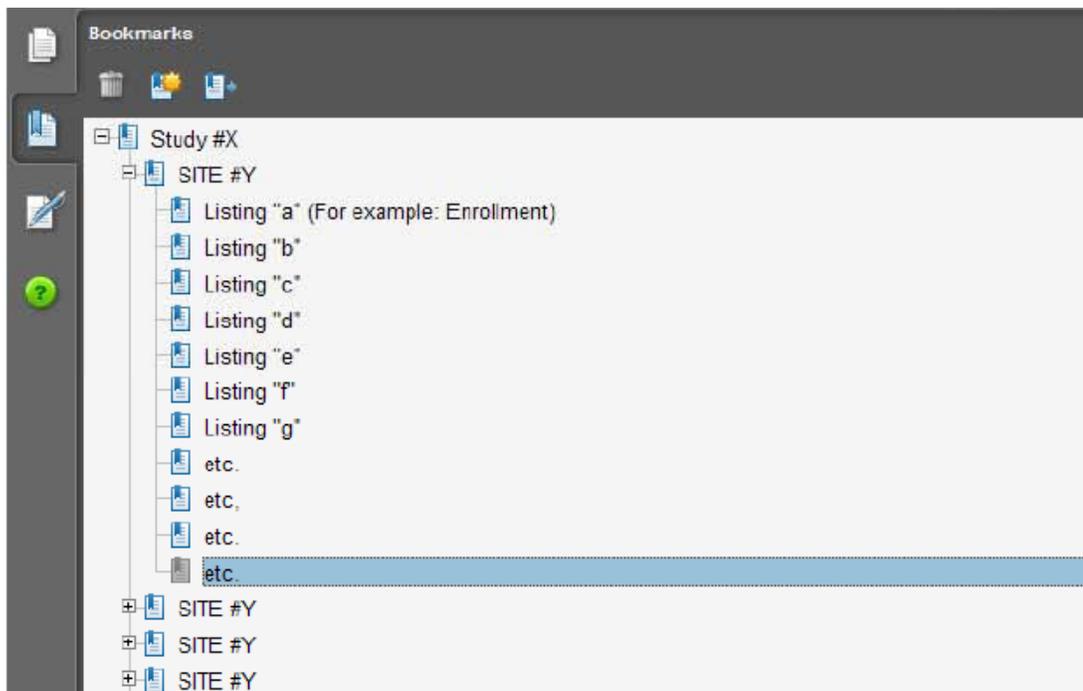
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format

- previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
- c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
 5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

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



III. Request for Site Level Dataset:

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

Attachment 1

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

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

this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item¹	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.

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

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

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

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

APPEARS THIS WAY ON ORIGINAL

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
11/02/2016