CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761102Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 100594

MEETING MINUTES

Baxalta USA Inc.
Attention: Shrenik Desai, MS, RAC
Manager, Regulatory Affairs
650 East Kendall Street
Cambridge, MA 02142

Dear Mr. Desai:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for EZN-2285, calaspargase pegol, SC-PEG E.coli L-asparaginase, BAX2303.

We also refer to the teleconference between representatives of your firm and the FDA on July 28, 2016. The purpose of the meeting was to discuss the upcoming BLA submission of calaspargase pegol and to obtain the Agency's advice and feedback on CMC, nonclinical, clinical, regulatory, and labeling questions.

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

If you have any questions, call me, Alycia Anderson, Regulatory Project Manager at (240) 402-4270.

Sincerely,

{See appended electronic signature page}

Donna Przepiorka, MD, PhD
Acting Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
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:	July 28, 2016; 3:00 p.m. – 4:00 p.m. (ET)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1419 Silver Spring, Maryland 20903
Application Number:	IND 100594
Product Name:	EZN-2285, calaspargase pegol, SC-PEG E.coli L-asparaginase, BAX2303
Indication:	Treatment of patients with acute lymphoblastic leukemia (ALL)
Sponsor/Applicant Name:	Baxalta USA Inc.
Meeting Chair:	Donna Przepiorka, MD, PhD
Meeting Recorder:	Alycia Anderson, CCRP

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)
Gregory Reaman, MD, Associate Director, Pediatric Hematology Oncology

OHOP/Division of Hematology Products
Ann T. Farrell, MD, Director
Albert Deisseroth, MD, PhD, Clinical Team Leader
Donna Przepiorka, MD, PhD, Acting Clinical Team Leader
Ashley Ward, MD, Clinical Reviewer
Theresa Carioti, MPH, Chief, Project Management Staff
Alycia Anderson, Regulatory Project Manager

OHOP/Division of Hematology Oncology Toxicology
Christopher Sheth, PhD, Pharmacology/Toxicology Team Leader
Michael Manning, PhD, Pharmacology/Toxicology Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Vicky Hsu, PharmD, Reviewer

Office of Biostatistics/Division of Biometrics V
Yuan-Li Shen, Dr.PH, Biometrics Team Lead
Lola Luo, PhD, Biometrics Reviewer

Office of Biotechnology Products/Division of Biotechnology Review & Research III
Susan Kirshner, PhD, Review Chief
Cecilia Tami, PhD, Product Quality Team Leader
Ramesh Potla, PhD, Product Quality Reviewer

Office of Process and Facilities/Division of Microbiology Assessment
Patricia Hughes, PhD, Branch Chief (Actg)
Monica Markovski, PhD, Product Quality Microbiology Reviewer

SPONSOR ATTENDEES

Baxalta Participants

Alejandro DeWindt, MD, Global Medical Safety Director
Bita Badiei, RAC, Associate Director, Regulatory Affairs
Chris Lockey, MS, Senior Manager, Manufacturing and Analytical Product Owner
Claudia Lebedinsky, MD, Senior Medical Director, Clinical Research
Daryl DeKarske VP/TA, Head Regulatory Affairs Oncology
Helmut Glantschnig, PhD, Associate Director Pharmacology, Non-Clinical Development
Hui Zhang, MS, Manager, Biostatistics
Jennifer Sherak, MBA, Senior Director, Global Program and Commercial Lead
Mantas Malisauskas, PhD, Manager, Research and Development
Michael Hale, PhD, Global Head of Biometrics
Rekha Abichandani, MD, VP Global Clinical Development, TA Head Oncology
Shrenik Desai, MS, RAC, Manager, Regulatory Affairs

1.0 BACKGROUND

Calaspargase pegol (EZN-2285, SC-PEG E.coli L-asparaginase, BAX2303) is being developed as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL).

The purpose of the requested meeting was to discuss the upcoming BLA submission for calaspargase pegol andobtain theAgency's advice and feedback on CMC, nonclinical, clinical, regulatory, and labeling questions.

FDA sent Preliminary Comments to Baxalta US Inc. on July 26, 2016.

2. DISCUSSION

Question 1:
Does the Agency agree that a BLA consisting of these components will be filed for review?

FDA Response to Question 1:
Your BLA submission must be complete in itself and include all five modules as described for eCTD. You should not refer to the withdrawn BLA as the source of any information. Acceptance for filing of the BLA will be determined based on BLA content at the time of submission.

Discussion:
No discussion occurred.

Question 2:
Does the Agency have any comments on the proposed USPI provided in the Appendix 1?

FDA Response to Question 2:
Yes, see the attached word document for comments regarding format and regulatory content. A detailed review will be conducted when the BLA is submitted.

Discussion:
No discussion occurred.

Question 3:
Does the Agency agree with the proposed acceptance criteria provided below to be included in the new BLA?

FDA Response to Question 3:
We do not object to include the proposed acceptance criteria in the new BLA application. The adequacy of proposed release and stability specifications will be a BLA review issue. Note that the specifications for release and stability testing of calaspargase pegol should be established and justified by appropriate clinical, manufacturing, and analytical experience. For details, we refer you to ICH Q6B "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products".

Discussion:
No discussion occurred.

Question 4:

Provided that the [redacted] study is fully demonstrated, does the Agency agree with the [redacted] described above for [redacted] the drug product?

FDA Response to Question 4:

The adequacy [redacted] will be a review issue after the BLA submission. The biochemical stability data from the [redacted] study performed on calaspargase pegol drug product lot 2071 should be sufficient for BLA filing.

[redacted]

Discussion:

The Sponsor indicated that submission of [redacted] validation study results for two additional lots will be available during the BLA review cycle (one lot in 2016 and one lot in 2017). The Agency stated that under The Program, the BLA must be complete at the time of submission. [redacted]

[redacted]

Question 5:

Does the Agency agree with the proposed specifications and analytical methods provided in the briefing package at release and at the end of the shelf life of calaspargase pegol drug product?

FDA Response to Question 5:

No, we do not agree. Address the following in your BLA application:

(a) [redacted]

(b) (4)

(b) The (b) (4) are the only tests proposed to evaluate purity of calaspargase pegol drug substance and drug product. The release (and stability, as appropriate) and stability program should include orthogonal techniques to assess purity such as RP-HPLC or a charge-based chromatography method (e.g., ion exchange chromatography) or a justification for not including additional purity assays in your specifications.

(c) The release specifications for calaspargase pegol drug substance do not include an evaluation of (b) (4) to ensure control of this process-related impurity. Include a method to monitor the (b) (4) in the drug substance release specifications. The method should be validated for its intended purpose.

(d) Your proposed stability specifications for calaspargase drug product do not include an evaluation of product purity by SDS-PAGE and potency by enzyme kinetics (Km/kcat/Vmax). Update the proposed stability specifications in your BLA application to include purity by SDS-PAGE and potency by enzyme kinetics.

(e) The endotoxin specification of ≤ (b) (4) appears to be too high. Please provide adequate justification for the endotoxin specification. The specification should be calculated based on the worst case dose given to patients. Additionally, this calculation should include a two-fold safety factor to account for assay variability. Please note that (b) (4) for endotoxin, including the endotoxin acceptance criterion (b) (4) should be lowered accordingly.

Note that the adequacy and approvability of the proposed specifications will be a BLA review issue.

Discussion:
No discussion occurred.

Question 6:
Does the Agency agree that calaspargase pegol drug product stability data would support the proposed shelf life of 36 months at 2 - 8° C?

FDA Response to Question 6:
No, we do not agree. Data provided in Table 11 of your Type B meeting package show that real-time stability data are available for up to 36 months for two drug product lots (Lots 2057 and 2071), and for up to 24 months for one drug product lot (Lot 3056). In order to support the proposed expiration dating period of 36 months at 2 - 8° C, you will need to provide 36 months of real-time stability data, under the recommended storage conditions, from at least three drug product batches representative of the proposed commercial-scale process. These data should be provided with the original BLA application or as a stability update to the BLA

during the review cycle to support your expiry dating request of 36 months for calaspargase pegol drug product. Note that the adequacy of stability data to support the proposed shelf-life of 36 months is a BLA review issue.

Additionally, the meeting package states that container closure integrity testing will be performed only at the end of drug product shelf life. Container closure integrity testing should be performed *in lieu* of sterility testing for stability samples (b) (4)

Discussion:
No discussion occurred.

Question 7:
Does the Agency agree with the conclusions obtained from the characterization by SEC-MALS, (b) (4) at release and stability?

FDA Response to Question 7:
Yes, we agree.

Discussion:
No discussion occurred.

Question 8:
Does the Agency agree that the presented nonclinical program is adequate to support filing of the BLA and licensure?

FDA Response to Question 8:
The Agency acknowledges the prior agreement to conduct the (b) (4) (b) (4) study (b) (4) As agreed to at the July 12, 2011 meeting you should submit study initiation, study completion, and final report submission milestone dates prior to submitting your BLA. Otherwise, your nonclinical development program appears adequate for filing. Approvability can only be determined after the review of your application.

Discussion:
No discussion occurred.

Question 9:
Does the Agency agree with the proposal that the COG and DFCI studies will be the basis for Agency review of safety and efficacy of calaspargase pegol in patients with ALL?

FDA Response to Question 9:
The COG and DFCI studies are appropriate to evaluate safety and efficacy. The acceptability of these trials to support approval will be a review issue.

Discussion:
No discussion occurred.

Question 10:
Does the Agency agree with the proposed content of the two clinical study reports (b) (4) [redacted]

FDA Response to Question 10:
The proposed content for the DFCI study is acceptable. (b) (4) [redacted] A full clinical study report for each study including complete datasets should be submitted to the new BLA. For information on the expected content of a clinical study report, see "Guideline for Industry Structure and Content of Clinical Study Reports" at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073113.pdf

Discussion:
No discussion occurred.

Question 11:
Does the Agency agree with the data collection plan for the DFCI Study?

FDA Response to Question 11:
The proposed data collection for the DFCI study appears acceptable.

Discussion:
No discussion occurred.

Question 12:
Does the Agency agree with the proposal that the data presented in (b) (4) [redacted]

FDA Response to Question 12:
No, all data that you have collected should be included in the initial BLA submission.

Discussion:
The Sponsor clarified that they will submit all available data in the initial BLA submission. FDA requested confirmation that full dates, including birth dates, would be included, and the Sponsor confirmed that full dates would be provided.

Question 13:
Does the Agency agree with the proposal that the BLA will contain safety and efficacy information from patients in the DFCI Study as conveyed in the Statistical Analysis Plan and additional data from the DFCI Study can be provided in the 120-day Safety Update?

FDA Response to Question 13:
The safety and efficacy information proposed in the Statistical Analysis Plan is acceptable. Please clarify what additional information will be in the 120-day safety update.

Discussion:
The Sponsor indicated that the 120-day safety update would include the 2-year EFS and OS from DFCI Study, the cardiac dysfunction follow up and Bone fracture long term follow up from DFCI Study, and a safety update for patients in DFCI Study in continuation phase or follow up. The Sponsor further clarified that the follow-up in the DFCI Study at the current data cut-off had a median of less than 2 years. FDA agreed to the proposed information to be included in the 120-day safety update.

Question 14:
Does the Agency agree with the proposal regarding the dataset and that the BLA will not contain an ISS or ISE, as summary information will be conveyed in Modules 2.5, 2.7.3 and 2.7.4 and that safety information in the USPI (b) (4)

FDA Response to Question 14:
It is acceptable to use the SCE and SCS in lieu of the ISS and ISE for this application. The SCS should include all elements required for an ISS. (b) (4) The COG study was a prospective randomized study and the safety information collected from that study should be included in the label.

Discussion:
No discussion occurred.

Question 15:
Does the Agency agree with the proposed efficacy analyses from the DFCI Study (b) (4)

FDA Response to Question 15:
For submissions for regulatory purposes, we have the following comments:

(a) We require the intent-to-treat (ITT) population, which includes all subjects (for ALL) as randomized, for all efficacy analyses.

(b) Include a missing data section in the statistical analysis plan for the analysis of nadir serum asparaginase activity to specify a missing data handling strategy and to evaluate the impact of any imputation method, if deemed necessary. Every subject should be accounted for in the analysis by either being measured for the endpoint or properly accounted for if not measured for the endpoint. The number of subjects not measured for the endpoint should be kept to a minimum. Too much missing data undermine the reliability and confidence of the results. Several sensitivity analyses

should be performed to account for the limitation of the data and to examine the potential impact of any missing data. Sensitivity analyses should include an appropriate method of imputation under the null. For further advice on missing data see the National Academies of Sciences report on The Prevention and Treatment of Missing Data in Clinical Trials. An electronic version of the document can be found from The National Academies Press at http://www.nap.edu/catalog.php?record_id=12955 A special report of the document can be found at http://www.nejm.org/doi/full/10.1056/NEJMsr1203730

(c) It is noted that the analyses of DFS, EFS and OS will be based on an event driven analysis, (b) (4) (e.g., at 1 year).

(d) We noted that there is no multiplicity adjustment for the analysis of efficacy endpoints.

(b) (4)

Discussion:
No discussion occurred.

Question 16:
Given the well-characterized properties of the active substance asparaginase, does the Agency agree with Baxalta's proposal to not conduct these dedicated studies and reflect this in the USPI (a draft USPI is provided in the briefing document Appendix 1)?

FDA Response to Question 16:
The need for a dedicated renal or hepatic impairment study will be review issue. It is our expectation that the NDA submission should provide complete information in order to write a complete Package Insert with dosing recommendations for all patients, including those with hepatic and/or renal impairment.

Discussion:
No discussion occurred.

Question 17:
Does the Agency agree with the proposed PK and PK/PD modeling and simulation plan?

FDA Response to Question 17:
Yes, your proposed population PK and PK/PD modeling/simulation approach appears appropriate.

Due to the short sampling schedule that was based on the PK properties of Oncaspar, your PK assessment did not fully characterize the PK profile of Calaspargase pegol which has much longer half-life than Oncaspar. This will be a review issue.

Discussion:
No discussion occurred.

Question 18:
Does the Agency agree with our approach to detect and measure anti-drug antibodies?

FDA Response to Question 18:
No, we do not agree. Although your overall approach to detect and measure anti-drug antibodies may appear acceptable, we have the following specific comments:

(a) [redacted] (b) (4) This approach is not acceptable unless parallelism between the reference standard and test sample is established. For details, we refer you to "FDA Guidance for Industry (Draft Guidance): Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products".

(b) In Table 8 "Summary of Performance Parameters for Neutralizing Antibody Assay", you indicated that the assay cut point factors for Anti-Pegaspargase and Anti-Calaspargase pegol neutralizing antibody (NAb) assays are [redacted] (b) (4) respectively. In your BLA application, provide a detailed description of how the above-mentioned cut point factors are calculated. [redacted] (b) (4)

Discussion:
No discussion occurred.

Question 19:
Does the Agency agree with our plan to present and summarize the immunogenicity data?

FDA Response to Question 19:
You proposal to provide brief immunogenicity summaries in each clinical study report, and in BLA Module 2, section 2.7.2.4, appears reasonable. Include full validation reports for the assays to detect for the presence of anti-drug antibodies in section 5.3.1.4 of the eCTD Module 5. In addition, provide in the BLA an integrated immunogenicity summary report in Section 5.3.5.3 Reports of Analyses of Data from More than One Study. This report should:

(a) Describe your multi-disciplinary immunogenicity risk assessment process and your immunogenicity testing strategy.
(b) Summarize your bioanalytical methods for measuring anti-Oncaspar/anti-calaspargase pegol and anti-PEG antibodies.
(c) Summarize the immunogenicity results for each clinical study, and include information on lots of drug product used.

(d) Evaluate the impact of anti-drug antibodies on PK (asparaginase activity), efficacy and safety.
(e) Provide a post-marketing plan to link adverse events to immunogenicity, if appropriate.
(f) Provide the immunogenicity datasets in an integrated SAS transport file.

Discussion:
No discussion

Additional Comments:

1. FDA would like to request the SAS programs used to derive the primary and major secondary efficacy endpoints from SDTM (or CRF data) data. SAS programs used for the primary and major secondary efficacy analyses (including sensitivity analysis) based on ADaM (or derived) data and for any new results included in the proposed labeling should also be included.

2. For each clinical study in your submission, please include a simple dataset to identify the tests used for confirmation of efficacy outcomes. This should include at least the following variables: study identification number, site identification number, subject number, treatment arm, demographic information, date of treatment start, best response category, date of response, date of marrow used to identify response, date of ANC used to identify response, date of platelet count used to identify response, date of MRD test used to identify response, event used for EFS, and date of event for EFS.

3. Ensure that the BLA includes a data file listing all available MRD assay results. Please also submit in Module 5 a description of each MRD assay used in the study, including where the assay was performed.
4. Please identify the laboratories used for the analysis of samples for the pharmacokinetics assessments. Include in your BLA submission the following information about these sites: site name, site address, site telephone number, site fax number, analytical investigator name, analytical investigator email address.

5. In your BLA application, provide a table with information on changes made to the calaspargase pegol manufacturing process since the time of your previous BLA submission. Information should include, but not limited to, modifications made to the production process, analytical test methods or testing requirements, facilities, equipment etc. In addition, provide a detailed risk assessment of the impact of these changes on the product quality, safety, and potency of calaspargase pegol.

Additional Product Quality Microbiology Comments:

We are providing additional product quality microbiology comments for you to consider for the preparation of your BLA submission.

All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). The facility should be in operation and manufacturing the product during the inspection. A preliminary manufacturing schedule for both the drug substance and drug product should be provided in the Module 1 of the BLA to facilitate the planning of the pre-license inspections during the review cycle. Please include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers.

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

- Bioburden and endotoxin levels at (b) (4) should be monitored using qualified bioburden and endotoxin tests. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).
- Bioburden and endotoxin data obtained (b) (4) (3.2.S.2.5).
- (b) (4) (3.2.S.2.5).
- Drug substance bioburden and endotoxin release specifications (3.2.S.4).
- Summary report and results from bioburden and endotoxin test methods qualification performed for (b) (4) and the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).

The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries to support the (b) (4) and sterility assurance. 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" at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf

The following information should be provided in sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.

(b) (4)

(b) (4)

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5:

(b) (4)

The following product testing and method validation information should be provided in the appropriate sections of Module 3:

- 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.
- Summary report and results for qualification of the bioburden, sterility and endotoxin test methods performed for (b) (4) (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. (b) (4)

[redacted] (b) (4)

Discussion:
No discussion occurred.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. Baxalta USA Inc. stated during the teleconference that their BLA submission would be complete with all information upon submission including the 120 safety information from Dana-Faber studies.

  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.

- . There was no preliminary discussion regarding the potential need for REMS.
- 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.

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. Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

SUBMISSION FORMAT REQUIREMENTS

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

Office of Scientific Investigations (OSI) Requests

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

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

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

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

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

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

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

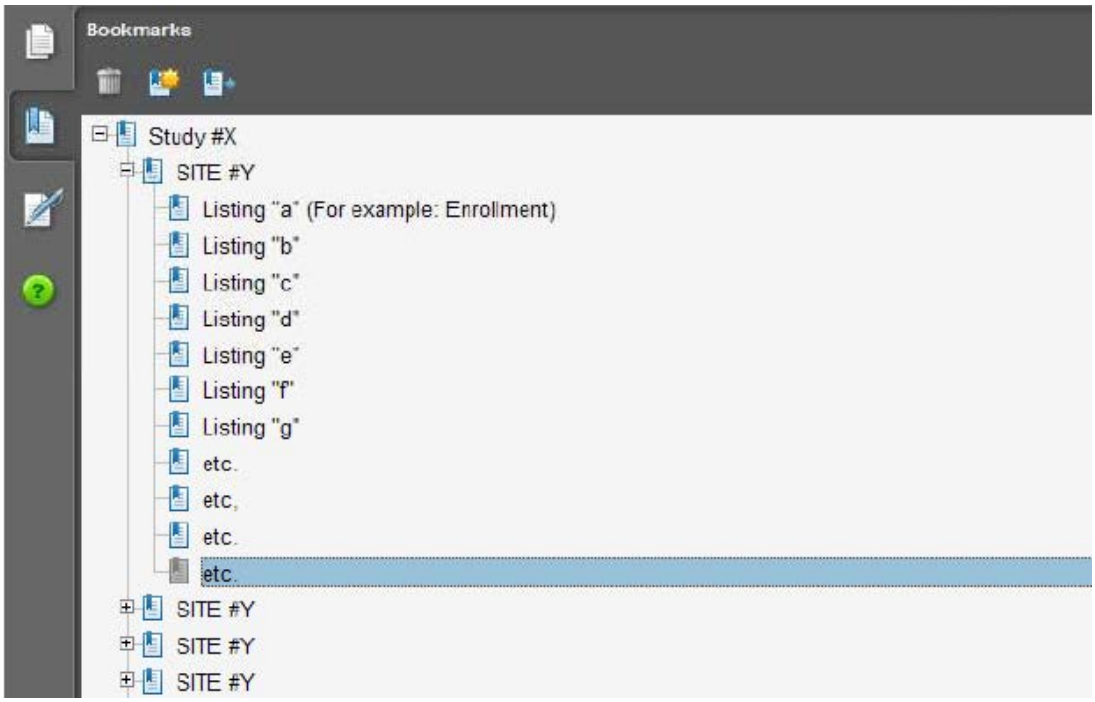
maintained. As above, this is the actual physical site where documents would be available for inspection.

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

II. Request for Subject Level Data Listings by Site

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

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

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

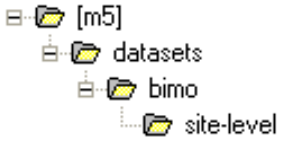
Attachment 1

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion.

5.0 ACTION ITEMS

There are no action items at this time.

6.0 ATTACHMENTS AND HANDOUTS

Baxalta USA Inc. provided the Agency with discussion points via email on July 27, 2016.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 100594

MEETING MINUTES

Sigma Tau Pharmaceuticals, Inc.
Attention: GianFranco Fornasini, PhD
Senior Vice President, Scientific Affairs
9841 Washingtonian Boulevard, Suite 500
Gaithersburg, MD 20878

Dear Dr. Fornasini:

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

We also refer to the meeting between representatives of your firm and the FDA on March 4, 2014. The purpose of the meeting was to discuss elements associated with the resubmission of your BLA.

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 Mara Miller, Regulatory Project Manager at (301) 796-0683.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Clinical Team Lead
Division of Hematology Products
Office of Hematology and Oncology Products
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: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: March 4, 2014 9:00-10:00 AM
Meeting Location: White Oak, Building #22

Application Number: IND 100594
Product Name: Calaspargase Pegol
Indication: ALL
Sponsor/Applicant Name: Sigma Tau Pharmaceuticals, Inc.

Meeting Chair: Albert Deisseroth
Meeting Recorder: Mara Miller

FDA ATTENDEES

Division of Hematology Products
Ann Farrell, MD, Division Director
Robert Kane, MD, Deputy Director for Safety
Albert Deisseroth, MD, PhD, Clinical Team Lead
Patricia Dinndorf, MD, Clinical Reviewer
Qin Ryan, MD, PhD, Safety Medical Reviewer
Mara Miller, MA Regulatory Project Manager
Diane Leaman, BS, Safety Project Manager

Office of Hematology and Oncology Products
Jonathan Jarow, MD, Deputy Director (Acting)
Gregory Reaman, MD, Associate Director for Oncology Sciences

Office of Hematology Oncology Toxicology
Chris Sheth, PhD, Reviewer

Office of Clinical Pharmacology
Julie Bullock, PharmD, Team Lead

Office of Biostatistics
Lei Nie, PhD, Team Lead (Acting)
Yun Wang, PhD, Reviewer

Office of Biotechnology Products, Division of Therapeutic Proteins
Maria Gutierrez Lugo, PhD, Team Lead
Ramesh Potla, PhD, Reviewer
Joslyn Brunelle, PhD, Reviewer

EASTERN RESEARCH GROUP ATTENDEES
Christopher Sese, Independent Assessor

SPONSOR ATTENDEES
GianFranco Fornasini, PhD Sr. Vice President, Scientific Affairs
Taha Keilani, MD Vice President Clinical Affairs
Karen Kuphal, PhD Sr. Project Manager, Product Development
Giuseppe Testa, Vice President, Product Development
Scott Rodgers, Sr. Clinical Research Manager
(b) (4) Consultant, Regulatory Affairs
Irene Franklin, PharmD Director, Drug Safety
Nadejda Soukhareva, MS Director, Regulatory Sciences
Raven Jaeger, MS, RAC Director, Regulatory Affairs
(b) (6)
(b) (4) (b) (6)

1.0 BACKGROUND

Currently, Sigma-Tau is preparing to resubmit their BLA for (b) (4) calaspargase pegol 2500 IU/m2 as a component of a multi-agent chemotherapeutic regimen for the (b) (4) treatment of patients with ALL. The initial BLA for calaspargase pegol was submitted in eCTD format on 28 September 2012. Sigma-Tau voluntarily withdrew the BLA (b) (4) The main FDA concerns for calaspargase pegol were related to (b) (4)

(b) (4)

2. DISCUSSION

Question 1
Does FDA have any comments regarding the contents of the BLA resubmission?

FDA Response
The application should not be resubmitted to BLA (b) (4) The application should be submitted as a new BLA.

(b) (4)

Question 2
Does the FDA agree that the proposed plan (b) (4) for the final BLA approval of calaspargase pegol as described above is acceptable?

FDA Response

(b) (4)

(b) (4)

DFCI 11-001 appears to be an acceptably designed study to determine that the substitution of calaspargase for Oncaspar does not lead to an erosion in the long term efficacy.

(b) (4)

Control Drug Treatments:
Oncaspar 2500 IU/m^2
Day 7 of Induction.
Beginning in Consolidation I (for VHR patients) or CNS therapy (SR and HR patients), administer every 2 weeks for 30 weeks (15 doses).

Study Drug Treatments:
Calaspargase pegol 2500 IU/m^2
Day 7 of Induction.
Beginning in Consolidation I (for VHR patients) or CNS therapy (SR and HR patients), administer every 3 weeks for 30 weeks (10 doses).

(b) (4)

In the DFCI 11-001 trial, please clarify

(b) (4)

(b) (4)

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. As part of the complete application submission, Sigma Tau will:
    - Cross-reference the prior withdrawn BLA for previously submitted information;
    - Provide analysis to support the data along with the safety (PK and clinical); and
    - Include interim Dana Farber data and reanalysis, at a minimum.

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

- A preliminary discussion on the need for a REMS was held and it was concluded that at present, the team does not feel that a REMS is necessary.

- 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: Sigma Tau will inform the FDA if the interim data and reanalysis of Dana Farber data will be submitted as a late component.

  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 NUMBER: LATE COMPONENT - BIOMETRICS
  BLA NUMBER: LATE COMPONENT - CLINICAL
  BLA NUMBER: LATE COMPONENT - CLINICAL PHARMACOLOGY
  BLA NUMBER: LATE COMPONENT - NONCLINICAL
  BLA NUMBER: LATE COMPONENT - QUALITY

PREA REQUIREMENTS

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

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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. As you develop

your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements of Prescribing Information* website including the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, regulations, related guidance documents, a sample tool illustrating the format for Highlights and Contents , and the Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor responses to preliminary comments received March 3, 2014.

Responses to FDA's Preliminary Meeting Comments

Provided following are Sigma-Tau Pharmaceuticals' (Sigma-Tau's) preliminary responses to FDA's preliminary meeting comments (dated 27 February 2014) for the pre-BLA meeting scheduled for 04 March 2014. For ease of review, Sigma-Tau's pre-BLA meeting questions are provided in italics, followed by FDA's comments in bold font, followed by Sigma-Tau's response in blue font.

Sigma-Tau Question 1:

(b) (4)

Does FDA have any comments regarding the contents of the BLA resubmission?

FDA Preliminary Comment 1:

The application should not be resubmitted to BLA (b) (4) **The application should be submitted as a new BLA.**

(b) (4)

Sigma-Tau's Preliminary Response:

Following the withdrawal of the BLA, Sigma-Tau performed extensive new analyses of PK data using a population PK approach to seek a possible correlation of the main PK parameters (AUC, C_{max} and C_{min}) with MRD and AEs, including L-asparaginase specific events; full PK reports and associated datasets will be included for FDA's assessment in the BLA resubmission. (b) (4)

The extensive analyses performed after the withdrawal of the BLA were conducted with the data obtained from the Children's Oncology Group (COG) study. These analyses included additional PK/PD and PK/AE correlations to establish a possible relationship between L-asparaginase activity, efficacy (asparagine levels and MRD), and toxicity (selected AEs and specific L-asparaginase events that had a higher incidence with calaspargase pegol treatment). These analyses also show evidence (b) (4)

Moreover, an independent Safety and Adjudication Consultant Committee (SACC) conducted a blinded safety assessment of AEs of interest (*i.e.*, deaths, selected L-asparaginase specific events, and sepsis). (b) (4)
.

It is Sigma-Tau's opinion that these analyses provide support to address the FDA's comments of 04 April 2013. As such, Sigma-Tau would like to have the opportunity to provide FDA with the results of these new analyses conducted using a population PK and PK/PD modeling approach (b) (4)

In conclusion, Sigma-Tau proposes to present this new evidence as support of calaspargase pegol in the treatment of ALL. (b) (4)

Sigma-Tau Question 2:

(b) (4)

(b) (4)

(b) (4) *The study design meets or exceeds all the criteria FDA requested during the 12 July 2011 meeting as follows:*

- *Multicenter, randomized, active controlled study*
- *Enrollment of 240 patients as compared to 123*
- *Patients concurrently randomized 1:1 to either Oncaspar or calaspargase pegol at 2500 IU/m^2. Note: The DFCI study administers more (up to 11 doses) of calaspargase pegol (dosed every 3 weeks for 30 weeks following the induction dose) and more (up to 16 doses) of Oncaspar (dosed every 3 weeks for 30 weeks following the induction dose) as compared to (5 to 10 doses of PEGylated asparaginase) in the AALL07P4 study.*
- *All patients will receive the same chemotherapy backbone*
- *Includes assessments for:*
    - *End of induction MRD*
    - *Toxicity (adverse events and serious adverse events)*
    - *Trough plasma asparaginase activity. Asparaginase activity levels for this study are being performed* (b) (4)
    - *Immunogenicity (anti-PEG, anti-calaspargase pegol and anti-Oncaspar) performed by the same lab used for Protocol AALL07P4*
    - *Disease progression and survival status.*

A synopsis of the DFCI 11-001 study is provided in Section 10.2.6 and the current study protocol is provided in Appendix 1 of this briefing package.

(b) (4)

Does the FDA agree that the proposed plan (b) (4) *for the final BLA approval of calaspargase pegol as described above is acceptable?*

FDA Comment 2:

(b) (4)

(b) (4)

DFCI 11-001 appears to be an acceptably designed study to determine that the substitution of calaspargase for Oncaspar does not lead to an erosion in the long term efficacy. (b) (4)

Control Drug Treatments:

Oncaspar 2500 IU/m^2

Day 7 of Induction.

Beginning in Consolidation I (for VHR patients) or CNS therapy (SR and HR patients), administer every 2 weeks for 30 weeks (15 doses).

Study Drug Treatments:

Calaspargase pegol 2500 IU/m^2

Day 7 of Induction.

Beginning in Consolidation I (for VHR patients) or CNS therapy (SR and HR patients), administer every 3 weeks for 30 weeks (10 doses).

(b) (4)

In the DFCI 11-001 trial, please clarify [redacted]

Sigma-Tau's Response:

[redacted] Since the withdrawal, Sigma-Tau has conducted the aforementioned new analyses to address the FDA's concerns [redacted] Although the actual reports were not included in the briefing package (due to the single volume size limitation), the brief summary provided in the briefing package Executive Summary and in Section 10.2 was intended to relay this information to the FDA (*i.e.*, that Sigma-Tau intended on submitting this new data to address FDA's concerns).

[redacted]

[redacted]

[redacted]

[redacted] Currently, the DFCI 11-001 study determines asparaginase activities at the following time points:

- Induction Phase: Days 7 (two samples: prior to IV asparaginase dose and 5-10 minutes after completion of infusion), 11, 18, 25 and 32.

- Post-Induction: Just prior to each dose of asparaginase administered during post-induction treatment phases (*i.e.*, every 3-weeks for patients randomized to calaspargase pegol and every 2-weeks for patients randomized to Oncaspar).

Using the validated population PK approach already developed for the COG study (additional analyses to be provided in the BLA resubmission), Sigma-Tau proposes to model the two dose regimens of the DFCI study fitting asparaginase activities measured after single and repeated doses of Oncaspar and calaspargase pegol. The estimated PK parameters will be compared between Oncaspar and calaspargase pegol to establish the extent of drug exposures and accumulation following the relative dose regimens. Further analysis will evaluate a possible correlation between summary PK parameters (*e.g.*, AUC, C_{max}, and C_{min}) and safety data (AEs).

In the DFCI study, disease assessment schedules are the same for both treatment arms. Only the dosing of Oncaspar vs calaspargase pegol is different. With regards to EFS, although the DFCI 11-001 study is not sufficiently powered to detect a difference between the arms, EFS and overall survival (OS) will be calculated using the Kaplan and Meier method for each arm. Event Free Survival will be defined as the time from achievement of complete remission to the time of relapse, death or second malignancy. Patients not achieving complete remission will be considered events at time zero. Overall survival is defined as the time from diagnosis until death. Five-year estimates of EFS and OS will be provided for each arm along with the 90% confidence intervals estimated using the Greenwood formula once sufficient follow-up data is obtained.

Finally, as mentioned in response to FDA's Comment 1, Sigma-Tau convened a SACC panel consisting of four experts in the field of ALL treatment. This panel consisted of members (b) (4) They were tasked with independently and blindly reviewing and adjudicating the reported cases of deaths and specific AEs of interest, which included anaphylaxis/hypersensitivity, pancreatitis, embolism, hyperbilirubinemia, hyperamylasemia, hyperlipasemia, febrile neutropenia, and sepsis.

(b) (4)

(b) (4)

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/s/

ALBERT B DEISSEROTH
03/14/2014