CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214383Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 116362

MEETING MINUTES

Oncopeptides AB
c/o B&H Consulting Services, Inc.
Attention: Birju Patel, MS
Senior Regulatory Affairs Project Manager
50 Division Street, Suite 206
Somerville, NJ 08876

Dear Mr. Patel:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for melphalan flufenamide.

We also refer to the meeting between representatives of your firm and the FDA on December 3, 2019. The purpose of the meeting was to discuss the content and format of the planned NDA. In addition, discuss resolutions to prior FDA concerns.

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

If you have any questions, call Thomas Iype, Regulatory Health Project Manager, at (240) 402-6861.

Sincerely,

{See appended electronic signature page}

Bindu Kanapuru, MD
Clinical Team Leader (Acting)
Division of Hematologic Malignancies 2
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:
- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	December 3, 2019; 2:00 pm – 3:00 pm (ET)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1417 Silver Spring, Maryland 20903
Sponsor Name:	Oncopeptides AB
Application Number:	IND 116362
Product Name:	Melphalan Flufenamide
Proposed Indication:	Melphalan flufenamide in combination with dexamethasone is indicated for the treatment of RRMM patients whose disease is refractory to at least one PI, one IMiD and one anti-CD38 monoclonal antibody.
Meeting Chair:	Bindu Kanapuru, MD
Meeting Recorder:	Thomas Iype, PharmD, RPh

FDA ATTENDEES

Office of Oncologic Diseases(OOD)/Safety
Elizabeth Everhart, MSN, RN, ACNP, *Program Manager*

OOD/Division of Hematologic Malignancies 2
Nicole Gormley, MD, *Director (Acting)*
Bindu Kanapuru, MD, *Clinical Team Leader (Acting)*
Andrea Baines, MD, PhD, *Clinical Reviewer*

OOD/Division of Hematology, Oncology and Toxicology Products
Michael Manning, PhD, *Pharmacologist/Toxicologist*

Office of Biostatics/Division of Biometrics IX
Yute Wu, PhD, *Team Leader*
Kunthel By, PhD, *Reviewer*

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Ruby Leong, PharmD, *Team Leader*
Hongfei Zhang, PhD, *Reviewer*

SPONSOR ATTENDEES
Jakob Lindberg, *Chief Executive Officer*
Elisabeth Augustsson, *Head of Regulatory Affairs*
Nicolaas Bakker, *Chief Medical Officer*
Christian Jacques, *Chief Scientific Officer*
Eva Nordstrom, *Head of Clinical Development*
Hanan Zubair, *Data Management Director*
Pontus Larsson, *Senior Project Statistician*

(b) (4), *Clinical Consultant,* (b) (4)
(b) (4), *Clinical Pharmacology Consultant,* (b) (4)
(b) (4), *Senior Safety Consultant,* (b) (4)
(b) (4), *Associate Manager, Biostatistics,* (b) (4)
(b) (4), *Vice President of Regulatory Affairs,* (b) (4)
Elizabeth Dupras, *Senior Director, B&H Consulting Services, Inc.*
Birju Patel, *US Agent for Oncopeptides AB, B&H Consulting Services, Inc.*

1.0 BACKGROUND

The Sponsor has had several meetings with the Food and Drug Administration to guide development of melphalan flufenamide for patients with relapsed multiple myeloma. The Sponsor plans to submit data from study OP-106 to support the proposed indication under an accelerated approval regulatory pathway.

The Sponsor also plans to (b) (4)

In the meeting background package received on November 4, 2019, the Sponsor has proposed to (b) (4). The objective of this meeting is to provide guidance on the content and format of the planned NDA.

Lastly, a separate Pre-NDA Chemistry, Manufacturing and Control meeting will be held on December 4, 2019.

2.0 DISCUSSION

Question 1: *Does the Agency agree that the Sponsor's proposed approach addresses the Agency's request for data isolating melflufen treatment effect?*

FDA Response to Question 1: No, we reiterate our previous comments provided on May 10, 2019, and September 11, 2019, regarding your plan to submit an NDA based on the results of the single arm trial OP-106 evaluating melflufen in combination with dexamethasone. It is at your discretion to submit results from the OP-106 study. Submit your statistical analysis plan (SAP) for study OP-106 to the FDA for review.

Discussion: **Please see the Discussion section under question 2.**

Question 2: *Does the Agency agree that* (b) (4) *?*

FDA Response to Question 2: We have significant concerns regarding your proposal to (b) (4)

Discussion: **The Sponsor stated that** (b) (4) **will not be included in the NDA submission. The Sponsor proposes to include information on response rates with single agent dexamethasone from historical trials to support the isolation of treatment effect of melphalan flufenamide. The Agency stated that comparing results across trials is challenging given the differences in patients population and changes in standard of care with respect to prior and subsequent therapies and supportive care medications. The Sponsor should include all relevant data to facilitate the review of the NDA submission. The Agency reiterated their concerns with the Sponsor's proposal to submit an NDA based primarily on the results of study OP-106. Ultimately, the acceptability of the data will be a review issue.**

The Agency emphasized that the Sponsor include the data regarding monotherapy dexamethasone and the historical rate of available therapies in the proposed population for comparison with the melphalan flufenamide + dexamethasone combination in the SAP.

Question 3: *Does the Agency agree there is an unmet medical need in relapsed refractory multiple myeloma patients with extramedullary disease (EMD)?*

FDA Response to Question 3: The reason for this question is unclear. Clarify the reason for your question with reference to your proposed NDA submission.

Discussion: **No discussion occurred.**

Question 4: *Does the Agency agree with the proposal on how to present the efficacy data in the 505(b)(1) NDA?*

FDA Response to Question 4: It is unclear why you plan to include only those patients dosed on/before

May 15, 2019. You should include data on all enrolled patients (N=157) in study OP-106. Enrolled patients who have not received treatment are to be categorized as non-responders in the calculation of ORR. We recommend including a minimum of 6 months of follow-up data for patients included in the efficacy analysis. In addition, clarify how you plan to present the IRC-assessed responses in the efficacy data presentation.

We note that your meeting package does not include data in patients who have received two PIs, two IMiDs, and an anti-CD38 monoclonal antibody.

Discussion: The Sponsor clarified that the original NDA submission will include efficacy and safety data from all enrolled patients (N=157) in study OP-106. The Agency stated that the Sponsor's proposal to include data from all enrolled patients appears reasonable. The Sponsor will submit the SAP for OP-106 to the agency for review. The proposal to use the 15 May cut-off date for ISS with a subsequent 90- or 120- day safety update as stated previously is reasonable.

The Agency reiterated their concerns with the use of a single arm combination trial as their primary trial to support the NDA submission.

Question 5: *Does the Agency agree with the Sponsor's proposed approach to provide available safety data and limited efficacy data from clinical studies OP-104 and OP-107 in the format of an abbreviated clinical study report?*

FDA Response to Question 5: Your approach to provide available safety and efficacy data from studies OP-104 and OP-107 appears reasonable.

Discussion: No discussion occurred.

Question 6: *Does the Agency agree that the Sponsor's proposed plan for submission of PK results from the completed and ongoing clinical studies is adequate to support the planned 505(b)(1) NDA?*

FDA Response to Question 6: No, we have the following recommendations for submission of PK results from the completed and ongoing clinical studies:

a. Since the bioanalytical methods for study O-05-001 and O-12-M1 do not appear to be the same, a cross validation is needed to compare validation parameters of the two bioanalytical methods.
b. Assess dose proportionality of melflufen and its metabolite, melphalan, with PK data from both Study O-05-001 and Study O-12-M1.
c. Provide a rationale for the selected dosing regimen based on integrated dose- and exposure-response analyses of pharmacokinetic, pharmacodynamic, safety, and efficacy data.

d. Evaluate the effect of severe renal impairment (creatinine clearance 15-29 mL/min per Cockcroft-Gault) on the PK and safety of melflufen in Study OP-107 and submit available results.
e. For guidance on PK datasets submission, refer to Additional Clinical Pharmacology comments below.

Discussion: No discussion occurred.

Question 7: *Does the Agency agree with the proposed Study Data Standardization Plan?*

FDA Response to Question 7: From a technical standpoint, the proposed Study Data Standardization Plan is acceptable.

Discussion: No discussion occurred.

Question 8: *Does the Agency agree with the Sponsor's proposal to share the safety data from both arms of study OP-103 via the DMC only and that it is acceptable not to include the pomalidomide/dexamethasone arm in the ISS?*

FDA Response to Question 8: Your proposal for submitting safety data from study OP-103 appears reasonable. Also see the FDA Response to Question 2 regarding efficacy data from study OP-103.

Discussion: No discussion occurred.

Question 9: *Does the Agency agree with the proposal on how to present the safety data in the NDA?*

FDA Response to Question 9: No, your safety population for the ISS should include all patients enrolled on study OP-106 who received at least one dose of melflufen. You should ensure that there is adequate follow-up data for safety to support a regulatory submission.

Discussion: See discussion under question 4.

Question 10: *Does the Agency agree to the proposed cut-off date for the 90-Day safety update and on the proposed format of an updated ISS?*

FDA Response to Question 10: The appropriateness of the cut-off date for the 90-Day Safety Update will depend on the timing of your NDA submission. In general, based on your proposed database cut-off date that is 6 months prior to submission of the 90-Day Safety Update, your approach appears reasonable.

Discussion: No discussion occurred.

Question 11: *Does the Agency agree with the Sponsor's approach to include only the specified case report forms (CRFs) and patient narratives in the 505(b)(1) NDA?*

FDA Response to Question 11: No, we do not agree with your proposed approach. The NDA should include CRFs for the pivotal study OP-106 for each patient who died during treatment or within 30 days of completion of treatment, for each patient who discontinued treatment due to an adverse event regardless of attribution, and for each patient who had a serious adverse event. You should also submit narratives for all SAEs regardless of attribution to study treatment and full narratives for all AEs leading to permanent treatment discontinuation (i.e., not limited to SAEs). Clarify whether you plan to submit death narratives for all deaths considered related to study treatment regardless of whether they occur while on study treatment or within 30 days of the last dose. Additional narratives may be requested during the review.

Discussion: The Sponsor clarified that the NDA submission will include narratives for all deaths considered related to study treatment regardless of whether they occur on study treatment or within 30 days of the last dose.

Question 12: *Does the Agency agree that due to the orphan drug designation of melflufen, the exemption from PREA requirements applies for the initial NDA submission planned for March 2020, and an agreed iPSP is not needed prior to the initial submission of the 505(b)(1) NDA?*

FDA Response to Question 12: Yes, we agree.

Discussion: No discussion occurred.

Additional Clinical Pharmacology Comments:

Take the following recommendation about labeling into your consideration:

a) We recommend the content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application be consistent with FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" (available at https://go.usa.gov/xn4qB). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

Address the following questions in the Summary of Clinical Pharmacology:

a) What is the basis for selecting the doses and dosing regimen used in the trials intended to support your marketing application? Identify individuals who required dose modifications and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.

b) What are the exposure-response relationships for efficacy, safety and biomarkers?
c) What is the effect of melflufen on the QT/QTc interval?
d) What are the characteristics of distribution, and elimination (metabolism and excretion)?
e) How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?

Apply the following advice in preparing the clinical pharmacology sections of the original submission:

a) Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
b) Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with minimum and maximum values as appropriate.
c) Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
    - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
    - Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.
d) Submit the following for the population pharmacokinetic analysis reports:
    - Standard model diagnostic plots
    - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
    - Model parameter names and units in tables.
    - Summary of the report describing the clinical application of modeling results.

    Refer to the following pharmacometric data and models submission guidelines http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.
e) Submit the following information and data to support the population pharmacokinetic analysis:
    - SAS transport files (*.xpt) for all datasets used for model development and validation
    - A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets

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

f) Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population. Refer to Guidance for Industry at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf for population PK, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for exposure-response relationships.

3.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. We make reference to section 2.0.

- 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 and it was concluded that this will be a review issue.

- 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) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 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 or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) 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*.

For the latest version of the molecular target list, please refer to FDA.gov.[1]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric

[1] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology

population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult FDA's Guidance on Formal Meetings Between the FDA and Sponsors or Applicants[2] to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

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[4] and Pregnancy and Lactation Labeling Final Rule[5] 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.

[2] See the guidance for industry *"Formal Meetings Between the FDA and Sponsors or Applicants."*
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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*.

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial

period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

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 FDA.gov.[6]

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 FDA.gov.[7]

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.

[6] http://www.fda.gov/ectd
[7] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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 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*.[8]

[8] https://www.fda.gov/media/85061/download

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[9]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- AssessmentAid[10]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues currently requiring further discussion.

5.0 ACTION ITEMS

Action Item/Description	Owner
Submit SAP for study OP-106 as soon as possible	Sponsor

6.0 ATTACHMENTS AND HANDOUTS

We make reference to your presentation submitted via email on December 3, 2019, and received on December 3, 2019.

5 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

[9] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[10] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

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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/

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 116362

MEETING MINUTES

Oncopeptides AB
c/o B&H Consulting Services, Inc.
Attention: Sandy Lee, MS, RAC
Senior Project Manager II
50 Division Street, Suite 206
Somerville, NJ 08876

Dear Ms. Lee:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Melflufen (J1; Melphalan flufenamide).

We also refer to the meeting between representatives of your firm and the FDA on June 14, 2016. The purpose of the meeting was to obtain the Agency's agreement on the adequacy of the clinical program and Chemistry, Manufacturing and Controls (CMC) plans to support initiation of phase 3 trials, as well as the marketing approval.

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 Beatrice Kallungal, Regulatory Project Manager, at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

Nicole Gormley, MD
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:	Type B
Meeting Category:	End-of-Phase 2
Meeting Date and Time:	June 14, 2016; 11:00 AM – 12:00 PM EDT
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1415 Silver Spring, Maryland 20903
Application Number:	IND 116362
Product Name:	Melflufen (J1; Melphalan flufenamide)
Indication:	Treatment of multiple myeloma
Sponsor/Applicant Name:	Oncopeptides AB
Meeting Chair:	Nicole Gormley, MD
Meeting Recorder:	Beatrice Kallungal, MS

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Albert Deisseroth, MD, PhD, Clinical Team Leader
Nicole Gormley, MD, Acting Clinical Team Leader
Hyon-Zu Lee, PharmD, Clinical Reviewer
Beatrice Kallungal, MS, Senior Regulatory Project Manager

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Stacy Shord, PharmD, Team Leader
Sriram Subramaniam, PhD, Reviewer

Office of Pharmaceutical Quality (OPQ)/Office of New Drug Products (ONDP)

Office of New Drug Quality Assessment
Sherita McLamore-Hines, PhD, Application Technical Lead (Acting)
William M Adams, PhD, Reviewer

Division of New Drug API/Branch I
Gene Holbert, PhD, Drug Substance Reviewer

SPONSOR ATTENDEES
Jakob Lindberg, CEO, Oncopeptides AB
Johan Harmenberg, CMO, Oncopeptides AB
Fredrik Lehmann, Director of CMC, Oncopeptides AB
Lina Rydner, CMC Manager, Oncopeptides AB
Eva Nordström, Head of Clinical, Oncopeptides AB
Elisabeth Augustsson, Director Regulatory Affairs, Oncopeptides AB
Hanan Zubair, Clinical Data Manager, Oncopeptides AB
Stephanie Pierson, Regulatory Consultant for Oncopeptides AB, B&H Consulting Services, Inc.
Markus Jerling, Pharmacokinetic Expert/Safety Officer, Oncopeptides AB
Joachim Gullbo, Scientific Adviser, Oncopeptides AB
(b) (4), Professor of Medicine, (b) (4)
Sandy Lee, RAC, US Agent for Oncopeptides AB, B&H Consulting Services, Inc.

1.0 BACKGROUND

Melflufen is a lipophilic alkylating agent designed for efficient targeting of tumor cells. The Sponsor states that melflufen is thought to exert a higher anti-tumor activity compared to the standard alkylator melphalan, but with a seemingly similar safety profile.

Based on available efficacy data from the ongoing clinical trial O-12-M1 in a relapsed and refractory multiple myeloma (RRMM) population, and feedback received from FDA at the Type C meetings held on December 16, 2015, and April 13, 2016, the Sponsor is proposing to conduct a pivotal trial in patients with MM (b) (4)

The purpose of the meeting is to obtain FDA's agreement on the adequacy of the available clinical data to support initiation of phase 3 clinical trial and the adequacy of the proposed clinical program to support marketing approval. Further, the Sponsor aims to obtain FDA's agreement on the designation of starting materials, on the drug product specification for phase 3 clinical supplies and on the stability plans to support phase 3 and marketing approval.

FDA sent Preliminary Comments to Oncopeptides on June 9, 2016.

2.0 DISCUSSION

Clinical

Question 1:
Does the Agency agree that the protocol instructions with respect to thrombocytopenia and neutropenia in relation to cycle prolongations, dose reductions and supportive care measures (primarily with respect to G-CSF and platelet transfusions) are appropriate for the study drugs, (b) (4) and melflufen?

FDA Response:
In general, the proposed treatment plan with respect to thrombocytopenia and neutropenia are acceptable for (b) (4) and melflufen. However, we have the following comments:

- **Melflufen should be held for grade 4 hematologic toxiticity. If ≥ grade 4 hematologic toxicity recurs, the dose should be reduced by one level.**
- **In table 1-4, "Day 4" under the "Day" column should be revised to "Day 43".**
- **In table 1-5, there is a typo in the second row under dose modification, "Interrupt therapy…If ANC returns to <500 cell/mm^3…." should be revised to Interrupt therapy…If ANC returns to >500 cell/mm^3….".**

For non-hematologic toxicity, melflufen should be held for ≥ grade 3 AEs until ≤ Grade 1 or baseline and when restarting treatment with melflufen, the dose should be reduced by one level.

Meeting Discussion:
The Sponsor proposed a dose reduction for melflufen, specifically that the treatment will be dose-reduced one level in the event of recurrence of grade 4 neutropenia or thrombocytopenia. The Agency stated that the proposal is acceptable.

The Sponsor also proposed criteria for new cycle initiation and treatment adjustment for non-hematologic toxicity. The Agency stated that the proposal appears reasonable for both arms. However, the Agency cannot comment at this time on the acceptability of requiring (b) (4).

Question 2:
Does the Agency agree that the doses and the dosing reduction instructions for dex are appropriate?

FDA Response:
No. With grade 3 GI toxicity, patients should be treated with H2-blockers, sucralfate or omeprazole and dexamethasone dose should be reduced by one level. Dexamethasone dose should also be decreased by one level with > grade 2 hyperglycemia that is uncontrolled despite treatment with insulin/oral hypoglycemic or > grade 2 edema.

Meeting Discussion:
No discussion.

Question 3:
Does the Agency agree that the available safety data for melflufen are sufficient to support initiation of phase 3?

FDA Response:
Yes. However, the Agency notes that you have decided to proceed to phase 3 trials with relatively little data in your intended patient population, which increases your risk associated with initiating a phase 3 trial.

Meeting Discussion:
No discussion.

Question 4:
Does the Agency agree that robust and clinically relevant results from the proposed single pivotal study may be sufficient to support approval for treatment of RRMM?

FDA Response:
Whether the results from the proposed single registration trial will be sufficient to support approval will be a review issue.

Meeting Discussion:
No discussion.

Question 5:
Does the Agency agree that no further QTc evaluations will be necessary to support an NDA submission, assuming that Holter data will be available from approximately 20 patients in study O-12-M1 and that the 90% upper confidence interval for change in QTc from baseline does not exceed 20 msec at the highest clinical dose?

FDA Response:
Yes, the Agency agrees that no further QTc evaluations are necessary, pending review of the ECG data. You will need to demonstrate that at the highest clinical dose the largest mean increase in QTc from baseline is less than 10 ms with the upper bound of the 2-sided 90% confidence interval not exceeding 20 ms. In addition, you should submit the following items after completion of study O-12-M1 for our review:

a. **Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed**

b. **Electronic copy of the study report**

c. **Electronic or hard copy of the clinical protocol**

d. **Electronic or hard copy of the Investigator's Brochure**

e. **Annotated CRF**

f. **A data definition file which describes the contents of the electronic data sets**

g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses

h. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g., QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)

i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point

j. Narrative summaries and case report forms for any

i. Deaths

ii. Serious adverse events

iii. Episodes of ventricular tachycardia or fibrillation

iv. Episodes of syncope

v. Episodes of seizure

vi. Adverse events resulting in the subject discontinuing from the study

k. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com). If you use Holter recording and select 10-second segments to measure, submit either the entire Holter recording or at least the entire analysis windows.

l. A completed Highlights of Clinical Pharmacology Table

Advancing in this field – and possibly reducing the burden of conducting QT studies – depends critically upon obtaining the most comprehensive understanding of existing data. Please consider making your data, at least placebo and positive control data, available for further research purposes; see, for examples, the Data Request Letter at www.cardiac-safety.org/library .

Meeting Discussion:
No discussion.

Chemistry, Manufacturing, and Controls

Question 6:
Does the Agency agree on the designation of starting materials?

FDA Response:
The Agency agrees with your designation of (b) (4) **as starting materials. Provide the following information for each starting material in your application:**

- **In-house acceptance criteria and Vendor's Certificate of Analysis**
- **Supplier's name and address and a brief description of synthetic scheme and method of manufacture**
- **Data to confirm the identity of the starting material (NMR, IR, MS, etc.)**
- **Impurity profile**
- **Detailed discussion of any impurities carried forward in the manufacturing process**
- **Controls and analytical methods to separate and measure appropriate impurities**
- **Detailed discussion on purging studies using impurities to demonstrate the ability of the manufacturing process to remove and control the impurities to desired levels**
- **Change of control strategies for any potential revisions to the manufacture of the proposed starting materials including vendor reporting of any changes in starting material specification or control**
- **Supportive literature data, if available**

Each of the proposed starting materials is available from several vendors. You should provide data to ensure that starting materials from different vendors do not result in different impurity profiles in the drug substance.

We will consider (b) (4) **.**

We also recommend that an identity test be added to the (b) (4) **specification.**

Meeting Discussion:
No discussion.

Question 7:
Does the Agency agree that the drug product specification is appropriate to support initiation of phase 3?

FDA Response:
We agree that the drug product specification presented in table 12-5 is acceptable to support initiation of the proposed phase 3 clinical studies in that there are tests, methods and criteria to establish identity, purity and assay.

We understand that the tests, analytical methods and acceptance criteria in this specification, as well as the drug product manufacturing process are still under development. To support the proposed acceptance criteria, you should amend your IND with a more detailed description of the manufacturing process (especially the lyophilization sequence) and in-process controls. The analytical method for reconstitution time should reflect the procedure used by the pharmacist and clearly describe the endpoint for complete dissolution.

Meeting Discussion:
The Sponsor stated that they will provide additional information regarding the lyophilization process and the method for reconstitution.

Question 8:
Does the Agency agree that the proposed stability programs for drug substance and drug product are adequate to support marketing approval?

FDA Response:

Drug Substance
You stated that a stability program has been initiated based on ICH guidelines.

ICH Q1A (R2) recommends that 12 months of stability data on at least three primary batches manufactured at a minimum of pilot scale, stored at the long term condition packaged in the same container closure system to be used for long term storage should be included in the initial NDA submission. The application should also include six months of data on samples of the same primary batches stored under the accelerated storage condition.

The Agency agrees in general with the proposed stability program for the drug substance as outlined in Table 12-6 provided that all stability batches are manufactured by the same synthetic route and manufacturing process to be used for commercial batches, and that the batches are packaged to simulate the packaging proposed for storage and distribution.

Batch GF406666 was (b) (4) **and may not reflect the stability behavior of samples stored** (b) (4) **. Stability data from batch GF406666 will be considered as supportive.**

Drug Product

The stability program presented in table 12-8 is not adequate to support approval of an NDA in that there are no commitments to a specific manufacturing site or manufacturing process, and the release specifications are still under development. The listed storage conditions and sampling sites appear to be acceptable to obtain data in support of a shelf life for the clinical drug product with storage in the described packaging system at 2-8^{o}C. We recommend that the protocol in table 12-8 be amended to include testing for Sterility at 24 months; and that profiles of impurities/degradants observed at or above the limit of quantitation for the analytical method be reported at each sampling site. The drug product protocol should also be revised to include detailed in-use stability studies which reflect the current drug product, reconstitution solvents, admixture solvents, and administration set materials.

Once the commercial product, manufacturing process and specification are finalized, you should submit a proposal for specification and stability protocol as an amendment to the IND with a request for comment.

Meeting Discussion:

No discussion.

Additional Comments

Clinical Pharmacology

In the full protocol for trial OP-103:

- **Include sparse pharmacokinetic (PK) sampling for melflufen and melphalan during at least two treatment cycles, to enable population PK and exploratory exposure-response (E-R) analyses. Also refer to the following two comments.**
- **Include a plan for exploration of the E-R relationships for melflufen and melphalan for measures of pharmacodynamic markers, effectiveness and toxicity. Refer to the FDA Guidance for Industry entitled "*Exposure-Response Relationships – Study Design, Data Analysis and Regulatory Applications*" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf.**
- **Include a plan for evaluation of the effect of intrinsic and extrinsic factors on the PK of melflufen and melphalan. Refer to the FDA Guidance for Industry entitled "*Population Pharmacokinetics*" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf.**

Meeting Discussion:

The Sponsor proposed to collect pharmacokinetic (PK) samples from about 150 patients using optimal sparse sampling during two cycles. The Agency stated that this proposal appears reasonable.

The Sponsor proposes to conduct population PK analysis using their PK data and compare the PK parameters to historical data available for melphalan. The Agency stated that this proposal appears reasonable.

The Sponsor asked the Agency questions regarding the conduct of the recommended exposure-response analyses for safety and efficacy. The Agency provided general advice for these analyses. The Sponsor asked if it would be possible to submit a detailed plan for these analyses for the Agency's review and the Agency agreed.

3.0 OTHER IMPORTANT MEETING INFORMATION

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.

DATA STANDARDS FOR STUDIES

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

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data*
(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide)
(See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17,

2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

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

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

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

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.

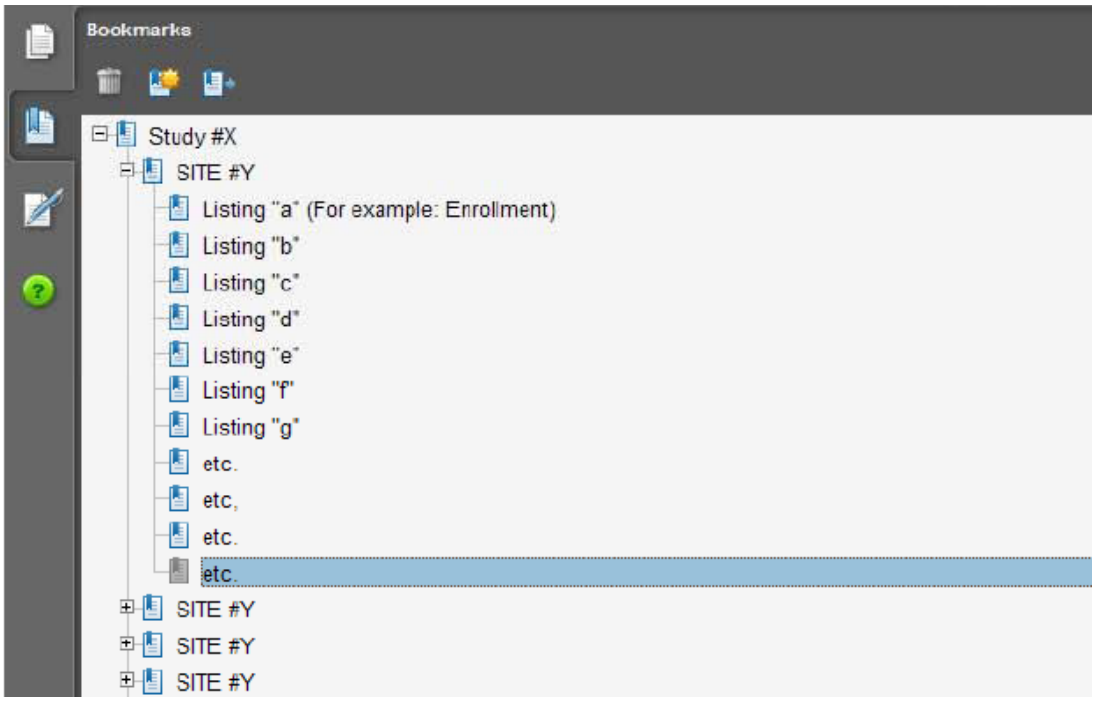
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

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.

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 were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items for this meeting.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor presentation used during the meeting has been appended to the meeting minutes.

8 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

NICOLE J GORMLEY
06/20/2016