CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216059Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 139876

MEETING MINUTES

Loxo Oncology, Inc.
Attention: Lars Holzhausen, PhD
Director, Regulatory Affairs
701 Gateway Blvd., Suite 420
South San Francisco, CA 94080

Dear Dr. Holzhausen:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for pirtobrutinib (LOXO-305).

We also refer to the teleconference between representatives of your firm and the FDA on October 18, 2021. The purpose of the meeting was to discuss the clinical efficacy and safety data to support the NDA submission of pirtobrutinib for treatment of mantel cell lymphoma and chronic lymphocytic leukemia or small lymphocytic lymphoma.

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, please contact me via email at denise.felluca@fda.hhs.gov or at 301-796-4574.

Sincerely,

{See appended electronic signature page}

Nicholas Richardson, DO, MPH
Clinical Team Leader
Division of Hematologic Malignancies II
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: October 18, 2021; 4:00 PM - 5:00 PM (ET)
Meeting Location: Teleconference

Application Number: IND 139876
Product Name: Pirtobrutinib (LOXO-305).
Indication: For the treatment of adult patients with mantle cell lymphoma (MCL) who have previously been treated with a BTK inhibitor

(b) (4)

Sponsor Name: Loxo Oncology Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Nicholas Richardson, DO, MPH
Meeting Recorder: Denise Felluca, PharmD, MBA

FDA ATTENDEES

Office of Oncologic Diseases (OOD)
Marc R. Theoret, MD – Supervisory Associate Director (Acting):

OOD/ Division of Hematologic Malignancies II
Nicole Gormley, MD – Director
Nicholas Richardson, DO, MPH – Clinical Team Leader
Pamela Seam, MD – Clinical Reviewer

OOD/ Division of Hematology, Oncology, Toxicology
Brenda Gehrke, PhD – Supervisory Pharmacologist/Toxicologist
Shwu-Luan Lee, PhD – Pharmacology/Toxicology Reviewer

Office of Biostatistics/ Division of Biometrics IX
Qing Xu, PhD – Statistical Team Lead
Kun Wang, PhD – Statistical Reviewer

Office of New Drug Product/ Division of New Drug Products I
Yang Nan, PhD – Team Leader
Paresma Patel, PhD – Product Quality Reviewer

Office of Clinical Pharmacology (OCP)/ Division of Cancer Pharmacology I
Vicky Hsu Xia, PhD – Team Leader (Acting)
Yue Xiang, PhD – Reviewer

Office of New Drugs/ Division of Safety
Felicia Diggs, BSN, MSN, RN – Safety Regulatory Project Manager

Office of Regulatory Operations/ Division of Regulatory Operations for Oncologic Diseases
Theresa Carioti, MPH – Chief, Project Management Staff
Denise Felluca, PharmD, MBA – Regulatory Health Project Manager

SPONSOR ATTENDEES

Jacob Van Naarden, Chief Executive Officer
Nisha Nanda, Chief Development Officer
David Hyman, MD, Chief Medical Officer
Nora Ku, MD, Vice President, Medical
Jennifer Kherani, MD, Head, Medical
Paolo Abada, MD, Senior Medical Director
Philip Johnson, MBA, Vice President, Regulatory Affairs
Katie Cairati, MS, Head, Regulatory Affairs
Lars Holzhausen, PhD, Director, Regulatory Affairs
Jennifer Keuhne-Willmore, PhD, Research Advisor, Global Regulatory Affairs
Richard Walgren, MD, PhD, Product Team Late Phase Development
Ming Yin, PhD, Executive Director, Biostatistics
Denise Wang, PhD, Vice President, Biostatistics
Maja Miloslavsky, PhD, Vice President, Biostatistics
Edward Zhu, PhD, Senior Director, Clinical Science
Binoj Nair, PhD, Director, Clinical Sciences
Kate Hillgren, Research Fellow, Drug Disposition
Sonya Chapman, Senior Research Scientist, Global PK/PD and Pharmacometrics
(b) (4) External Consultant, (b) (4)

1.0 BACKGROUND

Pirtobrutinib is an orally available, selective ATP-competitive small molecule inhibitor of the Bruton's tyrosine kinase (BTK). The purpose of the meeting is to discuss the safety and efficacy analyses from the Study 18001 (LOXO-BTK-18001, BRUIN) entitled "*A Phase 1/2 Study of Oral LOXO-305 in Patients with Previously Treated Chronic*

Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) or Non-Hodgkin Lymphoma (NHL) (NCT03740529) (BRUIN)" and to seek FDA feedback regarding the pirtobrutinib New Drug Application (NDA) submission.

2.0 DISCUSSION

Question 1: *Does the Agency agree that the PAS data are sufficient to form the basis for an NDA for pirtobrutinib in the indication stated above? (indication: For the treatment of adult patients with MCL who have previously been treated with a BTK inhibitor)*

FDA Response to Question 1:
No. At the time of NDA submission, it is expected that the efficacy data be robust and complete, including sufficient follow-up for duration of response. Data from a single-arm trial in 65 patients with MCL is inadequate to support a comprehensive assessment of efficacy and safety in the intended MCL population. We strongly recommend delaying submission of the NDA until there is sufficient follow-up in the PAS and SAS1 population in order to provide a robust data package in a sufficient number of patients. Additionally, the Agency recommends that all responders have a minimum follow-up of 9-12 months to adequately assess duration of response.

You have indicated that the intention-to-treat principle may be applied to patients enrolled in Phase I or Phase 2 portions of the study. We reiterate that if there is significant heterogeneity between Phase I and Phase 2 cohorts, this may impact the interpretability of results. Potential heterogeneity could create biased results. Provide the final version of the statistical analysis plan (SAP) for MCL indication. Ultimately, this will be a review issue.

Discussion:
The Agency stated that a NDA application for pirtobrutinib for patients with relapsed or refractory MCL from 65 patients is insufficient. The Agency stated that the initial NDA should include a sufficient number of patients previously treated with a BTK inhibitor meeting the PAS criteria. In the total population, responders should have at least 9 months of follow-up for duration of response, starting at the time of objective response. The Agency stated that efficacy data should be complete and robust at the time of NDA submission. Submission of a NDA application with a limited sample size or inadequate follow-up may constitute an incomplete application and may be considered a filing issue. The Agency recommended delaying submission of a NDA until there is an increased sample size and sufficient follow-up in the total PAS population. Additionally, the Agency noted that submission of updated efficacy data at the time of a NDA safety update is not recommended. If efficacy data were to be submitted during the NDA review, the data could be considered a major amendment, which impacts the PDUFA review timeline. The Agency recommended the Sponsor submit an updated timeline with the

proposed data package to be submitted with an initial application, which could include a submission for a rolling review.

Question 2: *Does the Agency agree that the DTAS data are sufficient to form the basis for an NDA for pirtobrutinib in the indication stated above? (Indication:* (b) (4)

FDA Response to Question 2:

No. (b) (4)

Discussion:

(b) (4)

Question 3: *Does the Agency agree that the safety database from Study 18001 and the planned analyses as indicated in the SCS Statistical Analysis Plan (submitted to IND 139876 as Serial 0215) are adequate to support the review of safety for pirtobrutinib?*

FDA Response to Question 3:

The pirtobrutinib safety database may be reasonable as 118 patients and 248 patients with relapsed or refractory MCL and CLL/SLL, respectively, have received the intended pirtobrutinib dose for registration. It is unclear what the exposure duration is for the safety population. Adequate exposure is necessary to support a comprehensive evaluation of safety and tolerability. Additionally, BTK inhibitors as a

class have been associated with several cardiac toxicities, therefore we recommend a broad approach to evaluating the incidence of cardiac toxicity with pirtobrutinib versus focusing on atrial fibrillation.

Discussion: No discussion occurred.

Question 4: *As per ICH E3, the Sponsor will prepare safety narratives for patients with deaths, SAEs, and AEs leading to discontinuations of study drug and provide full Case Report Forms (CRFs) for all patients meeting these criteria in the NDA. The Sponsor does not plan to provide additional CRFs. Does the Agency agree with this proposal?*

FDA Response to Question 4:
The proposed approach for safety narrative preparation and CRFs is reasonable.

Discussion: No discussion occurred.

Question 5: *The Sponsor will prepare SDTM datasets, ADaM datasets, program files for the analysis ADaM datasets, and program files for tables and figures as part of the clinical study report (CSR) for Study 18001. Does the Agency agree?*

FDA Response to Question 5:
Yes. Your proposal is acceptable. Additional requirement regarding SAS program include:

- The SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis should be included in the NDA submission. All programs should be thoroughly commented and have passed Sponsor's validation procedures.
- Ensure the SAS dataset file name are consistent with those in the SAS programs that call them and include all SAS macros, if included in the SAS programs, so that the Agency can run the programs smoothly to verify the results/figures/tables reported in the submission.
- Annotations for all efficacy and safety tables and figures should be included in the main text portion of the CSR. The annotations should indicate which analysis dataset variables and SAS program are used to produce the table or figure.

Discussion: No discussion occurred.

Question 6: *The Sponsor proposes the following plan for the NDA Safety Update:*

- to submit the NDA Safety Update at Day 120 as per 21 CFR 314.50
- to include an update of safety and efficacy in the Day 120 Update submission with data cut-off date of 15 December 2021 (about 5 additional months of follow-up compared to the initial NDA submission)
- to present these data as an addendum to the Assessment Aid

Does the Agency agree with this proposal?

FDA Response to Question 6:
In general, the safety update should include 4 months of additional follow-up. As outlined, the proposed approach to the NDA Safety Update is reasonable.

Discussion: No discussion occurred.

Question 7: *Should pirtobrutinib receive accelerated approval under 21 CFR 314.500, subpart H, a conversion strategy would be required. The Sponsor proposes* (b) (4)

FDA Response to Question 7:
For MCL, refer to response to Question 1. (b) (4)

(b) (4)

Discussion: No discussion occurred.

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

FDA Response to Question 8:
No, it is the Agency's expectation that the NDA submission should be complete at the time of Original NDA submission. Submission of data during the review cycle should be avoided and is subject to extension of the PDUFA clock. (b) (4)

Discussion: No discussion occurred.

Post-meeting Comment:
The Agency cannot agree [redacted] (b) (4)

Question 9: *Does the Agency agree that in addition to the drug substance and drug product stability data, and drug substance validation batch data, may be provided within 30 days of the initial submission without impacting the review cycle timing?*

FDA Response to Question 9:
Yes, in line with the prior EOP1-CMC only meeting, your proposal to submit additional drug substance and drug product stability data and batch release data from drug substance validation batches within 30 days of the initial submission appears acceptable.

Discussion: No discussion occurred.

Question 10: *Does the Agency recommend that the Sponsor provide an Assessment Aid with the NDA? If the Agency recommends the submission of an Assessment Aid, the Sponsor proposes to provide the Assessment Aid within 30 days of the initial NDA filing. Does the Agency agree to this proposal?*

FDA Response to Question 10:
This question is premature at this time given that the proposed data to be submitted in an NDA is inadequate to support a comprehensive evaluation of efficacy and safety in the intended populations (see responses to Question 1 and 2). However, at the time of a NDA submission, we would recommend use of an Assessment Aid. The submission of an Assessment Aid should occur at the time of NDA submission or within 30 days of NDA submission.

Discussion: No discussion occurred.

Additional Comments:

Chemistry

Include tests and acceptance criteria for microbiological attributes in the drug product specifications per USP<61> and USP<62>.

Clinical Pharmacology

Address the following questions in the Summary of Clinical Pharmacology:

1. 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.
2. What are the exposure-response relationships for efficacy, safety and biomarkers?
3. What is the effect of pirtobrutinib on the QT/QTc interval?
4. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion) of pirtobrutinib?
5. What are the effects of food on the pirtobrutinib's bioavailability? What are the dosing recommendations with regard to meals or meal types? Provide justification for recommendation with regard to meals or meal types.
6. 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:

The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application should 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://www.fda.gov/media/74346/download). 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.

1. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
2. 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.
3. 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.
    a. 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.

b. Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.

4. Submit the following for the population pharmacokinetic analysis reports:
   a. Standard model diagnostic plots
   b. Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
   c. Model parameter names and units in tables.
   d. Summary of the report describing the clinical application of modeling results.
5. Refer to the following pharmacometric data and models submission guidelines http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.
6. Submit the following information and data to support the population pharmacokinetic analysis:
   a. SAS transport files (*.xpt) for all datasets used for model development and validation
   b. 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
   c. 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). Submit these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)
7. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and safety) relationships in the targeted patient population. Refer to Guidance for Industry for population PK, and exposure-response relationships,
8. Use the laboratory analysis dataset (adlb.xpt) for the laboratory-based adverse reactions and the adverse event analysis dataset (adae.xpt) for the non-laboratory-based adverse reactions (individual and pooled terms as appropriate) to evaluate the exposure-response relationship for safety and the effect of intrinsic and extrinsic factors on safety based on the maximum toxicity grade compared to baseline.
9. Include a variable that identifies the maximum toxicity grade compared to baseline for laboratory-based adverse reactions in laboratory analysis dataset (adlb.xpt) and for non-laboratory-based adverse reactions (individual or pooled where applicable) in adverse event analysis dataset (adae.xpt) to support these analyses. A description of the pooled non-laboratory-based adverse reactions should be provided in the reviewer guide and consistent with common pooled terms used to inform labeling if applicable.

10. Include the following items when you submit your QT study report:
    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
        i. Narrative summaries and case report forms for any:
        ii. Deaths
        iii. Serious adverse events
        iv. Episodes of ventricular tachycardia or fibrillation
        v. Episodes of syncope
        vi. Episodes of seizure
        vii. Adverse events resulting in the subject discontinuing from the study
        viii. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
        ix. 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 http://cardiac-safety.org/ecg-database/.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed and are expected to be complete upon submission

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

  - Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. 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.[2]

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 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 the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, 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]

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

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.

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.

[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

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. 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)				

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

Corresponding names and titles of onsite contact:

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

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[8] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[9]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

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,* and the associated conformance guide, *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.*[10]

[8] https://www.fda.gov/media/84223/download
[9] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[10] 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[11]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid[12]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor's responses will be appended.

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

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/s/

NICHOLAS C RICHARDSON
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