CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216993Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 074552

MEETING MINUTES

Daiichi Sankyo, Inc.
Attention: Kristy Burns, PhD
Associate Director, Global Regulatory Affairs
211 Mount Airy Road
Basking Ridge, NJ 07920-2311

Dear Dr. Burns:[1]

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

We also refer to the telecon between representatives of your firm and the FDA on March 24, 2022. The purpose of the meeting was to discuss the content and format of a planned NDA submission.

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, contact Sheila Ryan, PharmD, MPH, RAC, Senior Regulatory Health Project Manager at (301) 796-2002 or sheila.ryan@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Kelly Norsworthy, MD
Clinical Team Leader
Division of Hematologic Malignancies I
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:	March 24, 2022, 4:00 PM – 5:00 PM EST
Meeting Location:	Teleconference
Application Number:	074552
Product Name:	quizartinib
Indication:	For use in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, and as continuation monotherapy following consolidation, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) who are FMS-like tyrosine kinase 3-internal tandem duplication (FLT3-ITD) positive as detected by a Food and Drug Administration (FDA)-approved test.
Sponsor Name:	Daiichi Sankyo, Inc. (DSI)
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair:	Kelly Norsworthy, MD
Meeting Recorder:	Sheila Ryan, PharmD

FDA ATTENDEES

Office of Oncologic Diseases (OOD)/Division of Hematologic Malignancies I
R. Angelo de Claro, MD, Division Director
Kelly Norsworthy, MD, Clinical Team Leader
Lori Ehrlich, MD, PhD, Clinical Team Leader
Joseph Wynne, MD, PhD, Clinical Reviewer
E. Dianne Pulte, MD, Clinical Reviewer

Office of Regulatory Operations/Division of Regulatory Operations for Oncologic Diseases/Hematologic Malignancies I
Amy Baird, Chief, Project Management Staff
Sheila Ryan, PharmD, MPH, RAC, Senior Regulatory Health Project Manager

OOD/Division of Hematology, Oncology, Toxicology
Brenda Gehrke, PhD, Nonclinical Supervisor
Shwu-Luan Lee, PhD, Nonclinical Reviewer

Office of Biostatistics/Division of Biometrics IX
Jonathon Vallejo, PhD, Acting Biometrics Team Leader
Haiyan Chen, PhD, Biometrics Reviewer

Office of Clinical Pharmacology/Division of Cancer Pharmacology I
Xiling Jiang, Acting Clinical Pharmacy Team Leader
Wentao Fu, Clinical Pharmacy Reviewer

Office of Pharmaceutical Quality (OPQ)/Office of New Drug Products I
Sherita McLamore, PhD, Product Quality Team Leader

Center for Device and Radiological Health/OHT7: Office of In Vitro Diagnostics/Division of Molecular Genetics and Pathology
Zivana Tezak, PhD, Chief, Molecular Genetics Branch
Weixin Wang, PhD, Biologist

Office of Surveillance and Epidemiology/Division of Risk Management
Ingrid Chapman, PharmD, Health Scientist

SPONSOR ATTENDEES

Daiichi-Sankyo, Inc.
Gilles Gallant, BPharm, PhD, Senior Vice President, Global Head, Oncology Development
Arnaud Lesegretain, MBA, Vice President, Global Oncology Clinical Development
James Hanyok, PharmD, Senior Director, Global Oncology Research and Development
Abdelaziz Benzohra, MD, Executive Director, Clinical Development
Yasser Mostafa Kamel, MD, Global Medical Monitor, QuANTUM-First Study
Natalie Cook, Associate Director, Clinical Operations
Eric Richards, MS, MPH, Senior Vice President, Regulatory Affairs
Naushad Islam, MS, RPh, Executive Director, Regulatory Affairs
Kristy Burns, PhD, Associate Director, Regulatory Affairs
Li-An Xu, PhD, Senior Director, Biostatistics
Li Liu, PhD, Director, Biostatistics
Jaime Rohrback, PhD, Associate Director, Global Companion Diagnostics Lead
Ming Zheng, PhD, Senior Director, Quantitative Clinical Pharmacology
Youngsook Choi, MD, Executive Director, Clinical Safety and Pharmacovigilance
Tsvetomir Mitov, MD, Director, Clinical Safety and Pharmacovigilance

1.0 BACKGROUND

Quizartinib (AC220) is an oral Class III receptor tyrosine kinase (RTK) inhibitor that is currently being studied as a treatment for AML. Clinical development of quizartinib (AC220) began in December 2009 by Ambi Biosciences. In September 2015, the IND

and sponsorship of the quizartinib clinical development program were transferred to Daiichi Sankyo, Inc (DSI).

DSI received a complete response letter (under NDA 212166) from FDA on June 19, 2021, for VANTLYA (quizartinib) for the treatment of adults with relapsed or refractory AML which FLT-ITD positive, as detected by an FDA-approved test.

The sponsor submitted a request fast track designation on February 16, 2022, for use of quizartinib in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, and as continuation monotherapy following consolidation, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) who are FMS-like tyrosine kinase 3-internal tandem duplication (FLT3-ITD) positive, as detected by an FDA approved test.

The purpose of this type B, Pre-NDA meeting is to share the results of the Phase 3 Study AC220-A-U302 (QuANTUM-First) with FDA and to discuss the proposed filing strategy and content of the planned Safety Update to support the proposed indication. The content/format of the NDA, Statistical Analysis Plan (SAP), Integrated Summary of Safety (ISS) SAP, Electronic Data Submission Plan, and Exposure-response Analysis Plan were agreed upon during the Type C Meeting between FDA and DSI on May 18, 2021.

FDA sent Preliminary Comments to DSI on March 22, 2022.

2.0 DISCUSSION

2.1. Clinical Efficacy and Safety

Question 1: *Does the Agency agree that the results of Study AC220-A-U302: A Phase 3, Double-blind, Placebo-controlled Study of Quizartinib Administered in Combination with Induction and Consolidation Chemotherapy, and Administered as Continuation Therapy in Subjects 18 to 75 Years Old with Newly Diagnosed FLT3-ITD (+) Acute Myeloid Leukemia (QuANTUM-First) are acceptable to support an NDA submission in the proposed indication?*

FDA Response to Question 1:
Yes. Study AC220-A-U-302 with reported topline results appears appropriate for NDA submission. However, whether the package is sufficient for review will be determined at filing.

Discussion:

None.

Question 2: *Does the Agency agree with the content of the proposed postsubmission Safety Update to the NDA with 90 days of the original submission?*

FDA Response to Question 2:
Yes. FDA agrees with the content and timing of the proposed safety update.

Discussion:

None.

2.2. Administrative

Question 3: *Does the Agency agree with the content of the Financial Disclosure Package?*

FDA Response to Question 3:
No. In addition to Forms 3454/3455 for financial certification and disclosure in Module 1.3.4, please submit the information in a spreadsheet (SAS transport file or xlxs file).

Discussion:

None.

Question 4: *Does the Agency agree with the Sponsor's plans to participate in the Assessment Aid Program?*

FDA Response to Question 4:
Yes. Your plan to participate in the OCE's Assessment Aid Program is acceptable.

In addition, the Agency recommends the Sponsor to consider Project Orbis for the submission of the proposed application. The Sponsor will need to submit a global submission plan for the proposed Project Orbis countries. Current Project Orbis countries include Australia, Brazil, Canada, Israel, Singapore, Switzerland, and the United Kingdom.

We also encourage the use of the Product Quality Assessment Aid (PQAA) to facilitate the review of the application under Project Orbis or Real-Time Oncology Review. We can send you the template for the PQAA.

Discussion:

None.

Question 5a: *Does the Agency agree with the proposed comprehensive table of contents for the NDA with regards to Modules 1, 2, 3, 4, and 5 will constitute a complete application for filing?*

FDA Response to Question 5a:
All sections proposed in the eCTD-IND Table of Contents appear to be acceptable. From a technical perspective, please refer to the Comprehensive Table of Contents Headings and Hierarchy for more details.

Please ensure that you also include protocols and amendments for all studies. The adequacy of the data for filing will be determined following our review of your NDA submission.

Discussion:

None.

Question 5b: *The sponsor would like to propose a rolling submission of completed non-clinical and CMC modules which have been previously reviewed in NDA 212166. Does the Agency agree with the Sponsor's plan to propose a rolling submission for Modules 3 and 4 followed by Modules 1, 2, and 5?*

FDA Response to Question 5b:
Yes, we agree with the proposed plan for a rolling submission for Modules 3 and 4; however, upon receiving Fast Track Designation, a formal request of rolling review should be submitted.

Alternatively, you can propose a submission plan under the Real-Time Oncology Review (RTOR) program.

Discussion:

None.

Question 6: *Daiichi Sankyo as the Sponsor of the NDA has partnered with Invivoscribe, Inc. (IVS), San Diego, CA, to develop a companion diagnostic as an aid in the identification of patients with FLT3-ITD mutations for whom quizartinib is being considered. IVS intends to submit a supplemental premarket approval (sPMA) for the LeukoStrat® CDx FLT3 Mutation Assay within 30 days of the NDA submission. Does the Agency agree that this could support contemporaneous approval of the NDA and sPMA?*

FDA Response to Question 6:
If it is determined that a companion diagnostic (CDx) is essential for the safe and effective use of quizartinib, a PMA supplement intended to expand the LeukoStrat®

CDx FLT3 Mutation Assay's indication to include quizartinib is needed, we do not object to IVS' plan to submit their PMA supplement within 30 days of the NDA submission to support contemporaneous approval of the NDA and sPMA.

To support a successful bridging study, to demonstrate the safety and effectiveness of the intended CDx assay and maintenance of drug efficacy, it is recommended that the Daiichi Sankyo work to obtain a high sample ascertainment rate by having a robust plan for banking, retrieval, and retesting of all specimens that were screened in the trial. As part of the proposed bridging study, IVS should plan to retest all marker-positive samples that were enrolled in the trial and a random subset of marker negative samples in the bridging study and account for missing samples as part of the planned sensitivity analysis.

CDRH is accepting pre-submissions for devices intended as a CDx for written feedback. Therefore, if IVS wishes to discuss their proposed bridging study, they should submit a pre-submission to CDRH for written feedback.

Discussion:

None.

Additional clinical comments:

1. Include narrative summaries of important AEs from study AC220-A-U302 (e.g., events leading to death, events leading to discontinuation, other SAEs, and AESIs) in your NDA submission. Narratives should provide the detail necessary to permit an adequate understanding of the nature of the adverse event experienced by the study subject. Narrative summaries should not merely provide, in text format, the data that are already presented in the case report tabulation, as this adds little value. A valuable narrative summary would provide a complete synthesis of all available clinical data and an informed discussion of the case, allowing a better understanding of what the patient experienced. The following is a list of components that would be found in a useful narrative summary:

    - Patient age and gender
    - Signs and symptoms related to the AE being discussed
    - An assessment of the relationship of exposure duration to the development of the AE
    - Pertinent medical history
    - Concomitant medications with start dates relative to the AE
    - Pertinent physical exam findings
    - Pertinent test results (e.g., lab data, ECG data, biopsy data)
    - Discussion of the diagnosis as supported by available clinical data
    - For events without a definitive diagnosis, a list of the differential diagnoses

- Treatment provided
- Re-challenge results (if performed)
- Outcomes and follow-up information.

2. Please provide the following information on differentiation syndrome (DS) for patients with AML treated with quizartinib on Study AC220-A-U302:

   a) Include narratives for all cases of DS.

   b) Provide a DS dataset for all cases of DS or suspected DS using an algorithmic approach based on the Montesinos et al scoring system (Blood 2009; see also Norsworthy et al, Clin Cancer Res, 2020) (i.e. 2 or more of each sign/symptom), in addition to using "acute promyelocytic leukemia differentiation syndrome" alone:

      a. Include all patients with investigator-reported DS.

      b. Identify additional subjects meeting ≥ 2 of the criteria in the table below. (You may add additional PTs to the different categories if applicable treatment-emergent adverse events were reported that are not already listed.)

      c. Use events only occurring within the first 90 days of therapy.

      d. At least 2 criteria should have a start date within 7 days.

      e. The DS data file should include at least the following information for all cases of DS or suspected DS based on the algorithmic approach: study identification number, site identification number, unique subject number, treatment arm, demographic information, date of start of study drug, criterion in the table below met, maximum grade of the criterion, date of occurrence of the criterion, time from start of treatment for the criterion, whether the study drug was held in response to the criterion, date study drug held, date study drug resumed, sponsor's conclusion regarding whether the patient had DS, and alternative etiology if applicable (e.g. infection, etc.), date of start of DS, and date of end of DS.

         i. Include a column to denote repeat cases (i.e. 1, 2, 3, etc.) of DS when subsequent cases are separated by > 14 days.

         ii. Add a column for presence of concomitant leukocytosis (Y/N), defined using PTs Leukocytosis, Hyperleukocytosis, or White blood cell count increased, or laboratory results showing

leukocyte count > 10 Gi/L within 7 days before or after clinical signs/symptoms.

f. For any cases that fulfilled ≥ 2 criteria from the table below that were not already designated as DS, provide a narrative explanation for each case, including your rationale for why the events were either possibly or unlikely related to DS.

Criteria (Montesinos sign/symptom)	Variable	Value
≥ 1 of these (pulmonary infiltrates or pleuropericardial effusion)	PT	Acute pulmonary oedema
	PT	Acute respiratory distress syndrome
	PT	Non-cardiogenic pulmonary edema
	PT	Pulmonary congestion
	PT	Pulmonary oedema
	PT	Pleural effusion
	PT	Pericardial effusion
	PT	Acute interstitial pneumonitis
	PT	Acute lung injury
	PT	Atypical pneumonia
	PT	Lower respiratory tract infection
	PT	Lower respiratory tract inflammation
	PT	Lung infection
	PT	Lung infiltration
	PT	Pneumonia
	PT	Pneumonitis
	PT	Pulmonary toxicity
≥ 1 of these (fever)	PT	Pyrexia
	PT	Febrile neutropenia
	VS result	Temperature *(any value ≥ 38.3)*
≥ 1 of these (weight gain > 5 kg)	PT	Capillary leak syndrome
	PT	Fluid overload
	PT	Fluid retention
	PT	Generalized oedema
	PT	Hydraemia
	PT	Hypervolaemia
	PT	Oedema
	PT	Oedema peripheral
	VS result	Weight (*any value > 5 kg from baseline)*
≥ 1 of these (hypotension)	PT	Hypotension
	VS result	Systolic Blood Pressure *(any value < 90 mmHg)*
≥ 1 of these (dyspnea)	PT	Acute respiratory failure
	PT	Cardiopulmonary failure
	PT	Cardio-respiratory distress
	PT	Cough
	PT	Dyspnoea

	PT	Respiratory arrest
	PT	Respiratory distress
	PT	Respiratory failure
≥ 1 of these (acute renal failure)	PT	Acute kidney injury
	PT	Anuria
	PT	Cardiorenal syndrome
	PT	Hepatorenal failure
	PT	Prerenal failure
	PT	Renal failure
	PT	Renal failure acute
	PT	Renal impairment
	PT	Renal injury
	Lab result	Creatinine (*any value > 26.52 µmol/L or 1.5x above baseline)*
("catch-all")	PT	Multi-organ dysfunction syndrome

3.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed:

  The Agency was able to agree with the Clinical, Statistical, Clinical Pharmacology, Non-clinical and Product Quality components of the NDA 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.

- 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 the final determination for the need for a REMS will be made during the NDA review. However, the clinical review division recommends submission of the communication-type REMS materials with the original submission to facilitate the review of this application. The REMS with communication plan should inform prescribers of the cardiac toxicities of quizartinib including risks of concomitant use of drugs with QTc prolonging effect

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

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]

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:

[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
[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

- 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.

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.

MANUFACTURING FACILITIES

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

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

Consider using a table similar to the one below as an attachment to Form FDA 356h.

Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

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

Corresponding names and titles of onsite contact:

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

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[6] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[7]. 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

[6] https://www.fda.gov/media/84223/download
[7] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

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]

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.

- Assessment Aid[10]

GENERALIZABILITY OF CLINICAL TRIAL DATA TO THE US POPULATION

An application based solely or in large part on foreign clinical data may be approved if the foreign data is applicable to the U.S. population and U.S. medical practice, the studies have been performed by investigators of recognized competence, and FDA can validate data through on-site inspections if deemed necessary.

You will be expected to address the applicability of your data to a U.S. population, including racial and ethnic minorities and standards of care in the U.S. FDA generally accomplishes this by comparing data from subgroups of patients treated in the U.S. to those treated in other regions of the world.

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

This will be a potential filing and/or approvability issue and should be addressed prior to submission of an application.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

The sponsor provided the attached responses to FDA's preliminary comments.

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

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/s/

KELLY J NORSWORTHY
03/30/2022 09:27:28 AM