

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211349Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 117548

MEETING MINUTES

Astellas Pharma Global Development, Inc.
Attention: Tim Farber
Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Mr. Farber:

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

We also refer to the meeting between representatives of your firm and the FDA on December 5, 2017. The purpose of the meeting was to discuss the content and submission plan to support a New Drug Application (NDA) for gilteritinib or the treatment of adult patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) with FMS-like tyrosine kinase 3 (FLT3) mutation.

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 Rosa Lee-Alonzo, Regulatory Project Manager, at (301) 348-3004.

Sincerely,

{See appended electronic signature page}

Donna Przepiorka, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



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

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: December 5, 2017; 2:00 – 3:00 PM EST
Meeting Location: White Oak Building 22, Room 1315

Application Number: IND 117548
Product Name: gilteritinib
Indication: Relapsed/refractory FLT3 mutated acute myeloid leukemia (AML)
Sponsor/Applicant Name: Astellas Pharma Global Development, Inc.

Meeting Chair: Donna Przepiorka
Meeting Recorder: Rosa Lee-Alonzo

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products

Albert Deisseroth, MD, PhD, Supervisory Associate Division Director
Donna Przepiorka, MD, PhD, Clinical Team Leader
Kelly Norsworthy, MD, Medical Officer
Rosa Lee-Alonzo, PharmD, Regulatory Project Manager

OHOP/Division of Hematology Oncology Toxicology

Ramadevi Gudi, PhD, Nonclinical Reviewer (on phone)

Office of Clinical Pharmacology/Division of Clinical Pharmacology V

Ruby Leong, PharmD, Clinical Pharmacology Team Leader
Vicky Hsu, PhD, Clinical Pharmacology Reviewer

Office of Biostatistics/Division of Biometrics V

Yuan-Li Shen, DrPh, Biostatistics Team Leader
Qing Xu, PhD, Biostatistics Reviewer

Center for Devices and Radiological Health (CDRH)

Allen Williams, PhD, Scientific Reviewer

SPONSOR ATTENDEES

Astellas Attendees

Erkut Bahceci, MD, Executive Medical Director, Medical Science

Steven Benner, MD, Senior Vice President, Oncology Therapeutic Area Head
Jana Cummings, Director, Global Project Management Lead
Timothy Farber, Director, Regulatory Affairs
Jason Hill, PhD, Director, Oncology Biomarkers
Angela James, PhD, Director, Clinical Pharmacology & Exploratory Development Science
Rumi Takeshita, MSc, Manager, Regulatory Affairs
Chaofeng (Charles) Liu, PhD, MBA, Director, Biostatistics
Itsuro Nagase, DVM, PhD, Senior Director, Global Development Project Leader
Mare Nishiura, Associate Director, Product & Project Management, Chemistry, Manufacturing and Controls
Donald Raineri, PharmD, Vice President, Regulatory Affairs

1.0 BACKGROUND

Gilteritinib (ASP2215) is a multikinase inhibitor in development for the treatment of relapsed or refractory acute myeloid leukemia (AML) for patients with a FLT3 mutation. Advice regarding an accelerated approval pathway for gilteritinib was provided in a Type C WRO on February 14, 2017 and at a Type C meeting on May 31, 2017. Astellas requested this Type B Pre-NDA meeting to discuss the content and submission plan for an NDA for gilteritinib for treatment of patients with relapsed or refractory AML having a FLT3 mutation.

FDA sent Preliminary Comments to Astellas on November 24, 2017.

2. DISCUSSION

Preamble: The Sponsor confirmed that they still plan to submit a complete New Drug Application (NDA) in March 2018.

2.1. Quality (Chemistry, Manufacturing, and Controls)

Question 1: *Does the Agency agree with the proposal to submit 1 executed batch record?*

FDA Response to Question 1:

Yes, the proposal is acceptable. Please ensure the submitted executed batch record is from a bioavailability or bioequivalence study or a primary stability study. Additional information may be requested during review of the NDA.

Meeting Discussion: There was no discussion.

2.2. Nonclinical

Question 2: *Does the Agency agree that the nonclinical pharmacology, pharmacokinetics and toxicology studies are adequate to support the filing and review of the NDA for gilteritinib in the proposed indication?*

FDA Response to Question 2:

The completed nonclinical studies appear adequate to support the filing and review of the NDA for gilteritinib in the proposed indication. Any final decisions on the sufficiency of the nonclinical package will be a review issue.

Meeting Discussion: There was no discussion.

2.3. Clinical

Question 3: *Does the Agency agree that the CR/CRh result from the phase 3 study (2215-CL-0301) is adequate to support submission and review of gilteritinib in the proposed indication as discussed at the Type C meeting held on May 31, 2017?*

FDA Response to Question 3:

We agree that CR/CRh may be an appropriate endpoint to assess clinical benefit for a treatment of patients with AML without curative intent, but additional information about transfusion independence and corroborating results from other protocols would improve the strength of evidence. Please clarify whether you will be submitting the CR/CRh assessment from the control arm of Study 2215-CL-0301. Whether the application submitted is adequate for review will be determined at filing.

Meeting Discussion:

The Sponsor indicated that the control arm CR/CRh was not available except through the independent statistician. The Agency requested that the control arm CRh be submitted for review in some form. The Sponsor agrees to submit via email in a password-protected file.

Question 4: *Does the Agency agree with the strategy for the ISE analyses, as well as the proposed presentation of these data within the eCTD?*

FDA Response to Question 4:

No, we do not agree. Please note the following comments:

- a. You should include your assessment of efficacy for all AML protocols, including Study 2215-CL-0103 (b) (4)

Meeting Discussion:

The Sponsor indicated that they would not have efficacy data from the two maintenance trials, 0201 or the expanded access protocol, and the Agency indicated that the justification was adequate. In addition, for 0103 (b) (4) the efficacy would simply be summarized in the SCE.

- b. Your primary analyses should follow the SAP for each protocol.

Meeting Discussion:

The Sponsor clarified that CRh was not prespecified in 0102, 0103 (b) (4) The Agency accepted that CRh would not be analyzed in these protocols.

- c. For the pooled RAS analysis, we recommend inclusion of all FLT3 mutation positive patients who received at least 1 dose of gilteritinib at the 120 mg dose level from Study 2215-CL-0101, not only those in the Full Analysis Set (who must have had at least 1 post-treatment data point).
- d. It is acceptable to use the SCE in lieu of the ISE. Please ensure, however, that the entire Clinical Summary (Modules 2.7.1 to 2.7.4) does not exceed the 400 page limit. Your submission of the SCE should follow Example 4 in the ISE/ISS guidance identified below with the SCE text in Module 2.7.4 and a mapping document, appendices and the integrated efficacy data set in Module 5.3.5.3.

The ISE/ISS Guidance is available at:

<https://www.fda.gov/downloads/drugs/guidances/ucm136174.pdf>

- e. Provide an analysis of efficacy by dose of gilteritinib in FLT3 mutation positive patients, including whether dose reductions to 80 mg or dose escalations to 200 mg affected efficacy.
- f. Please include an integrated time-to-event data file for all subjects with AML with at least the following information: study identification number, site identification number, unique subject number, treatment arm, stratification factors, prognostic factors, mutation status (local and central) at baseline, demographic information, date of randomization, date of start of study drug, best response, date of best response, date of CR, date of CR+CRh, date of relapse, date of transplantation if performed after study therapy, date of death, date of last contact, status at last contact (alive, dead or lost), proximate cause of death, and root cause of death as determined by the sponsor (e.g. active AML, treatment-related, intercurrent illness, etc.). Provide the simple and all-containing "Statistical Efficacy Analysis Data Set" in SAS transport format.
- g. In the assessment of transfusion independence, include all patients in the RAS in the denominator. Patients who withdrew early should be considered failures.
- h. Please include a transfusion analysis data file with at least the following information: study identification number, site identification number, unique subject number, treatment arm, demographic information, stratification factors, prognostic factors, mutation status at baseline, date of start of study drug, RBC transfusion dependence at baseline (Y/N), platelet transfusion dependence at baseline (Y/N), transfusion dependent of either RBC or platelets at baseline (Y/N), RBC transfusion independence (TI) for >56 days post-baseline (Y/N), platelet TI for >56 days post-baseline (Y/N), RBC and platelet TI for >56 days post-baseline (Y/N), date of start of RBC TI, date of end of RBC TI, date of start of platelet TI, date of end of platelet TI, date of start of RBC and platelet TI, date of end of RBC and platelet TI, time to RBC TI (time to the start of the ≥ 56 day TI period), time to

platelet TI, time to RBC and platelet TI, duration of RBC TI post-baseline, duration of platelet TI post-baseline, duration of RBC and platelet TI post-baseline, date of last contact, status at last contact (alive and TI, alive and transfusion dependent, dead or lost).

- i. Please clarify whether you can also provide in a separate file the dates of RBC transfusions post-baseline and the dates of platelet transfusions post-baseline for each patient.

Question 5: *Does the Agency agree with the strategy for the ISS analyses, as well as the proposed presentation of these data within the eCTD?*

FDA Response to Question 5:

(b) (4)

Given the number of studies to be included in this NDA, the application should include an ISS. The ISS is not a just an overview of the safety results in the pivotal and supporting clinical trials, but a detailed integrated review of all relevant safety data and analyses, including data from nonclinical studies, clinical pharmacology studies, studies in patients, and studies in healthy volunteers. The ISS should show the key results that contribute to the understanding of the safety of your drug, including analyses across studies, and should not simply reference the study reports. Your submission of the SCS and ISS should follow Example 1 in the ISE/ISS guidance with the SCS text in Module 2.7.4 and the ISS text, appendices and the integrated safety data set in Module 5.3.5.3.

Meeting Discussion: There was no discussion.

Question 6: *Does the Agency agree with the proposal for the safety update report?*

FDA Response to Question 6:

Your proposal to submit the safety update with a data cutoff of January 4, 2018 is acceptable if you follow your current submission plan.

Meeting Discussion: There was no discussion.

Question 7: *Does the Agency agree with the proposal for the narratives to be included in the NDA, and the proposal to submit CRFs only for patients with narratives in the integrated safety population?*

FDA Response to Question 7:

Yes, we agree.

Meeting Discussion: There was no discussion.

Question 8: *The Sponsors propose to submit Study Data Tabulation Model (SDTM) and derived Analysis Data Model (ADaM) statistical analysis system (SAS) datasets following Clinical Data Interchange Standards Consortium (CDISC) standards for key*

pharmacokinetic studies and completed phase 2 and phase 3 clinical studies supporting the gilteritinib NDA for the indication of R/R AML with FLT3 mutation.

Does the Agency agree with this proposal?

FDA Response to Question 8:

In general, your proposal is acceptable, but we have the following additional comments:

- a. For Study 2215-CL-0109, please provide safety data in the data set of the parent protocol(s), with a flag to indicate patients rolled over onto this study, along with the date of the transition.

Meeting Discussion:

The Sponsor indicated that only two patients from the solid tumor protocol have been enrolled in Study 0109, and they propose to provide only safety information. The Agency agreed.

- b. Data sets should have one and only one unique subject ID for each patient among all trials. If patients transition between protocols, the subject ID should not change.

Meeting Discussion:

The Sponsor clarified that there were several patients who were re-enrolled, and there is a flag in the data files to identify and exclude them from analyses, including the efficacy analysis. They will also ensure that the subgroup is clearly excluded in the SAS programs for the analyses. They will also clarify in the reviewer's guide how these patients are labeled in the data files.

- c. Each data file should contain a variable for study ID.
- d. The define.pdf file should contain the descriptions (how coded, which value stands for what) of variable names on SAS data sets. For a given quantity, the same variable name should be used for all datasets (i.e., one definition, well-annotated, per one variable)
- e. Include in the Reviewer's Guide an instruction for the use of variables and flags to identify the set of patients on which the primary analysis was performed.
- f. Provide the SAS programs (with adequate comments) used to create all ADaM datasets along with the tables and figures associated with primary and secondary efficacy analyses in order to help reviewers to better understand how the datasets, tables and figures were created. The main purpose of requesting the submission of these programs is to understand the process by which the variables for the respective analyses were created and to confirm the analysis algorithms.

Refer also to additional clinical pharmacology comments below regarding other general expectations for your NDA submission.

Question 9: *Does the Agency agree with the proposal for the BIMO clinical investigators list?*

FDA Response to Question 9:

No. Please also include columns for the protocol identifier (study number) and treatment arm. Please submit the file in xpt format.

Meeting Discussion: **There was no discussion.**

Question 10: *Does the Agency agree that the clinical pharmacology studies are adequate to support the filing and review of the NDA for gilteritinib in the proposed indication?*

FDA Response to Question 10:

Yes, FDA agrees that the proposed clinical pharmacology studies are adequate to support filing of the NDA. You propose to develop your population PK model using data from healthy subject and patient studies, but it is not clear if gilteritinib PK is similar between these two populations. In the NDA submission, provide a comparison of PK in healthy subjects versus patients.

Meeting Discussion: **There was no discussion.**

Question 11: *Does the Agency agree with updating the efficacy analysis for the companion diagnostic to align with the CR/CRh analysis for Study 2215-CL-0301?*

FDA Response to Question 11:

We agree with your request to update the PMA labeling for P160040 to include a companion diagnostic claim as an aid in the assessment of patients with FLT3 positive AML for treatment with gilteritinib. Invivoscribe will need to submit a PMA supplement with the updated indications for use and labeling in support of the new indication.

Meeting Discussion: **There was no discussion.**

2.4. Regulatory

Question 12: *Does the Agency agree that Astellas can apply for regular approval based on the results of the CR/CRh analysis for gilteritinib?*

FDA Response to Question 12:

In order to receive regular approval based on palliative endpoints, you would need to provide strong justification that the palliative benefits of gilteritinib outweigh its potential risks. Approval will be a review issue.

Meeting Discussion: **There was no discussion.**

Additional Clinical Comments:

1. Ensure that flags for each analysis population (RAS, FAS, etc.) are included consistently in each data file. Include a flag to identify patients determined to be FLT3 mutation positive using the proposed companion diagnostic.
2. Include in the subject level data file the specific FLT3 mutation (e.g., D835) for each subject.
3. Submit a data file in the NDA with all results of FLT3 mutation testing. For each result, specify the sample type, date of sample, assay used, and assay result.
4. Provide in the NDA submission the following information about the MRD assay:
 - a. a statement of intended use;
 - b. the specific test method (including instruments, reagents, and specimen handling);
 - c. confirmation that the lab has a process in place for reagent control;
 - d. a discussion of how the test method was validated analytically for each specimen type, and the results of the validation;
 - e. a statement of the performance obtained for accuracy and analytical sensitivity.
5. Include all results of MRD testing in a data file in the NDA submission. For each result, specify the sample type, date of sample, assay used and assay result.
6. We note that you have a rather low response rate for a targeted therapy. If you still plan to use an SCE in lieu of an ISE in your NDA, please ensure that the SCE includes a discussion of the potential mechanisms of resistance, a summary of the data demonstrating sensitivity of different FLT3 mutations to your drug, and whether there are mutations in other genes that might prohibit the efficacy of your drug. If you have mutational analyses for multiple genes for the patients in the clinical trial, the results should also be submitted in the NDA.

Meeting Discussion:

The Sponsor clarified that some of the genomics data will be available in the initial submission for the 0101 study alone, but full genotyping data will be submitted only at the time of the final OS analysis (approximately Q4 2018).

Additional Clinical Pharmacology Comments:

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 gilteritinib on the QT/QTc interval?

4. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?
5. What are the effects of food on the 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:

1. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
2. Provide a final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean $\pm$ 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.
 - 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.
4. 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>.

5. 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). Submit these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
6. 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/Guidance/ucm072137.pdf> for population PK, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/ucm072109.pdf> for exposure-response relationships, and <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm> for pharmacometric data and models submission guidelines.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- 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 marketing applications for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA determines 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. 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 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* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

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

SUBMISSION FORMAT REQUIREMENTS

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

SECURE EMAIL COMMUNICATIONS

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

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

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

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

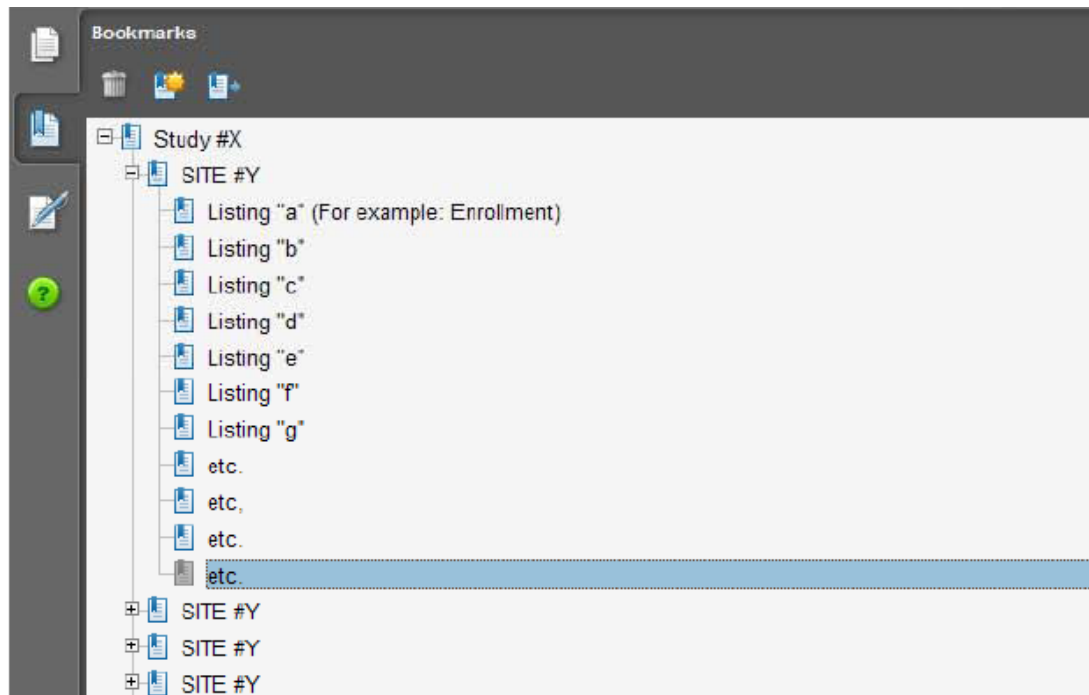
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is

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

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

II. Request for Subject Level Data Listings by Site

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



III. Request for Site Level Dataset:

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

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

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

DSI Pre-NDA Request Item¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

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

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor's responses to the preliminary comments are appended.

2.1 Quality (Chemistry, Manufacturing, and Controls)

Question 1: *Does the Agency agree with the proposal to submit 1 executed batch record?*

FDA Response to Question 1:

Yes, the proposal is acceptable. Please ensure the submitted executed batch record is from a bioavailability or bioequivalence study or a primary stability study. Additional information may be requested during review of the NDA.

Sponsor's response:

The sponsor acknowledges the Agency's comment and agrees to provide the executed batch record for the primary stability study in the NDA.

2.2 Nonclinical

Question 2: *Does the Agency agree that the nonclinical pharmacology, pharmacokinetics and toxicology studies are adequate to support the filing and review of the NDA for gilteritinib in the proposed indication?*

FDA Response to Question 2:

The completed nonclinical studies appear adequate to support the filing and review of the NDA for gilteritinib in the proposed indication. Any final decisions on the sufficiency of the nonclinical package will be a review issue.

Sponsor's response:

The sponsor acknowledges the Agency's comment.

2.3 Clinical

Question 3: *Does the Agency agree that the CR/CRh result from the phase 3 study (2215-CL-0301) is adequate to support submission and review of gilteritinib in the proposed indication as discussed at the Type C meeting held on May 31, 2017?*

FDA Response to Question 3:

We agree that CR/CRh may be an appropriate endpoint to assess clinical benefit for a treatment of patients with AML without curative intent, but additional information about transfusion independence and corroborating results from other protocols would improve the strength of evidence. Please clarify whether you will be submitting the CR/CRh assessment from the control arm of Study 2215-CL-0301. Whether the application submitted is adequate for review will be determined at filing.

Sponsor's response:

The sponsor acknowledges the Agency's comments. The first interim analysis (IA1) for study 2215-CL-0301 was performed to evaluate CR/CRh in the gilteritinib arm only and the sponsor remains blinded to the control arm results. Therefore, the sponsor does not plan to submit the CR/CRh assessment from the control arm in the NDA. Upon request, this data can be provided to the Agency directly through the Independent Contact Statistician (role defined in the DMC charter) to ensure that the Astellas team remains blinded.

Question 4: *Does the Agency agree with the strategy for the ISE analyses, as well as the proposed presentation of these data within the eCTD?*

FDA Response to Question 4:

No, we do not agree. Please note the following comments:

- a. You should include your assessment of efficacy for all AML protocols, including Study 2215-CL-0103 (b) (4)



(b) (4)

- b. Your primary analyses should follow the SAP for each protocol.**

Sponsor's response:

The sponsor agrees to follow the individual SAP for the efficacy analysis for each study. Please note that CRh was not defined in the SAP for studies 2215-CL-0102, 2215-CL-0103, (b) (4). For 2215-CL-0102, the required data to derive CRh was not collected. Since 2215-CL-0103 (b) (4) are conducted in first line combination with chemotherapy, CRh was not considered a relevant measure.

- c. For the pooled RAS analysis, we recommend inclusion of all FLT3 mutation positive patients who received at least 1 dose of gilteritinib at the 120 mg dose level from Study 2215-CL-0101, not only those in the Full Analysis Set (who must have had at least 1 post-treatment data point).**

Sponsor's response:

The sponsor acknowledges the Agency's comment and agrees.

- d. It is acceptable to use the SCE in lieu of the ISE. Please ensure, however, that the entire Clinical Summary (Modules 2.7.1 to 2.7.4) does not exceed the 400 page limit. Your submission of the SCE should follow Example 4 in the ISE/ISS guidance identified below with the SCE text in Module 2.7.4 and a mapping document, appendices and the integrated efficacy data set in Module 5.3.5.3.**

The ISE/ISS Guidance is available at:

<https://www.fda.gov/downloads/drugs/guidances/ucm136174.pdf>

Sponsor's response:

The sponsor acknowledges the Agency's comments.

- e. Provide an analysis of efficacy by dose of gilteritinib in FLT3 mutation positive patients, including whether dose reductions to 80 mg or dose escalations to 200 mg affected efficacy.**

Sponsor's response:

The sponsor acknowledges the Agency's comment and agrees to provide the requested pooled analysis of efficacy for the 2215-CL-0101 and 2215-CL-0301 studies.

- f. Please include an integrated time-to-event data file for all subjects with AML with at least the following information: study identification number, site identification number, unique subject number, treatment arm, stratification factors, prognostic factors, mutation status (local and central) at baseline, demographic information, date of randomization, date of start of study drug, best response, date of best response, date of CR, date of CR+CRh, date of relapse, date of transplantation if performed after study therapy, date of death, date of last contact, status at last contact (alive, dead or lost), proximate cause of death, and root cause of death as determined by the sponsor (e.g. active AML, treatment related, intercurrent illness, etc.). Provide the simple and all-containing “Statistical Efficacy Analysis Data Set” in SAS transport format.**

Sponsor’s response:

The sponsor will prepare a separate time-to-event dataset as requested.

- g. In the assessment of transfusion independence, include all patients in the RAS in the denominator. Patients who withdrew early should be considered failures.**

Sponsor’s response:

The sponsor acknowledges the Agency’s comments and agrees to provide the requested analyses to include all patients in the denominator and define early withdrawal patients as failures.

- h. Please include a transfusion analysis data file with at least the following information: study identification number, site identification number, unique subject number, treatment arm, demographic information, stratification factors, prognostic factors, mutation status at baseline, date of start of study drug, RBC transfusion dependence at baseline (Y/N), platelet transfusion dependence at baseline (Y/N), transfusion dependent of either RBC or platelets at baseline (Y/N), RBC transfusion independence (TI) for >56 days postbaseline (Y/N), platelet TI for >56 days post-baseline (Y/N), RBC and platelet TI for >56 days post-baseline (Y/N), date of start of RBC TI, date of end of RBC TI, date of start of platelet TI, date of end of platelet TI, date of start of RBC and platelet TI, date of end of RBC and platelet TI, time to RBC TI (time to the start of the ≥ 56 day TI period), time to platelet TI, time to RBC and platelet TI, duration of RBC TI post-baseline, duration of platelet TI post-baseline, duration of RBC and platelet TI post-baseline, date of last contact, status at last contact (alive and TI, alive and transfusion dependent, dead or lost).**

Sponsor’s response:

The sponsor will prepare a separate transfusion dataset as requested.

- i. **Please clarify whether you can also provide in a separate file the dates of RBC transfusions post-baseline and the dates of platelet transfusions post-baseline for each patient.**

Sponsor's response:

The sponsor will provide the requested information.

Question 5: *Does the Agency agree with the strategy for the ISS analyses, as well as the proposed presentation of these data within the eCTD?*

FDA Response to Question 5:

(b) (4)

Given the number of studies to be included in this NDA, the application should include an ISS. The ISS is not a just an overview of the safety results in the pivotal and supporting clinical trials, but a detailed integrated review of all relevant safety data and analyses, including data from nonclinical studies, clinical pharmacology studies, studies in patients, and studies in healthy volunteers. The ISS should show the key results that contribute to the understanding of the safety of your drug, including analyses across studies, and should not simply reference the study reports. Your submission of the SCS and ISS should follow Example 1 in the ISE/ISS guidance with the SCS text in Module 2.7.4 and the ISS text, appendices and the integrated safety data set in Module 5.3.5.3.

Sponsor's response:

The sponsor acknowledges the Agency's comments and agrees.

Question 6: *Does the Agency agree with the proposal for the safety update report?*

FDA Response to Question 6:

Your proposal to submit the safety update with a data cutoff of January 4, 2018 is acceptable if you follow your current submission plan.

Sponsor's response:

The sponsor acknowledges the Agency's comment.

Question 7: *Does the Agency agree with the proposal for the narratives to be included in the NDA, and the proposal to submit CRFs only for patients with narratives in the integrated safety population?*

FDA Response to Question 7:

Yes, we agree

Sponsor's response:

The sponsor acknowledges the Agency's comment.

Question 8: *The Sponsors propose to submit Study Data Tabulation Model (SDTM) and derived Analysis Data Model (ADaM) statistical analysis system (SAS) datasets following Clinical Data Interchange Standards Consortium (CDISC) standards for key pharmacokinetic studies and completed phase 2 and phase 3 clinical studies supporting the gilteritinib NDA for the indication of R/R AML with FLT3 mutation.*

Does the Agency agree with this proposal?

FDA Response to Question 8:

In general, your proposal is acceptable, but we have the following additional comments:



- b) Data sets should have one and only one unique subject ID for each patient among all trials. If patients transition between protocols, the subject ID should not change.**

The sponsor acknowledges the Agency's comment and agrees.

The sponsor also would like to confirm with the agency on the plan for the re-enrolled patients for the 2215-CL-0101 study. Six subjects were re-enrolled into the study after they were discontinued from the study. One subject was a screen failure at re-enrollment. For the other five subjects, the first starting doses were 40 mg (n=2), 80 mg (n=2), and

200 mg (n=1). The analyses for efficacy and safety exclude the data from the re-enrollment, as specified in the SAP and CSR, except that the overall survival analysis includes the survival information after the re-enrollment for these subjects. SDTM, ADaM, and listings will include data from before and after the re-enrollment for these subjects.

Re-enrolled subjects were assigned a new USUBJID and SUBJID, however the subjects can be traced back to their original subject ID using a variable called SUBJIDP (Previous subject number). For example:

USUBJID=2215-cl-0101-1000420024, SUBJID=1000420024 (1st enrollment)

USUBJID=2215-cl-0101-1000420158, SUBJID=1000420158, SUBJIDP=1000420024 (re-enrollment, SUBJIDP links this subject ID to the first enrollment subject ID)

- c) **Each data file should contain a variable for study ID.**

Sponsor's response:

The sponsor acknowledges the Agency's comments and agrees.

- d) **The define.pdf file should contain the descriptions (how coded, which value stands for what) of variable names on SAS data sets. For a given quantity, the same variable name should be used for all datasets (i.e., one definition, well-annotated, per one variable)**

Sponsor's response:

The sponsor acknowledges the Agency's comments and agrees.

- e) **Include in the Reviewer's Guide an instruction for the use of variables and flags to identify the set of patients on which the primary analysis was performed.**

Sponsor's response:

The sponsor acknowledges the Agency's comments and agrees.

- f) **Provide the SAS programs (with adequate comments) used to create all ADaM datasets along with the tables and figures associated with primary and secondary efficacy analyses in order to help reviewers to better understand how the datasets, tables and figures were created. The main purpose of requesting the submission of these programs is to understand the process by which the variables for the respective analyses were created and to confirm the analysis algorithms.**

Sponsor's response:

The sponsor agrees to provide SAS programs for the pivotal study 2215-CL-0301. Please confirm that ARM is not needed given that the SAS programs are provided.

Refer also to additional clinical pharmacology comments below regarding other general expectations for your NDA submission.

Question 9: *Does the Agency agree with the proposal for the BIMO clinical investigators list?*

FDA Response to Question 9:

No. Please also include columns for the protocol identifier (study number) and treatment arm. Please submit the file in xpt format.

Sponsor's response:

The sponsor acknowledges the Agency's comments and agrees.

Question 10: *Does the Agency agree that the clinical pharmacology studies are adequate to support the filing and review of the NDA for gilteritinib in the proposed indication?*

FDA Response to Question 10:

Yes, FDA agrees that the proposed clinical pharmacology studies are adequate to support filing of the NDA. You propose to develop your population PK model using data from healthy subject and patient studies, but it is not clear if gilteritinib PK is similar between these two populations. In the NDA submission, provide a comparison of PK in healthy subjects versus patients.

Sponsor's response:

The sponsor acknowledges the Agency's comments and agrees to provide the requested comparisons in the NDA.

Question 11: *Does the Agency agree with updating the efficacy analysis for the companion diagnostic to align with the CR/CRh analysis for Study 2215-CL-0301?*

FDA Response to Question 11:

We agree with your request to update the PMA labeling for P160040 to include a companion diagnostic claim as an aid in the assessment of patients with FLT3 positive AML for treatment with gilteritinib. Invivoscribe will need to submit a PMA supplement with the updated indications for use and labeling in support of the new indication.

Sponsor's response:

The sponsor acknowledges the Agency's comments.

Question 12: *Does the Agency agree that Astellas can apply for regular approval based on the results of the CR/CRh analysis for gilteritinib?*

FDA Response to Question 12:

In order to receive regular approval based on palliative endpoints, you would need to provide strong justification that the palliative benefits of gilteritinib outweigh its potential risks. Approval will be a review issue.

Sponsor's response:

The sponsor acknowledges the Agency's comments.

Additional Clinical Comments

- 1. Ensure that flags for each analysis population (RAS, FAS, etc.) are included consistently in each data file. Include a flag to identify patients determined to be FLT3 mutation positive using the proposed companion diagnostic.**

Sponsor's response:

The sponsor acknowledges the Agency's comments and agrees. The sponsor will indicate the subjects from study 2215-CL-0101 and study 2215-CL-0301 that tested positive using the proposed companion diagnostic. For study 2215-CL-0101, archived DNA from blood and bone marrow samples was retrospectively tested with the companion diagnostic.

Separation of mononuclear cells over a ficoll column, which is part of the companion diagnostic DNA extraction procedure, was not performed prior to DNA extraction.

In study 2215-CL-0301, samples were prospectively tested with the companion diagnostic, except for four subjects where a prospective sample was not received by the central lab.

For these four subjects, archived DNA from blood and bone marrow samples was retrospectively tested with the companion diagnostic. Separation of mononuclear cells over a ficoll column was not performed prior to DNA extraction for samples from these four subjects.

2. **Include in the subject level data file the specific FLT3 mutation (e.g., D835) for each subject.**

Sponsor's response:

The sponsor will provide subject level specific FLT3 mutation data from study 2215-CL-0101 and study 2215-CL-0301. The companion diagnostic detects FLT3-ITD and FLT3-TKD (D835/I836) mutations. The companion diagnostic does not distinguish between FLT3-TKD/D835 and FLT3-TKD/I836 mutations.

3. **Submit a data file in the NDA with all results of FLT3 mutation testing. For each result, specify the sample type, date of sample, assay used, and assay result.**

Sponsor's response:

The sponsor will provide all FLT3 mutation testing data from study 2215-CL-0101 and study 2215-CL-0301. For each result, the sponsor will provide the information as detailed in the table below.

Testing Type	Study	
	2215-CL-0101	2215-CL-0301
Central FLT3 testing (companion diagnostic)	Archived DNA from blood and bone marrow samples was tested retrospectively with the companion diagnostic. Sponsor will provide sample type, sample collection date, assay testing date and assay result.	Blood and bone marrow samples were prospectively tested with the companion diagnostic. Sponsor will provide sample type, sample collection date, assay testing date and assay result.
Local FLT3 testing	Sponsor will provide assay result. Sponsor does not have access to sample type, sample collection date, assay date or assay used.	Local FLT3 mutation test results were not collected for all subjects since subjects were enrolled based on central FLT3 mutation testing (companion diagnostic). Only subjects with rapidly progressive disease had the option to be enrolled based on a local FLT3 test result. Sponsor will provide assay testing date and assay result. Sponsor does not have access to sample type, sample collection date, or assay used.

- 4. Provide in the NDA submission the following information about the MRD assay:**
- a. statement of intended use;**
 - b. the specific test method (including instruments, reagents, and specimen handling);**
 - c. confirmation that the lab has a process in place for reagent control;**
 - d. a discussion of how the test method was validated analytically for each specimen type, and the results of the validation;**
 - e. a statement of the performance obtained for accuracy and analytical sensitivity.**

Sponsor's response:

- a. The sponsor will not propose a diagnostic use for the MRD assay in the NDA. The sponsor used the MRD assay in study 2215-CL-0101 to retrospectively evaluate the relationship between clinical response and molecular response.
- b. This information will be provided.
- c. This information will be provided.
- d. This information will be provided.
- e. This information will be provided.

- 5. Include all results of MRD testing in a data file in the NDA submission. For each result, specify the sample type, date of sample, assay used and assay result.**

Sponsor's response:

The sponsor acknowledges the Agency's comments and agrees.

- 6. We note that you have a rather low response rate for a targeted therapy. If you still plan to use an SCE in lieu of an ISE in your NDA, please ensure that the SCE includes a discussion of the potential mechanisms of resistance, a summary of the data demonstrating sensitivity of different FLT3 mutations to your drug, and whether there are mutations in other genes that might prohibit the efficacy of your drug. If you have mutational analyses for multiple genes for the patients in the clinical trial, the results should also be submitted in the NDA.**

Sponsor's response:

In study 2215-CL-0101, the sponsor sequenced the FLT3, AXL and c-CBL genes in baseline samples (per protocol). Few somatic mutations were detected in AXL and c-CBL and there was no relationship between clinical efficacy and FLT3 mutations co-occurring with either AXL or c-CBL mutations.

The sponsor will evaluate the effect of different baseline FLT3 mutations on efficacy in the NDA submission. However, the companion diagnostic only reports out as ITD or TKD (D835 or I836) without differentiating between TKD mutations.

In study 2215-CL-0301, the sponsor will evaluate mutations in multiple AML related genes in baseline samples. This data will be available at the completion of the study.

Although the CR/CRh rate is observed in a smaller fraction of patients, around half of patients do achieve complete morphologic elimination of leukemia (peripheral blood and bone marrow). The reason for the lack of full count recovery is not known. Although persistence of MRD has been proposed as one possible explanation, this is by no means clear. Other factors such as poor bone marrow reserve might also play a role. High rate of response seen in newly diagnosed AML supports the role of bone marrow function in recovery. Nevertheless, the sponsor does not believe patients who achieve complete morphological elimination of leukemia could be considered primary refractory. Furthermore, we believe the final analysis will demonstrate that elimination of leukemia and even control of leukemia translate into prolongation of survival.

Additional Clinical Pharmacology Comments:

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 gilteritinib on the QT/QTc interval?**
- 4. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?**
- 5. What are the effects of food on the 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:

- 1. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.**
- 2. Provide a final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean $\pm$ 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.**
 - **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.**
- 4. 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>.

- 5. 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). Submit these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).**
6. **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, and <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm> for pharmacometric data and models submission guidelines.**

Sponsor's response:

The sponsor acknowledges the Agency's comments and agrees to address the Clinical Pharmacology questions and advice in the NDA.

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

/s/

DONNA PRZEPIORKA
12/05/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 117548

MEETING MINUTES

Astellas Pharma Global Development, Inc.
Attention: Tim Farber
Associate Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Mr. Farber:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ASP2215.

We also refer to the meeting between representatives of your firm and the FDA on April 7, 2016. The purpose of the meeting was to discuss the adequacy of the proposed study design for a Phase 3 study to support regulatory approval of gilteritinib (b) (4)

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 Jessica Boehmer, Regulatory Project Manager, at (301) 796-5357.

Sincerely,

{See appended electronic signature page}

Donna Przepiorka, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End-of-Phase 2/Pre-Phase 3

Meeting Date and Time: April 8, 2016; 10:00 AM – 11:00 AM, ET
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: IND 117548
Product Name: ASP2215
Indication: [REDACTED] (b) (4)

Sponsor/Applicant Name: Astellas Pharma Global Development, Inc.

Meeting Chair: Donna Przepiorka, MD, PhD
Meeting Recorder: Jessica Boehmer, MBA

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products

Albert Deisseroth, MD, PhD, Clinical Team Leader
Donna Przepiorka, MD, PhD, Clinical Team Leader
Rosana Setse, MD, Clinical Reviewer
R. Angelo de Claro, MD, Clinical Team Leader
Yvette Kasamon, MD, Clinical Reviewer
Jessica Boehmer, MBA, Senior Regulatory Project Manager

Office of Biostatistics/Division of Biometrics V

Yuan-Li Shen, PhD, Statistical Team Leader
Qing Xu, PhD, Statistical Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V

Bahru Habtemariam, PharmD, Clinical Pharmacology Team Leader
Vicky Hsu, PharmD, Clinical Pharmacology Reviewer

SPONSOR ATTENDEES

Erkut Bahceci, MD, Executive Medical Director, Medical Science
Jana Cummings, Associate Director, Project Management
Stephen Eck, MD, Vice President, Global Head of Medical Oncology

Timothy Farber, Associate Director, Regulatory Affairs
Alison Hayles, Executive Director, Regulatory Affairs
Angela James, PhD, Associate Director, Global Clinical Pharmacology & Exploratory
Development Science
Chaofeng (Charles) Liu, PhD, MBA, Associate Director, Biostatistics
Rubina Mondal, MS, Manager, Regulatory Affairs
Itsuro Nagase, DVM, PhD, Senior Director, Global Development Project Leader

1.0 BACKGROUND

The purpose of this meeting is to discuss the adequacy of the proposed study design for a phase 3 study to support regulatory approval of gilteritinib (b) (4)

 (b) (4)

FLT3 is a member of the class III receptor tyrosine kinase family that is normally expressed on the surface of hematopoietic progenitor cells.

FDA sent Preliminary Comments to Astellas on April 6, 2016.

2. DISCUSSION

 (b) (4)

In addition, to establish a drug's effectiveness, FDA usually requires substantial evidence from at least two independent, adequate and well-controlled studies. The usual requirement for more than one adequate and well-controlled study reflects the need for independent substantiation or replication of experimental results to mitigate any inherent or unanticipated biases in a single efficacy trial. The Agency on occasion may consider data from one adequate and well controlled clinical trial to constitute substantial evidence if FDA determines that such data and evidence are sufficient to establish effectiveness. The trial must be well conducted, and the results of the trial must be internally consistent, clinically meaningful, and statistically very persuasive. Generally, this allowance is limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. Whether or not your proposed phase 3 study 2215-CL-0302 will be acceptable to support filing and review of an NDA or supplemental NDA will be a review issue.

Discussion:

The Sponsor clarified that the dose reduction rate in 0101 was only 7% for patients on the 120 mg dose. The Sponsor agreed to include an assessment of dose intensity for the DSMB to review interim safety analyses.

2.2. Clinical – Primary Endpoint

Question 2: *Does the Agency agree that RFS is acceptable as a primary endpoint?*

FDA Response to Question 2:

For regulatory decision making, Overall Survival (OS) is the accepted end point for phase 3 studies in the maintenance setting. Especially in this scenario where you are considering the use of one pivotal study to support filing and review of gilteritinib as maintenance therapy, demonstration of a statistically significant and clinically meaningful improvement in OS as the primary end point would enhance the internal validity of your study. To address the concern about post relapse FLT3 inhibitor use, data on subsequent treatments received by patients in both treatment arms should be collected.

Although Relapse Free Survival (RFS) is often used as a surrogate for OS and is not affected by subsequent therapies, RFS measurement requires frequent and balanced timing of assessments between treatment groups, may not be precisely measured and may not correspond adequately with improvement in OS if the interval between relapse and death is extended.

We recommend using OS as the primary endpoint in your study, with collection of data on subsequent treatments received by patients in both treatment arms. Relapse Free Survival (RFS) can be maintained as a key secondary endpoint to allow for comparison with the hazard ratio for OS.

In general a substantial, robust improvement in RFS that is clinically meaningful and statistically persuasive, and has an acceptable risk-benefit profile may be considered for regulatory decision. However, you should be aware that RFS is subject to ascertainment bias and the results of the analysis may be influenced by any imbalance in assessment dates or missing data between treatment arms. Also note that a statistically significant difference in RFS may not necessarily demonstrate a clinically meaningful difference.

If you intend to make a labeling claim for RFS, this endpoint should be adjudicated by an independent review committee.

Discussion:

The Sponsor explained their rationale for use of RFS, including a manageable sample size and meaningfulness of preventing relapse. FDA indicated there was no safety issue with RFS as the primary endpoint, but reiterated the potential regulatory hurdles. The Sponsor indicated they could provide independent data showing that RFS was a surrogate for OS at the time of submission of an sNDA.

2.3. Clinical – Placebo Control

Question 3: *Does the agency agree that placebo control is acceptable in this patient population?*

FDA Response to Question 3:

(b) (4)
[REDACTED]
we agree with the choice of placebo as the comparative arm as planned. However, if the field advances while this study is on-going, recruitment to a placebo-controlled trial may be challenging.

Discussion:

No discussion occurred.

2.4. Clinical – Target Population

Question 4: *Does the Agency agree with the target population, including the inclusion and exclusion criteria?*

FDA Response to Question 4: No. We have the following comments on the proposed eligibility criteria:

- a) Please clarify the discrepancy between the definition of CR and Inclusion criterion # 10, bullet 5. We recommend an ANC ≥ 1.0 Gi/L and platelets count of ≥ 100 Gi/L as per IWG criteria definition for complete remission.

Discussion:

The Sponsor agreed to maintain consistency between the two eligibility criteria. FDA agreed that patients with either CR or CRI by IWG criteria could be eligible.

- b) We recommend that inclusion criterion # 6 specify 2 months from the start of the last cycle of consolidation. Please also clarify the minimum number of cycles of consolidation for eligibility.
- c) Please also confirm that patients with FLT3 TKD activating mutation without a FLT3/ITD will be excluded.

2.5. Statistical Approach

Question 5: *Does the Agency agree with the proposed statistical analysis plan to evaluate the primary and secondary endpoints?*

FDA Response to Question 5:

- Please provide justification of the parameters that you used for the sample size calculation. You quote data for the control arm of the RATIFY trial, but that trial was randomized at induction, so it is not clear that the OS data will apply to your study where randomization is post remission.

Discussion:

FDA acknowledged that the DFS after CR in the placebo arm of ratify would be an acceptable basis for the sample size calculation.

- The planned number of events for the sample size calculation is different in the protocol synopsis and simulation report. In the protocol synopsis, the planned number of events is 184; in the simulation report, the planned number of events is 182.
- If you intend to make a labeling claim for RFS, please provide detailed descriptions of the timing and censoring for RFS including sensitivity analyses that consider the events in which patients have missing assessments and lost-to-follow-up in the statistical analysis plan. Please refer to the guidance “*Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*” at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm01590.pdf for more details. Please note that you should capture the reason why patients start new therapies and document how this new therapy will affect the PFS outcome.

We recommend establishing performance standards for having minimal missing data and monitoring the sites during the study on meeting the performance standards.

The efficacy analysis of RFS should be based on an event driven analysis, so the

specification of “subject will be followed for up to 5 years after randomization, or until 80% of the subjects have an RFS event, whichever comes first” should be removed from the description of the primary efficacy analysis. If the number of RFS events has not been met by 5 years, you may need to consider a longer follow-up for disease assessment.

Discussion:

The Sponsor clarified that the primary analysis would be conducted at 184 events, and 5 years of follow up would accrue for additional analyses. FDA agreed with this plan.

- A method for testing assumption of proportional hazard model for OS and RFS should be included in the protocol. If the hazards are not proportional, the impact of the varying hazard ratios on the conclusion should be evaluated.
- Subgroup analyses such as age, gender, race/ethnicity, region and other important baseline characteristics should be also included in the protocol.
- Randomization method should be specified in the protocol. FDA encourages using a pure block randomization with stratification factors.

2.6. Sample Size Re-estimation

Question 6: *Does the Agency agree with the plans for sample size re-estimation near the end of the enrollment period?*

FDA Response to Question 6:

- For sample size re-estimation, we have concerns that unblinding the data may potentially jeopardize the integrity of the study from the interim look. You must implement an adequate firewall to ensure that the personnel for the ongoing studies will remain blinded. Please submit the data safety monitoring board charter to the Agency for review.

Discussion:

The Sponsor agreed to provide the DSMB charter and the interim analysis plan for FDA review. The Sponsor also clarified that the interim analysis plan will be kept confidential so that the blinded investigators could not interpret any changes in the protocol.

- Please provide the simulation programs that you use for the interim analysis for our review.

2.7. Stratification Factors

Question 7: *Does the Agency agree with the proposed stratification factors?*

FDA Response to Question 7:

In general, stratification by age, geographic region and MRD status at screening is reasonable. We also recommend that you stratify by use of a FLT3 inhibitor during induction or consolidation. However, there is insufficient information in the briefing package about the MRD assay and how the cut point used to determine positivity was developed, so we cannot provide firm agreement at this time.

Discussion:

No discussion occurred.

Additional Clinical Comment

1. As this is a relatively new population for treatment with ASP2215, we recommend that you include in your interim safety analyses an assessment of dose intensity to confirm that you have chosen the appropriate dose.

Discussion:

See Discussion for Question 1.

Additional Clinical Pharmacology Comments

Regarding your Protocol 2215-CL-0302 synopsis, we have the following comments:

1. As conveyed in a previous meeting (02-25-15), include instructions in your protocol for ASP2215 dose adjustment if concomitant use of strong CYP3A4 inhibitors cannot be avoided.
2. Include dosing instruction in regards to food in your protocol.
3. We recommend sampling for pharmacodynamics to enable evaluation of exposure-response relationships for ASP2215 in the maintenance setting.

Discussion:

FDA recommended collecting trough concentrations for all patients and agreed that relapse would be acceptable measure of response for this evaluation.

3.0 OTHER IMPORTANT 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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

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

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the

availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdeler-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>.

SUBMISSION FORMAT REQUIREMENTS

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

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

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

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

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

Sponsor's responses are attached. These responses were not reviewed by the Agency.

IND 117,548, Type B meeting: April 8, 2016
Pre-meeting responses:

(b) (4)

In addition, to establish a drug's effectiveness, FDA usually requires substantial evidence from at least two independent, adequate and well-controlled studies. The usual requirement for more than one adequate and well-controlled study reflects the need for independent substantiation or replication of experimental results to mitigate any inherent or unanticipated biases in a single efficacy trial. The Agency on occasion may consider data from one adequate and well controlled clinical trial to constitute substantial evidence if FDA determines that such data and evidence are sufficient to establish effectiveness. The trial must be well conducted, and the results of the trial must be internally consistent, clinically meaningful, and statistically very persuasive. Generally, this allowance is limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. Whether or not your proposed phase 3 study 2215-CL-0302 will be acceptable to support filing and review of an NDA or supplemental NDA will be a review issue.

Sponsor Response (April 7, 2016):

Astellas proposes to discuss this issue with the Agency.

Question 2: *Does the Agency agree that RFS is acceptable as a primary endpoint?*

FDA Response to Question 2:

For regulatory decision making, Overall Survival (OS) is the accepted end point for phase 3 studies in the maintenance setting. Especially in this scenario where you are considering the use of one pivotal study to support filing and review of gilteritinib as maintenance therapy, demonstration of a statistically significant and clinically meaningful improvement in OS as the primary end point would enhance the internal validity of your study. To address the concern

about post relapse FLT3 inhibitor use, data on subsequent treatments received by patients in both treatment arms should be collected.

Although Relapse Free Survival (RFS) is often used as a surrogate for OS and is not affected by subsequent therapies, RFS measurement requires frequent and balanced timing of assessments between treatment groups, may not be precisely measured and may not correspond adequately with improvement in OS if the interval between relapse and death is extended.

We recommend using OS as the primary endpoint in your study, with collection of data on subsequent treatments received by patients in both treatment arms. Relapse free Survival (RFS) can be maintained as a key secondary endpoint to allow for comparison with the hazard ratio for OS.

In general a substantial, robust improvement in RFS that is clinically meaningful and statistically persuasive, and has an acceptable risk-benefit profile may be considered for regulatory decision. However, you should be aware that RFS is subject to ascertainment bias and the results of the analysis may be influenced by any imbalance in assessment dates or missing data between treatment arms. Also note that a statistically significant difference in RFS may not necessarily demonstrate a clinically meaningful difference.

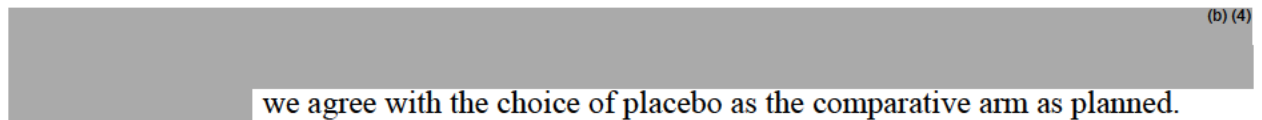
If you intend to make a labeling claim for RFS, this endpoint should be adjudicated by an independent review committee.

Sponsor Response (April 7, 2016):

Astellas proposes to discuss this issue with the Agency.

Question 3: *Does the agency agree that placebo control is acceptable in this patient population?*

FDA Response to Question 3:

 (b) (4)
we agree with the choice of placebo as the comparative arm as planned. However, if the field advances while this study is on-going, recruitment to a placebo-controlled trial may be challenging.

Sponsor Response (April 7, 2016):

Astellas acknowledges the Agency's comments.

Question 4: *Does the Agency agree with the target population, including the inclusion and exclusion criteria?*

FDA Response to Question 4: No. We have the following comments on the proposed eligibility criteria:

- a) Please clarify the discrepancy between the definition of CR and Inclusion criterion #10, bullet 5. We recommend an ANC >1.0 Gi/L and platelets count of >100 Gi/L as per IWG criteria definition for complete remission.

Sponsor Response (April 7, 2016):

Astellas proposes to discuss this issue with the Agency.

- b) We recommend that inclusion criterion # 6 specify 2 months from the start of the last cycle of consolidation. Please also clarify the minimum number of cycles of consolidation for eligibility.

Sponsor Response (April 7, 2016):

Astellas confirms that inclusion criterion #6 will be modified to specify 2 months from the start of the last cycle of consolidation. The minimum number of cycles of consolidation for eligibility will be 1 cycle.

- c) Please also confirm that patients with FLT3 TKD activating mutation without a FLT3/ITD will be excluded.

Sponsor Response (April 7, 2016):

Astellas confirms that patients with FLT3 TKD activating mutation without a FLT3/ITD mutation will be excluded.

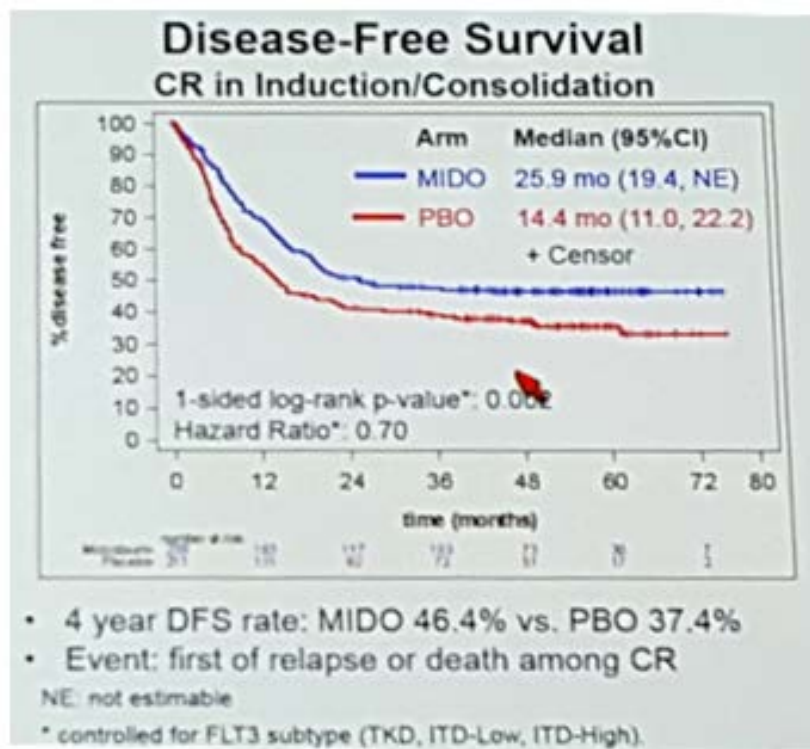
Question 5: Does the Agency agree with the proposed statistical analysis plan to evaluate the primary and secondary endpoints?

FDA Response to Question 5:

- Please provide justification of the parameters that you used for the sample size calculation. You quote data for the control arm of the RATIFY trial, but that trial was randomized at induction, so it is not clear that the OS data will apply to your study where randomization is post remission.

Sponsor Response (April 7, 2016):

Astellas proposes to discuss this issue with the Agency. The justification for the RFS sample size calculation is based on the DFS after CR1 for the placebo arm reported from the RATIFY trial as shown in the figure below.



- The planned number of events for the sample size calculation is different in the protocol synopsis and simulation report. In the protocol synopsis, the planned number of events is 184; in the simulation report, the planned number of events is 182.

Sponsor Response (April 7, 2016 – updated April 15, 2016):

The different number of events is a result of different rounding approaches in the calculation methods used by Astellas (synopsis) and Cytel (simulation report). Astellas confirms that the correct number of events is 182. Astellas will modify the synopsis and protocol accordingly.

- If you intend to make a labeling claim for RFS, please provide detailed descriptions of the timing and censoring for RFS including sensitivity analyses that consider the events in which patients have missing assessments and lost-to-follow-up in the statistical analysis plan. Please refer to the guidance “Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics” at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm01590.pdf for more details. Please note that you should capture the reason why patients start new therapies and document how this new therapy will affect the PFS outcome.

We recommend establishing performance standards for having minimal missing data and monitoring the sites during the study on meeting the performance standards.

The efficacy analysis of RFS should be based on an event driven analysis, so the specification of “subject will be followed for up to 5 years after randomization, or until 80% of the subjects have an RFS event, whichever comes first” should be removed from the description of the primary efficacy analysis. If the number of RFS events has not been met by 5 years, you may need to consider a longer follow-up for disease assessment.

Sponsor Response (April 7, 2016):

Astellas proposes to discuss this issue with the Agency. Astellas confirms that the specification of “subject will be followed for up to 5 years after randomization, or until 80% of the subjects have an RFS event, whichever comes first” is not a part of the description of the primary efficacy analysis.

(b) (4)

- A method for testing assumption of proportional hazard model for OS and RFS should be included in the protocol. If the hazards are not proportional, the impact of the varying hazard ratios on the conclusion should be evaluated.

Sponsor Response (April 7, 2016):

Astellas will specify the proportionality assumption testing procedure in the protocol and SAP.

- Subgroup analyses such as age, gender, race/ethnicity, region and other important baseline characteristics should be also included in the protocol.

Sponsor Response (April 7, 2016):

Astellas will include the subgroup analyses in the protocol.

- Randomization method should be specified in the protocol. FDA encourages using a pure block randomization with stratification factors.

Sponsor Response (April 7, 2016):

Astellas confirms that block randomization with stratification factors will be utilized and that it will be specified in the protocol.

Question 6: *Does the Agency agree with the plans for sample size re-estimation near the end of the enrollment period?*

FDA Response to Question 6:

- For sample size re-estimation, we have concerns that unblinding the data may potentially jeopardize the integrity of the study from the interim look. You must implement an adequate firewall to ensure that the personnel for the ongoing studies will remain blinded. Please submit the data safety monitoring board charter to the Agency for review.

Sponsor Response (April 7, 2016):

Astellas proposes to discuss this issue with the Agency. Astellas will provide the DSMB charter for the Agency's review.

- Please provide the simulation programs that you use for the interim analysis for our review.

Sponsor Response (April 7, 2016):

Astellas will provide the simulation programs for the interim analysis for the Agency's review.

Question 7: *Does the Agency agree with the proposed stratification factors?*

FDA Response to Question 7:

In general, stratification by age, geographic region and MRD status at screening is reasonable. We also recommend that you stratify by use of a FLT3 inhibitor during induction or consolidation. However, there is insufficient information in the briefing package about the MRD assay and how the cut point used to determine positivity was developed, so we cannot provide firm agreement at this time.

Sponsor Response (April 7, 2016):

Astellas acknowledges the Agency's comments.

Additional Clinical Comments

1. As this is a relatively new population for treatment with ASP2215, we recommend that you include in your interim safety analyses an assessment of dose intensity to confirm that you have chosen the appropriate dose.

Sponsor Response (April 7, 2016):

Astellas proposes to discuss this issue with the Agency.

Additional Clinical Pharmacology Comments

Regarding your Protocol 2215-CL-0302 synopsis, we have the following comments:

1. As conveyed in a previous meeting (02-25-15), include instructions in your protocol for ASP2215 dose adjustment if concomitant use of strong CYP3A4 inhibitors cannot be avoided.

Sponsor Response (April 7, 2016):

Astellas acknowledges the Agency's comment and has completed drug-drug interaction assessments in relapsed or refractory AML patients (2215-CL-0101) and healthy subjects (2215-CL-0108) coadministered ASP2215 with a strong or moderate CYP3A4 inhibitor. A comprehensive review of the safety and PK data indicate dose adjustment is not warranted for patients if concomitant use of strong CYP3A4 inhibitors cannot be avoided. Clinical study reports summarizing these data are currently being finalized and will be submitted to the Agency.

2. Include dosing instruction in regards to food in your protocol.

Sponsor Response (April 7, 2016):

Astellas confirms that dosing instructions in regards to food will be included in the protocol.

3. We recommend sampling for pharmacodynamics to enable evaluation of exposure-response relationships for ASP2215 in the maintenance setting.

Sponsor Response (April 7, 2016):

Astellas proposes to discuss this issue with the Agency.

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

/s/

DONNA PRZEPIORKA
04/15/2016