

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211155Orig1s000

211155Orig2s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 112486

MEETING MINUTES

Verastem, Inc.
Attention: Priya Jambhekar
Regulatory Affairs Consultant
117 Kendrick Street, Suite 500
Needham, MA 02492

Dear Ms. Jambhekar:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for duvelisib (IPI-145).

We also refer to the meeting between representatives of your firm and the FDA on October 17, 2017. The purpose of the meeting was to discuss the clinical, non-clinical and quality data in support of a proposed marketing application for duvelisib.

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 Rachel McMullen, Senior Regulatory Project Manager at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Kathy Robie Suh, MD, PhD
Clinical Team Lead
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: October 17, 2017; 2:00-3:00PM (ET)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Application Number: IND 112486
Product Name: duvelisib (IPI-145)
Indication: Treatment of patients with relapsed/refractory CLL and SLL
Sponsor/Applicant Name: Verastem Inc.

Meeting Chair: Kathy Robie Suh, MD, PhD, Clinical Team Lead
Meeting Recorder: Rachel McMullen, MPH, MHA, Senior Regulatory Project Manager

FDA ATTENDEES

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

Albert Deisseroth, MD, PhD, Supervisory Associate Deputy Director
Kathy Robie Suh, MD, PhD, Clinical Team Leader
Hyon Zu Lee, Pharm D, Clinical Reviewer
Bindu Kanapuru, MD, Clinical Reviewer
Rachel McMullen, MPH, MHA, Regulatory Project Manager

Division of Pharmacology Toxicology (DHOT)

Christopher Sheth, PhD, Pharmacology Toxicology Leader
Shwu-Luan Lee, PhD, Pharmacology Toxicology Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V

Olanrewaju Okusanya, PharmD, MS, Clinical Pharmacology Reviewer

Office of Biostatistics/Division of Biometrics V

Yuan Li Shen, DrPH, Statistical Team Leader

Office of Product Quality

Sherita McLamore-Hines, PhD, CMC Team Leader
Danuta Gromek-Woods, PhD, Product Quality Reviewer

Okpo Eradiri, PhD, Acting Biopharmaceutics Team Lead

SPONSOR ATTENDEES

Verastem Inc.

NgocDiep (Diep) T. Le, MD, PhD, Chief Medical Officer
Virginia Kelly, MD, Clinical Development
Ajit Chavan, PhD, MBA, Clinical Pharmacology/DMPK
Mahesh Padval, PhD, Pharmaceutical Sciences
Barry Turnbull, PhD, Biostatistics
Azita Razzaghi, PharmD, Safety/Pharmacovigilance
James Porter, PhD, Duvelisib Program Lead
Catherine Mesner, NDA Project Manager
Mary Matthew, Vice President, Regulatory Affairs
Priya Jambhekar, Regulatory Affairs

Consultants:

(b) (4)

Teleconference Attendees:

Robert Forrester, LLB, Chief Executive Officer
Dan Peterson, Chief Operation Officer

1.0 BACKGROUND

Verastem Inc. is developing duvelisib as a monotherapy for the treatment of relapsed/refractory CLL/SLL and FL. Verastem acquired the global development and commercialization rights to duvelisib from Infinity Pharmaceuticals Inc. in December 2016.

Duvelisib was granted Orphan Drug Designation for CLL/SLL on April 15, 2013 and Fast-Track Designation on August 3, 2015. Duvelisib was granted Orphan Drug Designation for FL on August 1, 2013 and Fast-Track Designation on October 7, 2015. The pivotal studies (Studies IPI-145-07 and IPI-145-06) for these indications have been completed, with both studies meeting their primary endpoints.

Previously, the sponsor had a Type C meeting with the Agency in December 2015 to discuss the clinical summaries of efficacy for CLL/SLL and this proposal has since been modified to now include data from Studies IPI-145-12 and IPI-145-06. Likewise, the safety data for the FL indication will contain data obtained from all the studies with duvelisib monotherapy, including IPI-145-07, IPI-145-06, IPI-145-12, and IPI-145-02. The Sponsor also had an EOP2 meeting with the Agency in August 2016.

On August 22, 2017, the Sponsor requested a Pre-NDA meeting to discuss the clinical, non-clinical and quality data in support of a proposed marketing application for duvelisib. Verastem plans to request Priority Review of the New Drug Application (NDA) at the time of submission.

FDA sent Preliminary Comments to Verstem on October 15, 2017.

2. DISCUSSION

Regulatory / Clinical

Question 1a: *Does the Agency agree with Verastem's proposal to submit a single NDA requesting regular approval for CLL/SLL and accelerated approval for FL?*

FDA Response to Question 1a: It is acceptable to submit a single NDA for the CLL/SLL and FL indications. However, it is likely that the application will need to be administratively split.

Discussion: **The Agency clarified that the administrative split is an internal FDA process that the Agency would undertake after receipt of the application. The Agency would contact the Sponsor prior to filing should any additional information be required.**

Question 1b: *Does the Agency agree that the proposed four clinical studies (Phase 3 Study IPI-145-07, Optional Crossover Extension Study IPI-145-12, Phase 2 Study IPI-145-06, and Phase 1 Study IPI-145-02) support filing an NDA for regular approval for patients with CLL/SLL (b) (4) ?*

FDA Response to Question 1b: Your proposal to submit an NDA for regular approval for CLL based on the pivotal phase 3 study (IPI-145-07) and three supporting studies (IPI-145-12, IPI-145-06 and IPI-145-02) is acceptable. A decision on filing will be made after the application has been received. However, note that only 7 patients (2%) with SLL were enrolled in the IPI-145-07 randomized trial which might not be sufficient to evaluate duvelisib in this patient population and therefore will be a review issue.

Also, note that current labeling for ofatumumab for relapsed/refractory CLL indicates it is approved (a) in combination with fludarabine and cyclophosphamide for the treatment of patients with relapsed CLL and (b) for the treatment of patients with CLL refractory to fludarabine and alemtuzumab. Your protocol for Study IPI-145-007 and the meeting background materials state that ofatumumab was administered consistent with the approved labeling but does not clearly specify concomitant treatments. Assessment of possible impact of prior and concomitant treatments (or lack thereof) on the study results will be a review issue.

Your proposal for regular approval for patients with CLL/SLL (b) (4) is based on a small number of these patients (n= 33) enrolled to the duvelisib arm in the IPI-145-07 trial which may not be sufficient to evaluate the safety and toxicity in this subpopulation. Acceptability will be a review issue.

Furthermore, we have the following concerns with regard to the results of the IPI-145-07 trial based on your summary results in the background package:

- a. Although the trial met the primary endpoint for PFS, the improvement in median PFS is modest (13.3 vs 9.9 months) with no difference in overall OS (HR: 0.99 [0.65, 1.50]).
- b. A higher proportion of patients in the duvelisib arm died before progression (duvelisib: 11.9%, ofatumumab: 5.7%) and fatal TEAEs (duvelisib: 12.0%, ofatumumab: 4.5%), serious TEAEs (duvelisib: 72.8%, ofatumumab: 32.3%) and \geq grade 3 TEAEs (duvelisib: 87.3%, ofatumumab: 48.4%) were also higher in the duvelisib arm, suggesting significant safety issues.
- c. The estimated PFS KM curves start to separate after 9 months which is after the patients in the ofatumumab completed the 7 cycles of treatment. It is not known whether additional cycles of ofatumumab would have been beneficial in these patients.
- d. (b) (4)

Discussion: There was no discussion.

Question 1c: *Does the Agency agree that the two proposed clinical studies, Study IPI-145-06 and IPI-145-02, support filing an NDA seeking accelerated approval for the treatment of FL patients who have received at least 2 prior therapies?*

FDA Response to Question 1c: Your proposal to submit an NDA for accelerated approval for the treatment of FL patients who have received at least 2 prior therapies based on the pivotal single-arm IPI-145-06 study and supporting IPI-145-02 study is acceptable. A decision on filing will be made after receipt of the application. Note that the safety profile of duvelisib in patients with FL in the IPI-145-06 trial appears in general consistent with the duvelisib safety profile in patients with CLL/SLL in the IPI-145-07 trial (with the exception of TESAE and TEAE leading to treatment discontinuation which appears worse in the IPI-145-07 trial). Thus, we have the same serious safety concerns with duvelisib for the FL indication as for the CLL/SLL indication.

Discussion: There was no discussion.

Question 2: *The Sponsor is planning to provide a pharmacovigilance (PV) plan in accordance with the FDA Guidance for Industry (ICH E2E Pharmacovigilance Planning dated April 2005); the PV plan will characterize the observed risks of duvelisib monotherapy, utilizing safety data from clinical studies and enhanced pharmacovigilance methodologies, and describe risk-mitigation strategies employed during clinical development. Does the FDA agree that a PV plan in conjunction with the USPI and Patient Medication Guide would be sufficient for the NDA filing?*

FDA Response to Question 2: It is highly likely that a risk evaluation and mitigation strategy (REMS) will be required for duvelisib. However, adequacy of your proposal to address safety concerns for duvelisib is a review issue.

Discussion: There was no discussion.

Question 3: Does the Agency agree with Verastem's proposal to present all integrated safety data (n=442 subjects) utilizing MedDRA version 16.1, and non-integrated safety data coded with the MedDRA version utilized for each study?

FDA Response to Question 3: Yes, your proposal is acceptable.

Discussion: There was no discussion.

Question 4: Does the Agency agree with Verastem's proposal

(b) (4)

(b) (4)

FDA Response to Question 4: No,

(b) (4)

(b) (4)

Discussion: There was no discussion.

Clinical Pharmacology

Question 5: The population pharmacokinetic and exposure-response analyses will examine intrinsic and extrinsic factors affecting duvelisib and IPI-656 exposures and their potential impact on the efficacy and safety of duvelisib. Does the Agency agree that the planned population pharmacokinetic and exposure-response analyses is sufficient to support the filing of NDA?

FDA Response to Question 5: Your approach appears acceptable.

Discussion: There was no discussion.

Question 6: Based on the discussion with the Agency (Type C meeting, dated 02 March 2015), exposure-response analyses, as an alternative to a thorough QT study, are being conducted to evaluate potential of duvelisib to cause QT prolongation. The analyses included healthy subjects and subjects with hematological malignancies dosed with duvelisib ranging from 8 to 100 mg BID. In addition to these analyses, the QT package will include protocols, study reports, modeling reports with associated datafiles and codes, and safety narratives aligned with the guidance received by the Agency. Does the Agency agree with the QT plan?

FDA Response to Question 6: Yes, overall the plan is acceptable. However, we have the following additional comments regarding your proposed analysis:

1. The Study IPI-145-02 may have adequate information to exclude large mean QTc effects (i.e. 20 ms) for this oncology indication. We recommend that you use this study for your

primary analysis rather than the pooled data from multiple studies. Pooling data from multiple studies is generally not recommended in cases where differences in the study conditions may cause bias in results: 1) the study control procedures (e.g., placebo, food control) are different; 2) ECG acquisition and ECG measurement at baseline and during the treatment are different; or 3) study subjects are taking concomitant medications or with comorbid conditions that increase the variability in the QTc interval in one study but not the other.

2. For Study IPI-145-02, please provide the by-time analysis (mean and 90% CI) per dose level (for 25 and 75 mg BID dose group) and outlier analyses for all the dose levels.
3. We recommend using Δ QTc as the dependent variable for your concentration-QTc analysis.

Include the following items when you submit your QT study report:

- a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
- b. Electronic copy of the study report
- c. Electronic or hard copy of the clinical protocol
- d. Electronic or hard copy of the Investigator's Brochure
- e. Annotated CRF
- f. A data definition file which describes the contents of the electronic data sets
- g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
- h. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
- i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
- j. Narrative summaries and case report forms for any:
 - i. Deaths
 - ii. Serious adverse events
 - iii. Episodes of ventricular tachycardia or fibrillation
 - iv. Episodes of syncope
 - v. Episodes of seizure
 - vi. Adverse events resulting in the subject discontinuing from the study
- k. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)

1. A completed Highlights of Clinical Pharmacology Table

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

Discussion: There was no discussion.

NDA Organization and Data Transfer

Question 7:

Does the Agency agree with Verastem's NDA organization and the layout of the proposed Table of Contents and the proposed datasets for the NDA?

FDA Response to Question 7: Appendix 4 data format is acceptable.

From a technical standpoint (not content related) yes, the proposed format for the planned NDA is acceptable. However, please see additional comments below

1. Please provide the hyperlinked Reviewer's Guide as a separate document, from the cover letter in m1.2
2. Regarding the use of m1.3.2, sponsor should notify the ORA office by letter, of the NDA eCTD submission, making explicit reference to the drug, application number, etc. State in the letter that "the application is being submitted in eCTD format to the Division of XXX, and as the field offices have access to the complete submission on the FDA network, an individual field copy is no longer required". A copy of this letter is what you place in m1.3.2

Sponsors options of cross referencing information submitted to another application (if any), would be to either place a cross reference document under module m1.4.4 (cross reference to other applications), or use cross application links.

3. To use the first option (placing a cross reference document in m1.4.4), a table formatted document can be submitted in section 1.4.4 of the eCTD, detailing previously submitted information (non- eCTD or paper) that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), (5) eCTD sequence number, (6) the eCTD heading location (e.g., m3.2.p4.1 Control of Excipients – Specifications), (7) the document leaf title and (8) the submission identification (e.g., submission serial number, volume number, electronic folder, file name, etc.) of the referenced document and if possible, hyperlinks to the referenced documents.

4. To use the second option (cross application links), both applications would need to be in eCTD format. The applications need to include the appropriate prefix in the href links (e.g. xlink:href=" ../indXXXXXX/0009/m2/24-nonclin-over/nonclinical-overview.pdf"). In the leaf titles of the documents, it is recommended that the leaf title indicate the words “cross reference to” and the application number (e.g. Cross Ref to indXXXXXX). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application.
5. Prior to using cross application linking in an application and to ensure successful use of cross application links, it is recommended that sponsor submits an "eCTD cross application links" sample.
6. To submit an eCTD cross application links sample, sponsor would need to request two sample application numbers from the ESUB team - esub@fda.hhs.gov. For more information on eCTD sample, please refer to the Sample Process web page which is located at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissions/UCM315023.pdf>
7. For archival purposes, also submit a pdf version of any labeling document submitted in word. When you submit word documents, make sure the leaf title includes "word", so reviewers could quickly identify the word version of the document.
8. Do not create additional nodes in the eCTD structure (e.g. m3), beyond what is in the specifications. Please make sure your approach fits the DTD and the “Granularity Annex”, located here:- <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073261.pdf>
9. The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be provided in tabular format and linked to the referenced studies in m5
10. All documents regarding ISS in m5.3.5.3, should be file tagged as “iss” and placed under the study tagging file of the ISS

Discussion: There was no discussion.

Quality/CMC

Question 8: *Based on current regulatory guidance, process knowledge, and previous feedback from the Agency, [REDACTED] ^{(b) (4)} have been established as the regulatory starting materials for the manufacture of duvelisib drug substance. Verastem proposes to submit the details in the NDA. Does the Agency agree with the approach and the designation of these three regulatory starting materials?*

FDA Response to Question 8: Your approach to the designation of the three regulatory starting materials appears acceptable.

Discussion: There was no discussion.

Question 9: Based on drug substance manufacturing development history, batch analysis, and impurity control strategies, Verastem is proposing the specifications for the commercial drug substance. Does the Agency agree with Verastem's overall control strategy and the proposed specifications for drug substance, including drug substance process impurities and degradants?

FDA Response to Question 9: The proposed specification for the drug substance appears to be reasonable. We remind you that final acceptability of the drug substance specifications will be determined during review of the NDA.

Discussion: There was no discussion.

Question 10: Does the Agency agree with Verastem's overall strategy (b) (4)

(b) (4)

FDA Response to Question 10: No, we do not agree with the overall strategy (b) (4)

(b) (4)

Discussion: The Agency agrees with the proposal to submit six months of stability data with the caveat that the proposed expiration date would be a review issue. The Agency agrees that the Applicant can submit additional stability data within 30 days of receipt of the NDA application.

Question 11: Based on drug product manufacturing development history, batch analysis and stability studies to date, Verastem is proposing the specifications for the commercial drug product. Does the Agency agree with Verastem's proposed specifications for duvelisib drug product including (a) amount (%) of dissolved drug (Q), and (b) (b) (4) levels in duvelisib drug product at release and stability?

FDA Response to Question 11: Overall, the proposed drug product specification tests are acceptable for review and potentially supportive of commercialization; however, the acceptability of the proposed acceptance criteria is a review issue that will be determined as a part of the NDA review.

In response to (a) amount (%) of dissolved drug (Q):

Please note that the adequacy of the proposed dissolution acceptance criterion for your products will be made during the review process based on the totality of the provided dissolution data.

- a. We recommend that the multipoint dissolution profile data (i.e., 15, 20, 30, 45, 60 minutes) from the bio-batches (pivotal clinical and PK) and the primary stability batches should be used for the setting of the dissolution acceptance criteria of your product (i.e., specification-sampling time point and specification value).
- b. Specifications should be established based on average in vitro dissolution data for each lot under study, equivalent to USP Stage 2 testing (n=12).
- c. The last time point should be the time point where at least $\frac{(b)}{(4)}\%$ of drug has been released. If the maximum amount of drug dissolved is less than $\frac{(b)}{(4)}\%$, the last time point should be the time when the plateau of the dissolution profile has been reached.
- d. The selection of the specification time point should be where $Q = \frac{(b)}{(4)}\%$ dissolution occurs.”

In response to (b) $\frac{(b)}{(4)}$ levels in duvelisib drug product at release and stability:

The proposed limit of $\frac{(b)}{(4)}$ ppm appears reasonable and is consistent with the agency’s previous recommendation for the proposed 50 mg per day dose. However we remind you that adequacy of the proposed acceptance criterion for $\frac{(b)}{(4)}$ will be determined as a part of the NDA review.

Additional Statistical Comments:

1. FDA requests that an Analysis Data Reviewer’s Guide (ADRG) and Study Data Reviewer’s Guide (SDRG), an important part of a standards-compliant study and analysis data submission, be prepared and submitted in the NDA. Please refer to the “Study Data Technical Conformance Guide: Technical Specifications Document,” available at: <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>.
2. Provide sufficient comments, adequate bookmarks, and hyperlinks in the define file(s) to ensure efficient review.
3. Provide executable SAS program(s) with adequate document(s) to allow FDA to duplicate the analysis datasets derivation from raw datasets
4. Provide the SAS programs as well as format library files used for efficacy and safety data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs.

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 your drug 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 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. Submitted 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.

Discussion: There was no discussion.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The Applicant noted that all components of the application will provided at the time of the NDA submission.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan. It was noted that the Agency would communicate further with the Sponsor as needed during the review.
- 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).

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).

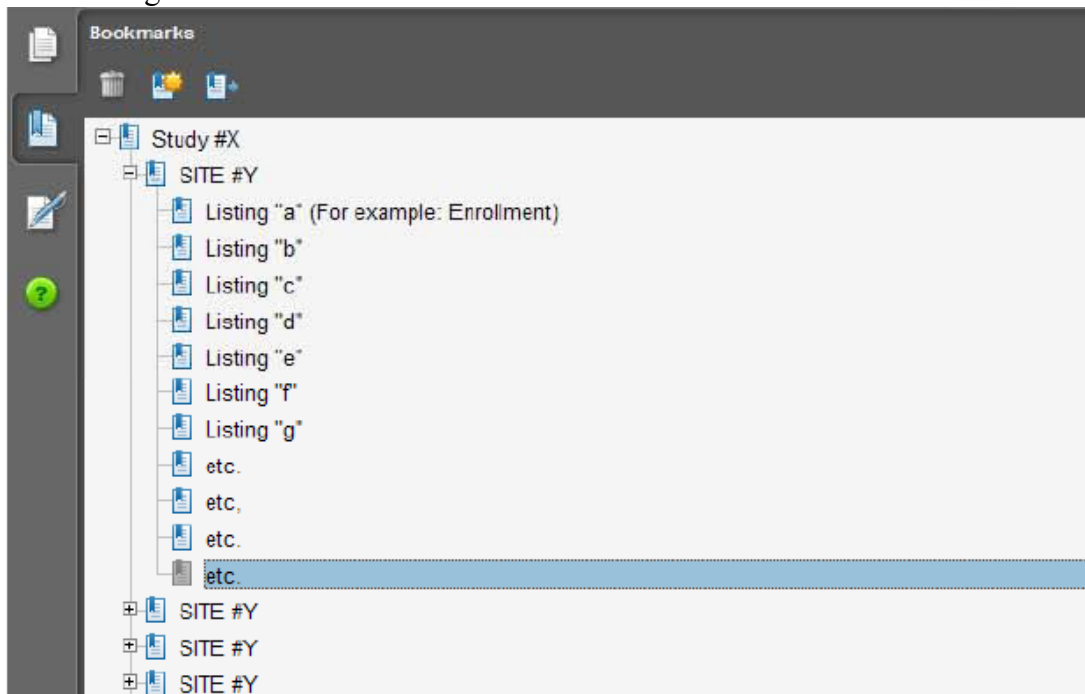
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - 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.

References:

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

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

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

None

6.0 ATTACHMENTS AND HANDOUTS

A copy of the sponsor's comments is attached for reference.

From: [Mary Matthew](#)
To: [McMullen Rachel](#); [Priya Jambhekar](#)
Subject: RE: IND 112486_ Pre-NDA Meeting- Preliminary Comments
Date: Monday, October 16, 2017 1:59:33 PM
Attachments: [image001.png](#)

Dear Rachel,

Thank you again for providing the Agency responses on a Sunday. We are very excited to have the opportunity to introduce the Verastem team to the FDA at tomorrow's meeting. With that, there are two questions that Verastem would like to discuss with the Agency, Question 1a and Question 10. Also included is the dial in information that can be used.

Question 1a: *Does the Agency agree with Verastem's proposal to submit a single NDA requesting regular approval for CLL/SLL and accelerated approval for FL?*

FDA Response to Question 1a: It is acceptable to submit a single NDA for the CLL/SLL and FL indications. However, it is likely that the application will need to be administratively split.

Additional Comment from Verastem for October 17, 2017 pre-NDA meeting:

It is Verastem's understanding that an administrative split is an action taken by the Agency. Is there anything Verastem can do or provide in our electronic filing to assist the Agency with this activity?

Question 10: *Does the Agency agree with Verastem's overall strategy* (b) (4)
(b) (4)
?

FDA Response to Question 10: No, we do not agree with the overall strategy. (b) (4)
(b) (4)

Additional Comment from Verastem for October 17, 2017 pre-NDA meeting:

Thank you for your feedback on the CMC questions. Verastem is seeking further clarification on question 10 specifically related to the 15 mg strength. We want to confirm that submission of the 15 mg strength, supported by stability data on three primary (registration) batches in the NDA is acceptable. We plan to include 6 month accelerated and RT data in the NDA. Based upon these data, we propose to request a (b) (4) month expiration date for the 15 mg strength. Does the FDA agree with this proposal? In the event that 9 month RT data for the 15 mg strength are available within 30-days of the NDA submission, is it acceptable for Verastem to submit these additional data to support an (b) (4) month expiration date?

Dial in information:

- Conference telephone # (b) (4)
- Participant Code: (b) (4)

Please let us know if there is any further information that you need. Also, we look forward to receipt of the Lobbyguard notification.

Mary

Mary A. Matthew
Vice President, Regulatory Affairs
Verastem, Inc.
117 Kendrick Street
Suite 500
Needham, MA 02494
Office: 781-292-4220
Cell: (b) (6)
mmatthew@verastem.com

From: McMullen, Rachel [mailto:Rachel.Mcmullen@fda.hhs.gov]
Sent: Sunday, October 15, 2017 4:25 PM
To: Mary Matthew <mmatthew@verastem.com>; Priya Jambhekar <pjambhekar@verastem.com>
Cc: McMullen, Rachel <Rachel.Mcmullen@fda.hhs.gov>
Subject: IND 112486_ Pre-NDA Meeting- Preliminary Comments

Importance: High

Good evening Mary and Priya,

Attached are the Agency's preliminary responses to your meeting questions. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (**contact me**).

Please note that we plan to capture real time meeting minutes during the meeting. This will involve projection of the preliminary sponsor questions and FDA responses during the meeting and the capture of summary statements to summarize the important discussion points, agreements, clarifications, and action items after discussion of each question. This will take some time during the meeting and require projection of the responses. As a consequence, it will not be possible for us to project a PowerPoint presentation. Sponsor presentations are generally discouraged. Please note that if there are any major changes to your development plan, to the purpose of the meeting or to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting.

Please email me an outline of which questions will need clarification/discussion at the meeting in order of priority, as well as any presentation materials or slides by **COB tomorrow, October 16th**. Please also designate the amount of time to be allocated for discussion and capturing of meeting comments for each question.

I will email you a Lobbyguard notification tomorrow.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue | Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574



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/s/

KATHY M ROBIE SUH
10/19/2017



IND 112486

MEETING MINUTES

Infinity Pharmaceuticals, Inc.
Attention: Tamyra Toole, JD, RN
Vice President, Regulatory Affairs and Quality Assurance
784 Memorial Drive
Cambridge, MA 02139

Dear Ms. Toole:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for duvelisib (IPI-145).

We also refer to the meeting between representatives of your firm and the FDA on August 30, 2016. The purpose of the meeting was to discuss the results of Study IPI-145-06, a phase 2 clinical study evaluating the safety and efficacy of duvelisib in 129 patients with indolent non-Hodgkin lymphoma, including follicular lymphoma, small lymphocytic lymphoma and marginal zone lymphoma, that are refractory to rituximab and to either chemotherapy or radioimmunotherapy and next steps in the development of duvelisib.

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 Rachel McMullen, Regulatory Project Manager at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Nicole Gormley, MD
Acting Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



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

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: August 30, 2016; 3:00-4:00PM (EDT)

Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

Application Number: 112486
Product Name: Duvelisib (IPI-145)
Indication: Treatment of patients with relapsed/refractory CLL and SLL
Sponsor/Applicant Name: Infinity Pharmaceuticals, Inc.

Meeting Chair: Nicole Gormley, MD
Meeting Recorder: Rachel McMullen, MPH, MHA

FDA ATTENDEES

OHOP/Division of Hematology Products

Ann Farrell, MD, Director
Nicole Gormley, MD, Acting Clinical Team Leader
Hyon-Zu Lee, Pharm D, Medical Officer
Ashley Ward, MD, Medical Officer
Kelly Norsworthy, MD, Medical Officer
Rachel McMullen, MPH, Regulatory Project Manager

Office of Biostatistics

Yuan Li Shen, DrPH, Lead Statistician
Lola Luo, PhD, Statistical Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V

Stacy Shord, PharmD Clinical Pharmacology Team Leader
Yuhong Chen, MD, PhD, Clinical Pharmacology Reviewer

SPONSOR ATTENDEES

Infinity Pharmaceuticals, Inc.

Julian Adams, PhD, President, Research and Development
Claudio Dansky-Ullmann, MD, Vice President, Clinical Development

Joseph Pearlberg, MD, Senior Director, Clinical Development
Lixin Han, PhD, Senior Director, Biostatistics
James Porter, PhD, Vice President, Product Development
Laura DiMarzio, MS, Director, Regulatory Affairs
Tamyra Toole, JD, RN, Vice President, Regulatory Affairs & Quality Assurance
Suresh Mahabhashyam, MD, Senior Medical Director, Safety & Risk Management

1.0 BACKGROUND

Duvelisib is being developed for the treatment of patients with follicular lymphoma (FL), small lymphocytic lymphoma (SLL), and chronic lymphocytic leukemia (CLL), which are characterized by the clonal proliferation and accumulation of malignant B lymphocytes in the blood and lymphoid tissues. As an investigational drug, duvelisib is currently not approved for marketing in any country.

(b) (4)

The purpose of this End of Phase 2 meeting is to discuss the results of Study IPI-145-06, a phase 2 clinical study evaluating the safety and efficacy of duvelisib in 129 patients with indolent non-Hodgkin lymphoma (iNHL), including FL, SLL and MZL, who are refractory to rituximab and to either chemotherapy or radioimmunotherapy (RIT), as well as the next steps in the development of duvelisib for the treatment of patients with FL and SLL.

FDA sent Preliminary Comments to Infinity on August 25, 2016.

2. DISCUSSION

CLINICAL

Question 1:

(b) (4)

(b) (4)

Does the FDA agree

(b) (4)

(b) (4)

FDA RESPONSE: No.

(b) (4)

Question 2:

Study IPI-145-21 is a phase 2 randomized study of duvelisib administered in combination with rituximab (DR) compared to R-CHOP in patients with relapsed/refractory FL. The primary endpoint of the study is progression-free survival (PFS), defined as the time from randomization to documented disease progression according to the revised IWG criteria as assessed by the IRC, or death due to any cause. The design of Study IPI-145-21 was discussed at a Type B meeting on 16 July 2015, and additional feedback was received from FDA on 23 November 2015 and 05 February 2016. The revisions recommended by FDA were incorporated into Protocol Amendment 1 submitted to the IND on 16 February 2016 (SN [0325](#)).

a. Does the FDA agree that PFS as defined is an acceptable primary endpoint?

FDA RESPONSE: Yes.

DISCUSSION: There was no discussion.

b. Does the FDA agree that the eligibility criteria adequately define the patient population that is intended to support the proposed indication?

FDA RESPONSE: Yes.

DISCUSSION: There was no discussion.

c. Does the FDA agree [REDACTED] (b) (4) ?

FDA RESPONSE: No. [REDACTED] (b) (4)

(b) (4)

DISCUSSION: There was no discussion.

Question 3:

In study IPI-145-21, patients will be randomized in a 1:1 ratio to 1 of 2 treatment arms:

- *Arm 1 (experimental arm): DR*
- *Arm 2 (comparator arm): R-CHOP*

FL patients will be stratified by the following two stratification factors:

- *Number of prior treatment regimens (1 vs 2)*
- *Timing of progression after initiation of most recent alkylator-based chemotherapy regimen (≤ 12 months vs $> 12-24$ months)*

Does the FDA agree that the proposed stratification schema for the FL patients in Study IPI-145-21 is acceptable?

FDA RESPONSE: You could consider stratifying patients with FL by rituximab relapsed type (rituximab monotherapy vs. rituximab + chemotherapy).

DISCUSSION: There was no discussion.

Question 4:

The Sponsor proposes to amend protocol IPI-145-21 to include a cohort of approximately 50 patients with SLL. The synopsis of the proposed protocol amendment is attached ([Appendix 1](#)). This cohort is proposed in consideration of the relative rarity of SLL, and in an effort to generate potential confirmatory data in patients with SLL, if warranted, based on the efficacy observed in study IPI-145-06. Two inclusion criteria specific to the SLL patients are proposed in the attached draft protocol synopsis. In the proposed amendment, lymphoma subtype (FL

vs SLL) will be added as the initial stratification factor for randomization. Subjects with FL will subsequently be stratified as described in Question 3 and in the current protocol. Subjects with SLL will not be further stratified.

Does FDA agree that the proposal to amend the protocol to add the cohort of SLL patients, including sample size, eligibility criteria and stratification schema, are acceptable?

FDA RESPONSE: Yes.

DISCUSSION: There was no discussion.

BIOSTATISTICS

Question 5:

(b) (4)

Does the FDA agree

(b) (4)

(b) (4)

FDA RESPONSE: No. While the interim analysis plan for PFS and sample size calculation based on PFS appear reasonable, we have the following comment on the SAP:

(b) (4)

DISCUSSION: The sponsor clarified (b) (4). The proposal appears acceptable and the sponsor plans to provide a revised statistical analysis plan (SAP). The sponsor clarified that the (b) (4) will be revised in the revised SAP.

Post Meeting Comments:

[Redacted] (b) (4)

Question 6:

[Redacted] (b) (4)

- a. *Does the FDA agree that the proposed statistical analysis plan for the primary endpoint of PFS is acceptable for the FL population?*
- b. *Does the FDA agree that the proposed statistical analysis plan for the primary endpoint of PFS is acceptable for the SLL population?*

FDA RESPONSE:

- a. No, see response to question 5.

DISCUSSION: Please refer to discussion for Question 5. Per the discussion in Question 5, FDA considers the proposed primary efficacy analysis to be acceptable.

FDA RESPONSE:

- b. No, FDA disagrees. [Redacted] (b) (4)

[Redacted] (b) (4)

DISCUSSION: The Sponsor's proposal may be acceptable; however, the Agency will need to review the revised SAP prior to concurrence.

REGULATORY

Question 7:

[Redacted] (b) (4)

a. *Does the FDA agree* [Redacted] (b) (4)
[Redacted] (b) (4)

FDA RESPONSE: No. See our response to question #2c and also #1.

DISCUSSION: The Agency stated that the design of Trial 21 appears reasonable; the adequacy of the trial to support approval will be a review issue.

b. *Does the FDA agree that the proposed amendment to Study IPI-145-21 to incorporate SLL patients is acceptable to support registration in the proposed indication for the treatment of SLL?*

FDA RESPONSE: The overall synopsis to incorporate SLL appears acceptable. Also see our response to question #1.

DISCUSSION: The Agency stated that from a clinical standpoint the incorporation of the SLL cohort appears reasonable. From a statistical standpoint, the Agency will need to review the SAP prior to concurrence.

c. *Does the FDA agree* [Redacted] (b) (4)
[Redacted] (b) (4)

FDA RESPONSE: No. See our response to question #2c and also #1.

DISCUSSION: The Agency noted that it could not agree to the proposal [Redacted] (b) (4)
[Redacted] (b) (4).

Additional Clinical Pharmacology Comments:

Revise the protocol IPI-145-21 to address the following recommendation:

1. Conduct ECG collection at baseline, around the anticipated maximal plasma concentrations after single dose and at steady-state to capture the effects of duvelisib on QT interval.
2. Exclude patients receiving sensitive CYP3A4 and CYP2C8 substrates from study entry and prohibiting administration of such substrates during trial, or provide data to justify that such prohibition is not necessary.

During the clinical development of duvelisib, address the following recommendations:

1. Conduct population pharmacokinetic analyses to evaluate the effect of intrinsic and extrinsic factors on the pharmacokinetics of duvelisib and its active metabolites, if any. Refer to the FDA Guidance for Industry entitled “Population Pharmacokinetics” found at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf>.

2. Explore the exposure-response relationships for duvelisib and its active metabolites, if any, for measures of effectiveness, toxicity and pharmacological responses including pharmacodynamic biomarkers. Refer to the FDA Guidance for Industry entitled “Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf>.
3. Complete a clinical pharmacokinetic drug interaction trial to assess the impact of duvelisib on the exposure to a sensitive or narrow therapeutic CYP2C8 substrate. Refer to the FDA draft Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>. Include the final study report with all supporting datasets in the NDA application package. Alternatively, provide justification to support the lack of need of pharmacokinetic studies.
4. Determine bioavailability of duvelisib per the FDA Guidance for Industry entitled “Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM389370.pdf>.
5. Conduct a ‘thorough QT’ study to evaluate duvelisib for its QT prolongation potential. Submit a QT evaluation plan to the IND for FDA review and comment. Conduct an adequate assessment early in clinical development to rule out the QT prolongation potential of duvelisib and to avoid the need for conducting intensive ECG monitoring in clinical trials. Refer to the FDA Guidance for Industry entitled “E14 Clinical Evaluation of QT/QTc Interval Prolongation” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf>.
6. Validate the analytical methods used to determine the concentrations of duvelisib and its metabolites, if any. Refer to the FDA draft Guidance for Industry entitled “Bioanalytical Method Validation” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf>.
7. Investigate the solubility of duvelisib as a function of pH. Evaluate the potential for concomitant gastric acid-reducing agents (i.e., proton pump inhibitors, histamine receptor antagonists, antacids) to affect the oral absorption of duvelisib if duvelisib shows pH-dependent solubility (e.g. solubility at pH 6.0–6.5 < solubility at pH 1–2) and becomes poorly soluble as gastrointestinal pH increases (e.g. solubility at pH 6.0–6.5 < clinical dose/250 ml).

DISCUSSION: The sponsor provided a response to the Agency’s clinical pharmacology comments, but there was no discussion at the meeting. The Sponsor plans to follow up on the clinical pharmacology comments post meeting.

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

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

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

DATA STANDARDS FOR STUDIES

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

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdcr-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>.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA to sponsors/applicants 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), sponsors/applicants 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).

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).

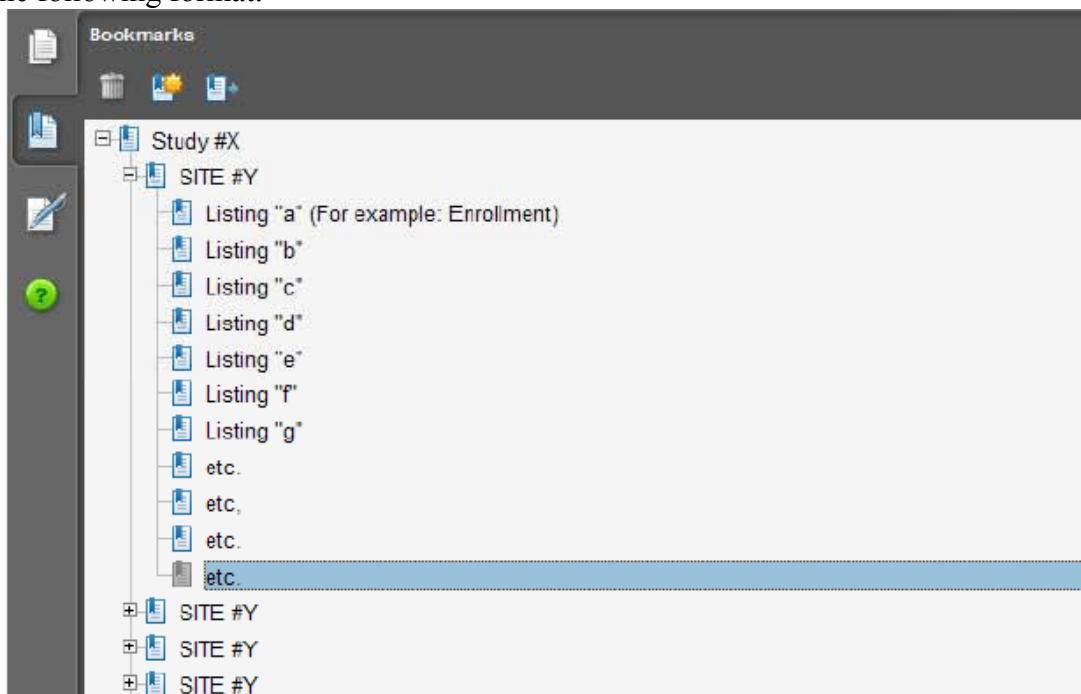
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - 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

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

There were no issues requiring further discussion.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

A copy of the sponsor's responses is attached for reference.

On July 25, 2016, Infinity Pharmaceuticals, Inc. (Infinity) submitted the meeting package in advance of the Type B End-of-Phase 2 meeting scheduled on August 30, 2016 to discuss the results of Study IPI-145-06 and the design of Study IPI-145-21. FDA provided preliminary responses to the questions proposed by Infinity on August 25, 2016. Below the Infinity question is in bold followed by the FDA preliminary response and then the Infinity response.

Question 1:

(b) (4)

Does the FDA agree

(b) (4)
(b) (4)

FDA Response to Question 1:

No.

(b) (4)

Infinity Response:

The Sponsor would like to discuss the following FDA preliminary positions:

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Question 2:

Study IPI-145-21 is a phase 2 randomized study of duvelisib administered in combination with rituximab (DR) compared to R-CHOP in patients with relapsed/refractory FL. The primary endpoint of the study is progression-free survival (PFS), defined as the time from randomization to documented disease progression according to the revised IWG criteria as assessed by the IRC, or death due to any cause. The design of Study IPI-145-21 was discussed at a Type B meeting on 16 July 2015, and additional feedback was received from FDA on 23 November 2015 and 05 February 2016. The revisions recommended by FDA were incorporated into Protocol Amendment 1 submitted to the IND on 16 February 2016 (SN 0325).

- a. Does the FDA agree that PFS as defined is an acceptable primary endpoint?

FDA Response to Question 2a:

Yes.

Infinity Response:

No additional discussion requested.

- b. Does the FDA agree that the eligibility criteria adequately define the patient population that is intended to support the proposed indication?

FDA Response to Question 2b:

Yes.

Infinity Response:

No additional discussion requested.

- c. Does the FDA agree

(b) (4)

FDA Response to Question 2c:

No.

(b) (4)

(b) (4)

Question 3:

In study IPI-145-21, patients will be randomized in a 1:1 ratio to 1 of 2 treatment arms:

- Arm 1 (experimental arm): DR
- Arm 2 (comparator arm): R-CHOP

FL patients will be stratified by the following two stratification factors:

- Number of prior treatment regimens (1 vs 2)
- Timing of progression after initiation of most recent alkylator-based chemotherapy regimen (≤ 12 months vs $> 12-24$ months)

Does the FDA agree that the proposed stratification schema for the FL patients in Study IPI-145-21 is acceptable?

FDA Response to Question 3:

You could consider stratifying patients with FL by rituximab relapsed type (rituximab monotherapy vs. rituximab + chemotherapy).

Infinity Response:

Infinity will consider adding this stratification factor when amending the protocol. No additional discussion requested.

Question 4:

The Sponsor proposes to amend protocol IPI-145-21 to include a cohort of approximately 50 patients with SLL. The synopsis of the proposed protocol amendment is attached ([Appendix 1](#)). This cohort is proposed in consideration of the relative rarity of SLL, and in an effort to generate potential confirmatory data in patients with SLL, if warranted, based on the efficacy observed in study IPI-145-06. Two inclusion criteria specific to the SLL patients are proposed in the attached draft protocol synopsis. In the proposed amendment, lymphoma subtype (FL vs SLL) will be added as the initial stratification factor for randomization. Subjects with FL will subsequently be stratified as described in Question 3 and in the current protocol. Subjects with SLL will not be further stratified.

Does FDA agree that the proposal to amend the protocol to add the cohort of SLL patients, including sample size, eligibility criteria and stratification schema, are acceptable?

FDA Response to Question 4:

Yes.

Infinity Response:

No additional discussion requested.

Question 5:

[Redacted]

(b) (4)

Does the FDA agree

[Redacted]

(b) (4)
(b) (4)

FDA Response to Question 5:

No. While the interim analysis plan for PFS and sample size calculation based on PFS appear reasonable, we have the following comment on the SAP:

- [Redacted]

(b) (4)

Infinity Response:

Infinity proposes the following strategy:

[Redacted]

(b) (4)

Does FDA agree?

Question 6:

[Redacted]

(b) (4)

(b) (4)

- a. Does the FDA agree that the proposed statistical analysis plan for the primary endpoint of PFS is acceptable for the FL population?**

FDA Response to Question 6a:

No, see response to question 5.

Infinity Response:

(b) (4)

- b. Does the FDA agree that the proposed statistical analysis plan for the primary endpoint of PFS is acceptable for the SLL population?**

FDA Response to Question 6b:

No, FDA disagrees.

(b) (4)

(b) (4)

Question 7:

[Redacted] (b) (4)

a. Does the FDA agree [Redacted] (b) (4)
[Redacted] (b) (4)

FDA Response to Question 7:

No. See our response to question #2c and also #1.

Infinity Response:

The Sponsor agrees to the request in #2c. [Redacted] (b) (4) does FDA agree that Study IPI-145-21 as designed is acceptable to support registration, if positive, in the proposed indication for the treatment of FL?

b. Does the FDA agree that the proposed amendment to Study IPI-145-21 to incorporate SLL patients is acceptable to support registration in the proposed indication for the treatment of SLL?

FDA Response to Question 7b:

The overall synopsis to incorporate SLL appears acceptable. Also see our response to question #1.

Infinity Response:

[Redacted] (b) (4)

c. Does the FDA agree [Redacted] (b) (4)
[Redacted] (b) (4)

FDA Response to Question 7c:

No. See our response to question #2c and also #1.

Infinity Response:

[Redacted] (b) (4)

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References

- Sehn, L. H. (2016). Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3. *Lancet Oncol* 2016;17: 1081-1093.
- Hamlin, P. (2016). Obinutuzumab plus bendamustine in rituximab-refractory indolent lymphoma. Comment *Lancet Oncol*. Published Online June 23, 2016 [http://dx.doi.org/10.1016/S1470-2045\(16\)30157-7](http://dx.doi.org/10.1016/S1470-2045(16)30157-7).

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/s/

NICOLE J GORMLEY
09/01/2016