CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761121Orig1s008

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 109409

MEETING MINUTES

Genentech, Inc.
Attention: Ashley Weber, PharmD.
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Dr. Weber:

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

We also refer to the telecon between representatives of your firm and the FDA on September 24, 2021. The purpose of the meeting was to discuss the clinical results from the primary analysis of efficacy and safety data from the pivotal POLARIX study and the final results from supportive Study GO29044, and obtain feedback on the acceptability of the results to form the basis of a sBLA for POLIVY in the proposed indication.

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

If you have any questions, call Wanda Nguyen, PharmD, Regulatory Project Manager, at 301-796-2808.

Sincerely,

{See appended electronic signature page}

Yvette Kasamon, MD
Clinical Team Leader
Division of Hematologic Malignancies II
Office of Oncologic Diseases
Center for Drug Evaluation and Research (CDER)

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-sBLA
Meeting Date and Time:	September 24, 2021, 3:00-4:00PM (EST)
Meeting Location:	Teleconference
Application Number:	IND 109409
Product Name:	polatuzumab vedotin
Indication:	in combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone, is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma
Sponsor Name:	Genentech, Inc.
Regulatory Pathway:	351(a) of the Public Health Service Act
Meeting Chair:	Yvette Kasamon, MD
Meeting Recorder:	Wanda Nguyen, PharmD

FDA ATTENDEES

OOD/Division of Hematologic Malignancies 2
Nicole Gormley, MD, Director
Yvette Kasamon, MD, Clinical Team Leader
Nicole Sunseri, MD, PhD, Clinical Reviewer
Nicholas Richardson, DO, Clinical Team Leader

Office of Biostatistics/Division of Biometrics IX
Haiyan Chen, Statistical Reviewer
Qing Xu, Statistical Team Leader

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Ruby Leong, PharmD, Clinal Pharmacology Team Leader
Mathew John, PhD, Clinical Pharmacology Reviewer

Office of Regulatory Operations/Division of Regulatory Operations for Oncologic Diseases
Theresa Carioti, MPH, Chief Project Management Staff
Wanda Nguyen, PharmD, Senior Regulatory Health Project Manager

SPONSOR ATTENDEES

Genentech, Inc/Roche
Rong Deng, PhD - Senior Principal Scientist, Clinical Pharmacology
Charles Fuchs, MD, MPH - Senior Vice President - Global Head of Hematology and Oncology Product Development
Jamie Hirata, PharmD - Global Development Leader
Rucha Kothari, MD - Senior Safety Scientist, Safety Science
Ginna Laport, MD - Global Head, Lymphoma/CLL Development Franchise
Bea Lavery, MSc - Vice President, Global Oncology Regulatory Head
Calvin Lee, MD - Medical Director, Clinical Science
Madeleine Ma, MS - Biometrics Submission Leader
Gabriel Man, MD - Safety Strategy Leader, Safety Science
Jiaheng Qiu, PhD - Project Lead Statistician, Biostatistics
Steven Slater, PhD - Global Franchise Head for Heme Oncology, Product Development Regulatory
Florence Tao, PhD - Senior Program Director, Product Development Regulatory
Ashley Weber, PharmD - Associate Program Director, Product Development Regulatory
Mark Yan, PhD - Principal Statistical Scientist, Biostatistics

1.0 BACKGROUND

Genentech, Inc., requested a Type B, pre-sBLA meeting to discuss the primary data from POLARIX, and to obtain feedback on the acceptability of the results to support an sBLA for the following indication: POLIVY in combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone, is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL).

FDA sent Preliminary Comments to Genentech, Inc. on September 21, 2021.

2.0 DISCUSSION

2.1. CLINICAL/STATISTICAL

Question 1: *Does the Agency agree that the efficacy and safety results from the pivotal Phase III Study POLARIX and supportive Study GO29044 provide sufficient evidence to support regular approval of the use of POLIVY plus R-CHP in patients with previously untreated DLBCL?*

FDA Response to Question 1:
No. Submission of the proposed sBLA is premature because of concerns regarding the interim overall survival (OS) outcomes. Based on the information presented, there are significant review issues with the proposed sBLA:

a. *Magnitude of the treatment effect on PFS*: While POLARIX appears to have met its primary endpoint, with a statistically significant improvement in PFS with Pola+R-CHP versus with R-CHOP in patients with previously untreated DLBCL, the magnitude of this treatment effect is modest. Coupled with the lack of improvement in the depth of response with Pola+R-CHP and the uncertainty in the OS outcomes (described below), we cannot draw definitive conclusions regarding the benefit/risk of this regimen in the intended population.

b. *OS data*: Based on the modest improvement in PFS and the interim OS data provided, it is unclear if Pola+R-CHP will provide an OS benefit over R-CHOP, and the early results suggest a potential detriment in OS in the Pola+R-CHP arm. At earlier time points between approximately 8 to 18 months, the KM estimate for OS suggests that this study regimen may be detrimental to patients. This observation may be due to a safety issue, an efficacy issue, confounding factors, or immaturity of the data. The OS data, while not mature, are an important aspect of the benefit-risk analysis particularly for the intended population, where the majority of patients with DLBCL are cured with standard front-line therapy.

   More mature and favorable OS data are needed to support an application in this front-line, potentially curative setting. We strongly advise that you postpone submission of the sBLA pending the results of a more mature OS analysis, which should be conducted at the time point pre-specified in the SAP.

In light of the modest improvement in PFS and the uncertainty of the treatment effect on OS, you may consider conducting a second confirmatory trial in order to provide sufficient evidence to support a clinically meaningful benefit.

Discussion: The Agency acknowledged the Sponsor's position regarding the PFS and OS data, but stated that significant concerns remain with the OS data. Given that the Sponsor intends on pursuing regular approval in the frontline, potentially curative setting, the Agency reiterated the importance of having more mature data to support that there is no detriment in OS with the polatuzumab + RCHP regimen. Based on the interim OS analysis, it is uncertain if an overall detriment may exist in the polatuzumab + RCHP arm. Thus, a more robust data package is necessary in order to inform the benefit/risk assessment. To that end, the Agency strongly advised the Sponsor to have the final OS data, based on the prespecified June 2022 data cut-off, available during review of the application.

2.2. REGULATORY

Question 2: *Does the Agency agree that the results of the primary analysis of POLARIX fulfill PMR 3630-1 under the provisions for 21 CFR 314 Subpart H, and therefore PMR 3630-2 (MO40598/POLARGO) is no longer applicable and will be removed as a post-marketing requirement?*

FDA Response to Question 2:
No. See response to Question 1. At this time, we do not agree that PMR 3630-2 (MO40598/POLARGO) is no longer applicable.

Discussion: No discussion occurred.

Question 3: *Does the Agency agree that the planned sBLA based on the pivotal Phase III POLARIX study and supportive study GO29044 is eligible for priority review?*

FDA Response to Question 3:
See response to Question 1. In general, the timeline for review will be communicated upon filing of the application.

Discussion: No discussion occurred.

Question 4: *Does the Agency agree that the planned sBLA based on the pivotal Phase III POLARIX study and supportive study GO29044 is eligible for Real Time Oncology Review (RTOR) and Project Orbis pilot programs?*

FDA Response to Question 4:
As communicated in the Agency's email dated 31 August 2021, this sBLA was not selected for RTOR. The concerns outlined in the response to Question 1 preclude participation in Project Orbis at this time.

Discussion: No discussion occurred.

Question 5*: Does the Agency agree with the proposed timing, content and format for the safety update report?*

FDA Response to Question 5:
See response to Question 1. We do not advise submitting an sBLA at this time. However, we have the following general comments:

In general, a safety update should provide at least 4 months of additional follow-up

Overall, the proposed content of the Safety Update Report appears acceptable. However, we request that the Sponsor also provide updated OS data In addition to the narratives of any death occurring within 90 days of the end of treatment, the Sponsor should submit an updated dataset with new deaths.

Discussion: No discussion occurred.

Additional Comments
We have the following additional, general comments:

1. Efficacy assessments: Ensure that, for patients censored for DOR and PFS, the time-to-event efficacy dataset includes detailed reasons for censoring and the date of the last applicable radiographic disease assessment. Censoring is to be based on the date of radiographic disease assessment, rather than clinical exam findings of continued remission.

2. Address the following questions in the Summary of Clinical Pharmacology:
   a. What is the basis for selecting the doses and dosing regimen used in the registration trials to support your marketing application? Identify individuals who required dose modifications and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.
   b. What are the exposure-response relationships for efficacy, safety and biomarkers?
   c. How do extrinsic (e.g., other drugs) and intrinsic factors (such as sex, race, body weight, organ dysfunctions, and disease) influence the exposure, efficacy, or safety of your drug? What dose modifications are recommended?
   d. What is the impact of immunogenicity on exposure, efficacy and safety?

3. Apply the following advice in preparing the clinical pharmacology sections of the supplemental BLA submission:
   a. Submit bioanalytical methods and validation reports for clinical pharmacology data.
   b. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate.
   c. Provide complete datasets for clinical pharmacology data. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
   d. 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.
   e. Identify individual subjects with dosage modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dosage modifications in the datasets.
   f. 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 pharmacometric data and models submission guidelines.

g. 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).

h. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and safety) relationships in the targeted patient population. Refer to Guidance for Industry for population PK and exposure-response relationships.

i. Use the laboratory analysis dataset (adlb.xpt) for the laboratory-based adverse reactions and the adverse event analysis dataset (adae.xpt) for the non-laboratory-based adverse reactions (individual and pooled terms as appropriate) to evaluate the exposure-response relationship for safety and the effect of intrinsic and extrinsic factors on safety based on the maximum toxicity grade compared to baseline.

j. Include a variable that identifies the maximum toxicity grade compared to baseline for laboratory-based adverse reactions in laboratory analysis dataset (adlb.xpt) and for non-laboratory-based adverse reactions (individual or pooled where applicable) in adverse event analysis dataset (adae.xpt) to support these analyses. A description of the pooled non-laboratory-based adverse reactions should be provided in the reviewer guide and consistent with common pooled terms used to inform labeling if applicable.

Discussion: **No discussion occurred.**

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or

biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

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

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

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

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the

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

Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

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

[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[5]

[5] http://www.fda.gov/ectd

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[6]

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)				

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

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[7] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[8]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[9]

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to

[7] https://www.fda.gov/media/84223/download
[8] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[9] https://www.fda.gov/media/85061/download

participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

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

- Assessment Aid[11]

ADVANCING ONCOLOGY DECENTRALIZED TRIALS

FDA Oncology requests that applicants submitting data to support NDA/BLA applications to voluntarily add flags to datasets in order to discriminate between REMOTE assessments and TRIAL SITE assessments. The intent is to allow FDA to learn from trials conducted in the COVID-19 pandemic that permitted some aspects of trial conduct to be performed remote from trial sites to reduce potential COVID exposure. The FDA hopes to learn more about the opportunities and challenges of these REMOTE modifications in order to foster use of "decentralize" aspects of clinical trials prospectively in the post-COVID era.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items from this meeting.

6.0 ATTACHMENTS AND HANDOUTS

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

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

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

YVETTE L KASAMON
09/27/2021 09:40:38 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 109409

MEETING MINUTES

Genentech, Inc.
Attention: Megan Salt, PhD
Regulatory Program Manager
1 DNA Way, MS #355e
South San Francisco, CA 94080-4990

Dear Dr. Salt:

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

We also refer to the meeting between representatives of your firm and the FDA on April 3, 2017. The purpose of the meeting was to discuss the proposed Phase III clinical development plan for polatuzumab vedotin for the treatment of previously untreated patients with diffuse large B-cell lymphoma.

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 Suria Yesmin, Regulatory Project Manager at (301) 348-1725.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Medical Officer, Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End-of-Phase 2
Meeting Date and Time:	April 3, 2017, 3:00PM – 4:00PM ET
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room 1313 Silver Spring, MD 20903
Application Number:	IND 109409
Product Name:	Polatuzumab vedotin
Indication:	Polatuzumab vedotin in combination with rituximab and CHP for the treatment of patients with previously untreated diffuse large B-cell Lymphoma (DLBCL)
Sponsor/Applicant Name:	Genentech, Inc.
Meeting Chair:	R. Angelo de Claro, MD
Meeting Recorder:	Suria Yesmin, BS, CCRP

FDA ATTENDEES

OHOP, Division of Hematology Products (DHP):
Ann T. Farrell, MD, Division Director
R. Angelo de Claro, MD, Clinical Team Leader
Yvette Kasamon, MD, Clinical Reviewer
Suria Yesmin, BS, CCRP, Regulatory Project Manager

Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology V:
Bahru Habtemariam, PharmD, Team Leader
Vicky Hsu, PhD, Pharmacologist

Office of Clinical Pharmacology (OCP), Division of Pharmacometrics
Jee Eun Lee, PhD, Pharmacometrician

Office of Biostatistics, Division of Biometrics V (DBV):
Lei Nie, PhD, Team Leader
Kyung Y Lee, PhD, Statistics Reviewer

SPONSOR ATTENDEES
Brian Baum, MBA, Lifecycle Team Lead, Global Product Strategy

John Bergan, Global Regulatory Lead, Regulatory Affairs
Jamie Hirata, PharmD, Global Development Team Lead, Clinical Science
Bea Lavery, MS, Global Regulatory Franchise Head, Hematology Oncology
Calvin Lee, MD, Clinical Scientist, Clinical Science
Huan Jin, PhD, Project Lead Statistician, Biostatistics
Dan Lu, PhD, Clinical Pharmacology Lead, Clinical Pharmacology
Vidya Maiya, MD, MBA, Safety Science Lead, Safety Science
Dale Miles, PhD, Pharmacology Sub-team Lead, Clinical Pharmacology
Megan Salt, PhD, US Regulatory Partner, Regulatory Affairs
Michael Wenger, MD, Sr. Group Medical Director, Clinical Science

1.0 BACKGROUND

Genentech, Inc., requested an End-of-Phase 2 meeting with FDA on January 19, 2017, to discuss the proposed Phase III clinical development plan for polatuzumab vedotin for the treatment of previously untreated patients with diffuse large B-cell lymphoma.

The Sponsor was seeking advice and obtain agreement on the following:

- The design of the proposed study, including the dosing regimen, study endpoints, target patient population, and safety monitoring plan.
- The statistical analysis proposal.
- The proposed clinical pharmacology plan.

FDA sent Preliminary Comments to Genentech, Inc., on March 24, 2017.

2. DISCUSSION

2.1. Clinical/Statistical

Question 1: *Does the Agency agree that the body of evidence, including data available for pola in combination with R-CHP support the initiation of the proposed Phase III study in 1L DLBCL?*

FDA Response to Question 1: Yes.

Discussion: There was no discussion.

Question 2: *Does the Agency agree with the overall design of the Phase III study to support full approval of polatuzumab vedotin for the proposed indication? In particular, does the Agency agree with:*

a) The 1:1 randomization, double blinding, and dosing regimen?

FDA Response to Question 2 (a): No.

- Stratification for randomization should consider the prognostic heterogeneity of the histologic subtypes of large B-cell lymphoma.

- Preemptive dose reduction in CHOP is a commonly adopted safety measure for patients aged ≥ 80 (i.e., "mini CHOP"). The draft protocol has no upper age restriction, but does not have such preemptive dose reductions. For safety, the protocol should either mandate dose reduction in patients aged ≥ 80, with potential stratification of randomization according to this age category, or restrict enrollment to patients aged < 80.

- The guidelines for toxicity management and supportive care are unacceptable; see response to Question 2d.

Also, based on the information provided in the briefing package, we are unable to determine if 1.8 mg/kg PV is the optimal dose for the phase 3 trial. We notice that exposure-response for efficacy and safety to justify the dose is based on a relatively narrow exposure range with the majority of data from 1.8 mg/kg PV. Therefore, we remain concerned that you have not done adequate dose-finding studies in order to identify the most effective dose with minimal adverse events.

Discussion: The Agency provided general feedback to the Sponsor regarding selection of randomization stratification factors. The Agency clarified that histologic subtype referred to WHO classification. The Agency also discussed with the Sponsor regarding continued use of 8 cycles of chemotherapy for the proposed trial given the available data with 6 cycles of chemotherapy as standard-of-care.

b) *The target patient population, including enrollment of IPI 2-5 and all cell-of-origin subtypes, and that the target population is adequately defined in the study eligibility criteria?*

FDA Response to Question 2 (b): Yes.

Discussion: There was no discussion.

c) *The primary endpoint of PFS based on investigator assessment by modified Lugano 2014 criteria, and that the proposed primary and secondary endpoints are appropriate for the demonstration of clinical benefit in the patient population to be studied?*

FDA Response to Question 2 (c): The primary endpoint of investigator-based PFS is acceptable. However:

- For EFS,
    - include biopsy confirmation of residual (but not necessarily progressive) lymphoma after 6 cycles as an EFS event, in addition to relapse, progression, and death.
    - for regulatory purposes, we do not generally support consideration of initiation of unplanned therapy as an EFS event, because the timing of initiation of such

therapy may be affected by safety or efficacy concerns. However, it would be acceptable to consider initiation of unplanned lymphoma therapy due to efficacy concerns as an EFS event.

Should imaging suggest residual (but not progressive) disease and lead to biopsy confirmation and/or unplanned treatment, the protocol or SAP should clearly specify which date counts as the EFS failure date.

- For the key secondary objectives of CR and ORR, investigator-based response assessment (even if blinded) is not acceptable to support an efficacy claim, chiefly because of issues with FDG-PET interpretation. Instead obtain centralized, independent radiographic review.

- Regarding secondary efficacy analyses, also see response to Question 2d.

- Should investigator-based PFS outcomes raise question of potential assessment bias, an audit including independent radiographic review may be necessary.

Discussion: The Agency recommended that the Sponsor submit their revised EFS definition and censoring rules for Agency comment. The Agency does not accept a time to next therapy (TTNT) component for an efficacy endpoint because TTNT may reflect factors other than efficacy.

With respect to the key secondary endpoint CR, the Agency strongly advised this be determined by an IRC rather than by an investigator because of the multiple challenges inherent to FDG-PET interpretation. It is recommended that scans be collected for centralized review at minimum for patients who the investigator determines PR or better in addition to baseline scans for those patients.

d) *The proposed primary and secondary efficacy analyses, including the Type I error control plan?*

FDA Response to Question 2 (d): No.

- Key secondary analyses: Although hierarchical testing of key secondary endpoints is acceptable, we recommend prioritizing CR rate then OS over EFS and PFS 24. As written, should the primary PFS endpoint be met but EFS or PFS 24 not be met, no efficacy claims could be made on the basis of improved CR or improved OS, even if such improvements occurred.

  As treatment is given with curative intent, CR is a more meaningful response metric in DLBCL than ORR. As such, the utility of including both CR and ORR as key secondary endpoints is questionable.

- Include descriptive comparisons of safety as non-key secondary endpoints. We recommend that you specifically include as safety endpoints:
  - Comparison of dose intensity

- Comparison of peripheral neuropathy rates and severity. Although the GOG-NTX-4 might inform peripheral neuropathy symptoms, the use of questionnaires risks missing information. To complement PRO measurements, the study calendar should specifically include peripheral neuropathy assessments prior to each cycle and at end of treatment.

- Every subject should be accounted for in the analysis by either being measured for the primary endpoint or properly accounted for if not measured for the primary endpoint. The number of subjects not measured for an endpoint should be kept to a minimum. Too much missing data undermine the reliability and confidence of the results. Sensitivity analyses should be performed to account for the limitation of the data and to examine the potential impact of any missing data. For further advice on missing data see the National Academies of Sciences report on The Prevention and Treatment of Missing Data in Clinical Trials.

  Discussion: The Agency agrees with the following hierarchy for key secondary endpoints: CR by IRC, EFS, PFS-24, and OS.

e) The safety monitoring plan and risk mitigation strategy for the proposed Phase III study?

FDA Response to Question 2 (e): No. The toxicity management and supportive care guidelines (e.g., protocol Table 6), particularly with respect to peripheral neuropathy and hyperbilirubinemia, are unacceptable. For example:

- For grade 2 or 3 neurotoxicity including peripheral neuropathy, the protocol recommends delaying all treatment. For curative treatment, the appropriate measure would be to hold only the vincristine/blinded vincristine and polatuzumab/blinded polatuzumab, and reinstitute them at reduced dosing once neurotoxicity resolves to grade ≤ 1.

- For bilirubin:
  - For bilirubin between 1.5 and 3.0 mg/dL, the protocol recommends reducing the doxorubicin dose by at least 25%. However, a) vincristine and potentially polatuzumab dose reductions may also be appropriate, and b) dose reductions should not be recommended if the hyperbilirubinemia is from non-hepatic origin or Gilbert's. Dose reductions in the latter case should be guided by direct bilirubin.
  - For bilirubin >3.0 mg/dL, the protocol states to delay all study treatment until resolution to grade ≤ 1. However, this would not be appropriate if the bilirubin elevation were of non-hepatic origin. Additionally, consideration should be given to administering rituximab, cyclophosphamide and steroids alone in the interim.

- For grade 3 or 4 neutropenia, the protocol recommends to administer growth factors, e.g., GCSF "as indicated and for all subsequent cycles." However, a) there is no basis for giving GCSF for uncomplicated grade 3 neutropenia, and b) since the protocol mandates

preemptive GCSF from Cycle 1 onward, there is no basis to recommend additional GCSF.

- Guidelines are missing on ileus, obstipation, and constipation.

- The protocol should mandate rather than recommend consideration of infection prophylaxis, including PJP prophylaxis, in particular due to the potentially increased risk of neutropenia and infection with the addition of polatuzumab.

The above is not a comprehensive list of issues with the protocol guidelines.

Discussion: The Agency discussed with the Sponsor protocol options including mandatory anti-infective prophylaxis or a safety monitoring committee recommendation to implement prophylaxis upon reaching a predefined threshold.

f) The proposed patient-reported outcomes (PRO) measurement strategy to assess the important disease- and treatment-related symptoms of DLBCL?

FDA Response to Question 2 (f): We support the inclusion of patient reported outcomes (PROs) in cancer clinical trials. The core patient-reported concepts we would like to see collected and analyzed include disease related symptoms, treatment related symptoms, and patient reported physical function. We are particularly interested in assessing pain (e.g., Brief Pain Inventory item #3), fatigue (e.g., Brief Fatigue Inventory item #3), anorexia (e.g., anorexia global item), and physical function (e.g., one of the PROMIS physical function measures).

Inclusion of PRO data in the product label will depend on the adequacy of submitted data, the strengths and limitations of the instrument within the given context of use, and the design and conduct of the trial.

- If a claim of superiority in a particular PRO concept is sought, pre-specify the PRO hypothesis and test it within the statistical hierarchy of hypothesis testing in the clinical trial. Control the overall type I error rate for testing hypotheses based on primary and all secondary endpoints. Prospectively define the statistical analysis methods, especially procedures for handling missing values. Provide justification in advance for the endpoint definition, including what constitutes meaningful change, for FDA review and comment.

- PRO findings without a prospectively specified statistical analysis plan are considered descriptive. FDA will review these data as part of the totality of submitted information, and will evaluate and consider whether inclusion of descriptive PRO data in labeling is appropriate on a case-by-case basis, taking into consideration any factors that may affect the interpretability and reliability of the findings.

Disease-specific symptoms: Where appropriate and feasible, items of interest may include disease-specific symptoms that patients have reported as being important across advanced cancer settings, such as pain, anorexia, and fatigue, either individually, or within a composite

"symptom score" with other important disease-specific symptoms (e.g., dyspnea and cough in lung cancer). The Brief Pain Inventory is a commonly used pain instrument that may be considered. Because measurement of time to symptom deterioration is challenging, consider enriching for symptomatic patients in the current trial or in a separate trial to measure symptom improvement.

Physical functioning, fatigue, and treatment related symptoms (EORTC QLQ-C30)

The EORTC QLQ-C30 is modular in its design and scoring of items and domains. This may facilitate modification when incorporating additional tools to customize symptom and functional measures to match specific disease and treatment contexts. We recommend you prioritize analyses of collected PRO data by the most important patient-reported symptoms and functional impacts (i.e., physical function) that are responsive to treatment. We also recommend separate measurement of treatment-related symptoms using an unbiased selection set of symptom concepts from an item library such as the PRO-CTCAE.

Lymphoma-specific symptoms (FACT-Lym LymS)

The FACT-Lym and LymS is challenging to interpret because it combines disease-related symptoms, treatment-related symptoms, and disease impacts into one summary score, which makes it difficult to describe the clinical benefit in labeling.

Peripheral Neuropathy (FACT/GOG-NTX-4)

The FACT-GOG-NTX-4 is limited by individual questions that ask about two different concepts: “numbness or tingling”. We recommend that you instead consider the EORTC-QLQ-CIPN20 instrument for assessment of treatment-induced peripheral neuropathy. This instrument keeps the concepts of numbness, tingling, and pain separate and has a broader symptom inventory including sensory, motor, and autonomic neuropathy.

You have also included the EQ5D-5L instrument in the package, though it is not pre-specified in the question. We acknowledge that the EQ-5D-5L/EQ VAS may be needed for other regulatory authorities and/or payers; it may continue to be used as an exploratory endpoint. The EQ- 5D/VAS is a generic preference-based measure intended to provide a single health utility index value for use in economic analyses. As such, the EQ-5D/VAS lacks evidence of content validity for use in estimating treatment benefit for labeling claims.

Discussion: There was no discussion.

Additional Clinical Comments

- We recommend 6 planned cycles, rather than 6 to 8, of chemotherapy. Although 8 cycles of R-CHOP is still considered a standard course, as you have noted, there is no demonstrated advantage to 8 cycles over 6 (at least with CHOP-14), whereas cumulative toxicity, including neurotoxicity, is a risk in either arm.

- Consider specifying that rituximab be administered prior polatuzumab/polatuzumab placebo. As infusion-related reaction is an overlapping risk of rituximab and polatuzumab, attribution will be simpler if rituximab is administered first.

- Histology: a) Exclude grey-zone lymphoma (with features of DLBCL and Hodgkin lymphoma). b) Exclude Burkitt lymphoma, rather than "transformation to Burkitt lymphoma" as worded in the protocol. c) Clarify whether eligible histologies include ALK+ large B-cell lymphoma and the provisional category of HHV8+ DLBCL NOS. d) Since FL grade 3a is not necessarily indolent, we recommend specifically excluding lymphoma with features of both FL grade 3a and 3b. e) The protocol inclusion criteria (Section 5.3.1) describe previously untreated patients with "CD20-positive DLBCL", then list diagnoses other than DLBCL, such as FL grade 3b.

- Laboratory eligibility: Rather than serum creatinine or CrCl, select one measure of renal function (CrCl preferred) for eligibility purposes.

2.2 Clinical Pharmacology/Safety

Question 3: *Does the Agency agree that the pharmacokinetic data collected in Phase I and II studies with the plan for collecting sparse PK sampling of pola in Phase III study is sufficient to characterize possible drug-drug interactions (DDI) between pola and R-CHP?*

FDA Response to Question 3: Your approach appears to be acceptable, assuming the sparse PK samples will be collected from all enrolled patients. However, the adequacy of the population PK modeling will be a review issue at the time of BLA submission. In addition, your drug-drug interaction evaluation should include the influence of CYP3A4 inhibitors/inducers on unconjugated MMAE.

Discussion: There was no discussion.

Question 4: *Does the Agency agree that the collection and analyses of high-quality triplicate electrocardiogram (ECG) data and cardiac safety data from Phase I and II studies along with the plans for cardiac safety monitoring in the Phase III would be sufficient to assess the QTc prolongation and cardiac safety risks for pola?*

FDA Response to Question 4: Yes, we agree.

Discussion: There was no discussion.

Question 5: *Does the Agency agree that the pharmacokinetic and safety data collected in Phase I and II studies in patients with renal and hepatic impairment coupled with plans for continued PK and safety assessments in Phase III would be sufficient to inform the label use of pola in patients with organ impairment?*

FDA Response to Question 5: Your approach appears to be acceptable, however note that the need for a hepatic or renal impairment study will be a review issue at the time of BLA submission. You should include a sufficient number of subjects in each category of hepatic/renal

impairment to be able to draw reasonable conclusions regarding the effect of organ function on the PK of unconjugated MMAE. It is our expectation that the BLA submission should provide complete information to write Full Prescribing Information with dosing recommendations for all patients, including those with hepatic and/or renal impairment. If patients with higher degree of organ impairment are not included in the Phase 3 trial, you should conduct dedicated hepatic and renal impairment trials in order to properly characterize the PK and safety property of polatuzumab vedotin.

Discussion: There was no discussion.

Question 6: *Does the Agency agree that the results from Study GO29044 evaluating polatuzumab vedotin in combination with R-CHP in patients previously untreated DLBCL support an application for Breakthrough Therapy Designation?*

FDA Response to Question 6: No. You have not provided sufficiently robust preliminary evidence that the addition of polatuzumab vedotin substantially improves CR rate in DLBCL.

Discussion: There was no discussion.

3.0 OTHER 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.

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 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP 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 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 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 (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a Study Data Standards Resources web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

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

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

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies,

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

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

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 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.

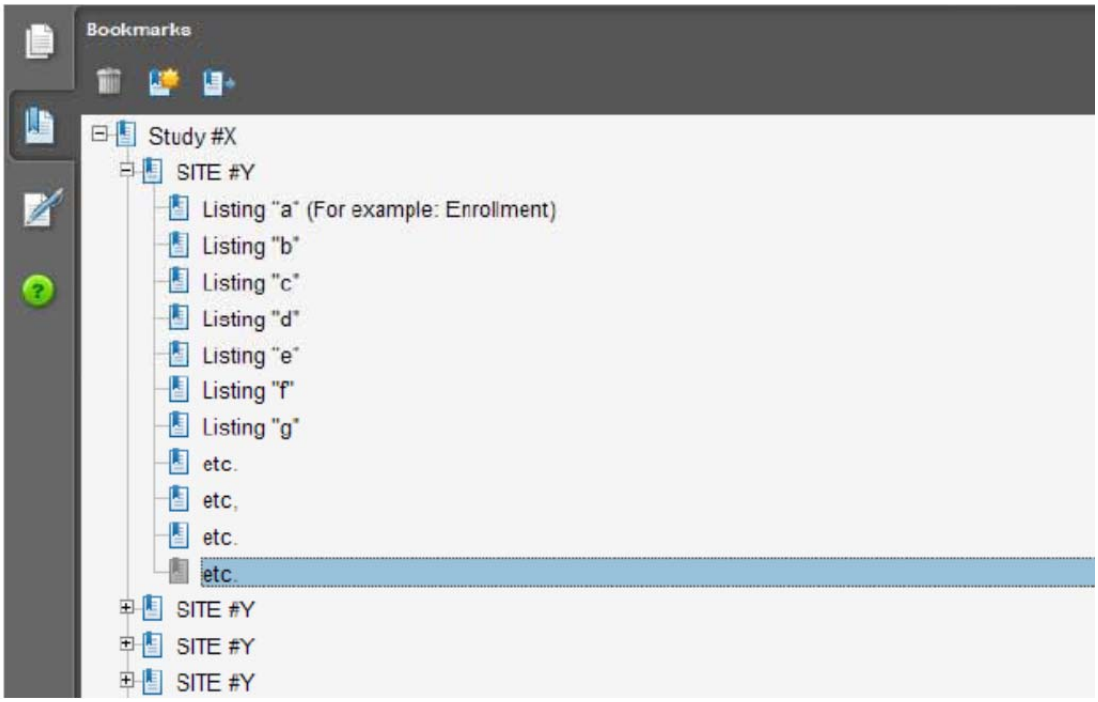
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

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.

[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

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor provided the attached response document for the meeting.

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

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

/s/

ROMEO A DE CLARO
04/06/2017