CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761263Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 120651

MEETING MINUTES

Genentech, Inc.
Attention: Sharni Sandhar
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Ms. Sandhar:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for mosunetuzumab (BTCT4465A).

We also refer to the teleconference between representatives of your firm and the FDA on January 21, 2021. The purpose of the meeting was to discuss the proposed content and format of the BLA of mosunetuzumab for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies.

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

If you have any questions, call Kimberly Scott, Senior Regulatory Project Manager, at (240) 402-4560.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
- Meeting Minutes

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

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-BLA
Meeting Date and Time:	Thursday, January 21, 2021 11:00AM -12:00PM (ET)
Meeting Location:	Teleconference
Application Number:	IND 120651
Product Name:	Mosunetuzumab (BTCT4465A)
Indications:	Treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies.
Sponsor Name:	Genentech, Inc.
Regulatory Pathway:	351(a) of the Public Health Service Act
Meeting Chair:	Nicholas Richardson, DO, MPH
Meeting Recorder:	Kimberly Scott, RN, BSN, OCN®

FDA ATTENDEES

Office of Oncologic Diseases/Division of Hematologic Malignancies II
Nicole Gormley, MD, Division Director
Nicholas Richardson, DO, MPH, Clinical Team Leader
Nicole Sunseri, MD, PhD, Clinical Reviewer

Office of Regulatory Operations/Division of Regulatory Operations for Oncologic Diseases
Kimberly Scott, RN, BSN, OCN®, Senior Regulatory Project Manager
Theresa Carioti, MPH, Chief, Project Management Staff

Office of Translational Sciences (OTS)/Office of Clinical Pharmacology/Division of Cancer Pharmacology I
Olanrewaju Okusanya, MS, PharmD, Deputy Division Director (Acting)
Xiling Jiang, PhD, Clinical Pharmacology Team Leader (Acting)
Huiming Xia, PhD, Clinical Pharmacology Reviewer
Raman Baweja, PhD, Clinical Pharmacology Reviewer

OTS/Office of Biostatistics/Division of Biometrics IX
Yu-Te Wu, PhD, Team Leader
Laura Fernandes, PhD, Reviewer

Office of Pharmaceutical Quality (OPQ)/Office of Biotechnology Products
Kirsten Nickens, PhD, Product Quality Team Lead
Sean Fitzsimmons, PhD, Product Quality Reviewer

Office of Surveillance and Epidemiology/Office of Medication Error Prevention and Risk Management/Division of Medication Error Prevention and Analysis (DMEPA)
Hina Mehta, PharmD, Team Leader

Office of New Drug Products/Division of Cardiovascular and Renal Products
Devi Kozeli, MS, Reviewer

SPONSOR ATTENDEES
Brendan Bender, PhD, Scientist, Clinical Pharmacology
Michelle Clement Biometrics Submission Team Lead, Biometrics
Huang, MSc, Senior Statistical Scientist, Biostatistics
Josephine Ing, Global Regulatory Lead, Regulatory
Antonia Kwan, MD, PhD, Senior Medical Safety Director, Clinical Safety
Ginna Laport, MD, Lymphoma/CLL Development Franchise
Chi-Chung Li, PhD, Principal Scientist, Clinical Pharmacology
Xuyang Lu, PhD, Principal Statistical Scientist, Biostatistics
Carol O'Hear, MD, PhD, Global Development Leader, Clinical Science
Sharni Sandhar, Program Manager, Regulatory
Roshni Shah, PharmD, Associate Program Director, Regulatory
Michael Wei, MD, PhD, Senior Medical Director, Clinical Science
Christine Wu, PhD, Program Director, Technical Regulatory
Shen Yin, PhD, Senior Clinical Scientist, Clinical Science

1.0 BACKGROUND

Genentech submitted IND 120651 for mosunetuzumab in March 2015 and received Study May Proceed letter for IND 120651 on April 16, 2016 (b) (4) (b) (4).

On December 17, 2018, mosunetuzumab received orphan designation for the treatment of follicular lymphoma.

On June 2, 2020, Genentech was granted Breakthrough Therapy Designation for the treatment of adult patients with R/R FL who have received at least 2 prior systemic therapies, based on Study GO29781*"An Open-Label, Multicenter, Phase Ib/II Trial Evaluating The Safety, Tolerability, Pharmacokinetics, and Efficacy Of Mosunetuzumab (BTCT4465A) in Combination with Polatuzumab Vedotin in Patients with B-Cell Non-Hodgkin Lymphoma".*

Reference ID: 5709082

The Sponsor submitted their Initial Pediatrics Study Plan (iPSP) to the Agency on January 31, 2020, [redacted] and received the Agreed iPSP on November 9, 2020.

The purpose of this pre-BLA meeting is discuss the proposed content and format of a planned Biologics License Application (BLA) mosunetuzumab for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies.

FDA sent Preliminary Comments to Genentech on January 13, 2021.

2.0 DISCUSSION

Question 1: *Does the Agency agree that the proposed content and format of the planned BLA for mosunetuzumab outlined in the Table of Contents is adequate and could constitute a complete BLA to support the proposed indication of mosunetuzumab for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies (hereafter referred to as R/R FL ≥2 Prior Therapies)?*

FDA Response to Question 1:
The format of the table of contents is appropriate. However, the adequacy of the content to support filing will be determined following receipt of the completed application.

Discussion: No discussion occurred.

Question 2: *Does the Agency agree with the planned analyses and presentation of efficacy data in the Summary of Clinical Efficacy (SCE)? Specifically,*

a. *Given the analyses included in the SCE, does the Agency further agree with Sponsor's proposal that the Integrated Summary of Effectiveness (ISE) in Module 5 will be a cross-reference to the SCE in Module 2?*

FDA Response to Question 2a:
It is acceptable to submit a Summary of Clinical Efficacy (SCE) in lieu of an Integrated Summary of Effectiveness with cross-reference to the SCE in module 5 as long as the SCE provides a comprehensive evaluation of efficacy of mosunetuzumab in patients with R/R FL after 2 lines of prior systemic therapy within the SCE requirements.

Discussion 2a: No discussion occurred.

b. *Does the Agency agree with the planned presentation of efficacy data in the SCE to support the support the proposed R/R FL ≥2 prior therapies indication?*

FDA Response to Question 2b:
In general, the proposed presentation of the efficacy data in the SCE is acceptable. Whether the content will be adequate to support the treatment of patients with R/R FL following ≥2 prior therapies will be a review issue.

Discussion 2b: No discussion occurred.

Question 3: *Does the Agency agree that the proposed statistical analysis plan is sufficient to support an efficacy assessment for mosunetuzumab for the treatment of the proposed indication? In particular, can the Agency comment on the acceptability of the following:*

- *The efficacy and safety analysis population*
- *The sample sizes*
- *The timing of the efficacy analysis*
- *The subgroup analyses*

FDA Response to Question 3:

1. *The efficacy and safety analysis population*
   The proposed populations used for the efficacy and safety analyses appear acceptable. In general, the safety database should provide a sufficient number of patients with relapsed/refractory FL treated with IV mosunetuzumab at the dose and schedule proposed for registration to adequately evaluate the incidence of toxicities with an appropriate confidence interval. This population should also have a median exposure to mosunetuzumab similar to the potential exposure for the indicated population. Data from patients treated with other dosing regimens may supplement the safety database. However, we suggest not including the one patient with melanoma erroneously enrolled.

2. *The sample size*
   Since the sample size consists of 90 patients with R/R FL who have been treated with at least 2 prior therapies and have been administered mosunetuzumab at the regimen proposed for registration, the sample size appears acceptable for the efficacy and safety analysis to support the initial BLA.

3. *The timing of the efficacy analysis*
   The proposed follow-up for DOR is inadequate. In a single arm trial in patients with follicular lymphoma, the magnitude of the treatment effect and durability of response are critical components to establish efficacy. In patients with an indolent lymphoma, such as FL, sufficient follow-up for duration of response is needed. We recommend that all responders have at least 9 to 12 months for DOR follow-up.

4. *The subgroup analyses:*
   The planned subgroup analyses appears reasonable. Due to the limitations of small sample size in subgroups and no proper control of type I error, all analyses results are considered descriptive and exploratory.

We have the following additional comment:

- Revise the censoring rule in table 6 of the statistical analysis plan (SAP). An event occurring after the start of new anti-lymphoma treatment (NALT) should be censored on the date of last adequate assessment prior to the NALT.

Discussion 3:

3.1. The Agency agreed with inclusion of the patient with melanoma treated with mosunetuzumab in the safety database and the safety analysis population.

For exposure, the Agency agreed with reporting the median number of cycles, but also requested that exposure be provided based on the number of days.

3.3. The Agency reiterated the expectation for sufficient DOR follow-up for responders at the time of BLA submission. The proposed DOR follow-up with a planned data cutoff of 15 March 2021 may be reasonable. The adequacy of the data to support a determination of substantial evidence of efficacy will be a review issue.

Question 4: *Does the Agency agree with the planned analyses and presentation of safety data in the dossier? Specifically,*

a. Does the Agency agree with the Sponsor's proposal to cross-refer the ISS in Module 5 to the SCS in Module 2 for the BLA as all safety analyses will be included in the SCS?

FDA Response to Question 4a:
It is acceptable to submit a Summary of Clinical Safety (SCS) in lieu of an Integrated Summary of Safety with cross-reference to the SCS in module 5 as long as you include a comprehensive evaluation of safety of mosunetuzumab in patients with R/R FL after 2 lines of prior systemic therapy within the requirements of the SCS.

Discussion 4a: No discussion occurred.

b. Does the Agency agree with the proposed CSR safety narrative categories?

FDA Response to Question 4b:
The proposed patient safety narrative categories are overall acceptable. We have the following recommendations:

1. Include any death occurring within 90 days of study treatment as opposed to death due to AE, unless occurring after initiation of NALT. For patients with progressive disease as the reported cause of death, include sufficient information to discern whether there is a potential contribution of study treatment to the outcome.

2. Include narratives for pneumonitis/interstitial lung disease (ILD) of grade 2 or greater and other potential pulmonary toxicity regardless of attribution. We recommend an SMQ broad definition for ILD (ILD, pneumonitis, acute respiratory distress syndrome, pulmonary fibrosis, and organizing pneumonia). Additional preferred terms may be appropriate for inclusion, such as "pulmonary toxicity". The narratives should provide sufficient information to inform the suspected etiology, such as infection. Include a flag for such pneumonitis events in the ISS and disease-specific AE datasets, as an AE of special interest (AESI).

3. To better inform the tolerability of the regimen, provide a table that briefly explains the following:
    - Study drug action (interrupted, modified, discontinued)
    - If discontinued, the reason for study drug discontinuation if *other than AEs or inefficacy*.
    - Duration of the event and its outcome
    - If available, any rechallenge information
    - Investigator and sponsor assessment regarding the causality of the event to either the investigational drug or an alternative etiology

4. To enhance navigability of the narratives, provide a table of contents within the navigation pane that organizes narratives by topic (death, SAE, AESIs, etc.) with hyperlinks to each case, separated by study group. Include a tabular summary of the subject numbers with narratives by category and hyperlinks to those narratives. An example table is provided below:

Study and Treatment Arm					
Subject No.	**SAE**	**Death**	**Discontinuation due to AE**	**AESI #1**	**AESI #2**
0001	Y	N	Y	Y	Y
0002	Y	Y	Y	N	N
0003	N	N	Y	N	Y

5. The Sponsor should be aware that selected narratives for grade 2 neurological AEs may be requested during the course of the review.

Discussion 4b:

4b.2. The Agency clarified the rationale for inclusion of pneumonitis in the CSR narrative category, including the identification of pneumonitis as a potential safety signal based on IND safety reports of pneumonitis with mosunetuzumab monotherapy and the need for adequate information to inform the incidence and characterization of pneumonitis. The Agency also noted that pneumonitis should be considered an AESI in mosunetuzumab study protocols to further evaluate the incidence and because mosunetuzumab in combination with other agents may potentiate the risk of pneumonitis.

4b.3. The Agency agreed with inclusion of the proposed tolerability information in the AESI section of the CSR. Further, the Agency clarified that rechallenge information is defined as treatment reinitiation following interruption due to an adverse event.

4b.5. To inform neurologic adverse events, the following list are the CTCAE preferred terms of interest.

- **Encephalopathy: includes encephalopathy, cognitive disorder, confusional state, depressed level of consciousness, disturbed attention, hypersomnia, leukoencephalopathy, memory impairment, mental status changes, paranoia, somnolence, stupor, cerebral edema**
- **Delirium: includes agitation, delirium, delusion, disorientation, hallucination, hyperactivity, irritability, restlessness**
- **Headache: includes headache and migraine**
- **Dizziness: includes dizziness, presyncope, syncope**
- **Aphasia: includes aphasia, dysphasia**
- **Motor dysfunction: includes muscle spasms, muscular weakness**
- **Sleep disorder: includes sleep disorder, insomnia, nightmares**
- **Tremor**
- **Ataxia**
- **Seizure**
- **Dyscalculia**
- **Myoclonus**
- **Anxiety**

c. *Does the Agency agree with the proposed plan for characterizing CRS?*

FDA Response to Question 4c:
The proposed plan for characterizing CRS is acceptable.

Discussion 4c: No discussion occurred.

d. *Does the Agency agree with the Sponsor's proposal to include all patients with major protocol deviations of eligibility and screening criteria who were treated*

with mosunetuzumab in the safety evaluable population, and that the B11 NHL expansion group excludes the one patient diagnosed with metastatic melanoma?

FDA Response to Question 4d:
The proposal to include all patients treated with at least one dose of IV mosunetuzumab, irrespective of protocol deviations, in the overall safety analysis population is acceptable. Removal of the patient with melanoma from histology specific analyses is appropriate.

Discussion 4d: No discussion occurred.

***Question 5:* Pharmacology**
Does the Agency agree with the planned analyses and presentation of the clinical pharmacology data, including population pharmacokinetic analysis plan, exposure-response analyses plan, concentration-QTc analyses plan, physiologically based pharmacokinetics (PBPK) analyses plan and immunogenicity assessment plan?

FDA Response to Question 5:

1. Your overall clinical pharmacology plan appears reasonable. A final determination of the adequacy of the clinical pharmacology package will be determined at the time of BLA review. Refer to Additional clinical pharmacology comments regarding FDA's recommendation regarding the content and format of the clinical pharmacology package.

2. Regarding your exposure-response analysis plan, we recommend that you use both CD20 receptor occupancy and AUC as exposure matrices for the planed exposure-response analyses for efficacy and safety. The conclusion of E-R relationship will be made based on the totality of data and analyses.

3. Regarding your QT assessment plan, we agree with your proposal to not conduct a dedicated QT study. Because mosunetuzumab is a large protein which in theory has a low likelihood of direct interaction with cardiac ion channels, the white paper model for concentration-QTc analysis based on serum mosunetuzumab concentration is not expected to be meaningful. Unless additional data suggest significant QT prolonging risks, we recommend that you include ECG findings in the Summary of Clinical Safety and a separate QT evaluation report is not necessary.

4. Regarding your PBPK analyses, it appears that the observed transient IL-6 could be elevated up to 60,000 pg/mL. In the literature, the in vivo DDI studies evaluating the effect of IL-6 on the PK of CYP substrates were generally at lower concentration levels of IL-6 (such as less than 100 pg/mL). In your PBPK report, provide justification if the model was developed and validated based on low IL-6 levels and then applied to higher IL-6 levels.

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Refer to draft "*Guidance for Industry: Drug-Drug Interaction Assessment for Therapeutic Proteins*" (https://www.fda.gov/media/140909/download) for details regarding DDI assessment for pro-inflammatory cytokine modulator therapeutic proteins.

Discussion 5: No discussion occurred.

***Question 6:* Administrative/Regulatory**
Does the Agency agree with the critical eCRF pages that the Sponsor has identified for prioritization of source data verification by site monitors during the COVID-19 pandemic to ensure data integrity is maintained for the BLA?

FDA Response to Question 6:
The source data required for verification from clinical sites to ensure data integrity will be determined during the review. Our expectation is that the necessary documentation to support data verification, as part of an inspection, should be available

Discussion 6: No discussion occurred.

Question 7: *Does the Agency agree with the proposal for rolling review? Specifically, for the proposed timing for CMC sections, does the Agency agree that the method validation sections for Roche Diagnostics GmbH, Mannheim, Germany as an additional drug product QC testing site can be provided at the same time of the submission of clinical sections to the BLA?*

FDA Response to Question 7:
The overall proposal for the rolling review submission is acceptable. However, regarding the CMC sections, clarify if the validation section for Roche Diagnostics GmbH, Mannheim, Germany will consist of method transfer reports for the non-compendial methods or if these methods will be fully validated at this site.

Discussion 7: No discussion occurred.

Question 8: *The Sponsor has received feedback that the Agency is not currently accepting submissions containing Established Conditions. However, the Sponsor intends to include a Product Lifecycle Management document including Established Conditions, as described in the ICH Q12 guideline currently awaiting adoption and following the general principles described in the 2015 FDA Draft Guidance, in the July 2021 Module 3 submission. Does the Agency have any comments on this plan?*
FDA Response to Question 8:
Consistent with good guidance practices described in 21 CFR 10.115, until ICH Q12 is published as a final FDA guidance, FDA is unable to implement a process to assess and explicitly approve established conditions as part of the Product Lifecycle

Management (PLCM) document. However, elements discussed in ICH Q12 that are already described in regulation and guidance (e.g., a comparability protocol in 21 CFR 601.12(e)) can be proposed prior to finalization. Should ICH Q12 be published as final guidance during the BLA review of mosunetuzumab, a PLCM containing other Q12 elements could potentially be submitted as an amendment for consideration, if agreed by the assessment team.

Discussion 8:
The Agency stated that if ICH Q12 is published prior to September 2021 when the final sections of the BLA are submitted, it would be acceptable to include your Product Lifecycle Management document including Established Conditions. The Agency restated that if ICH Q12 is published as final FDA guidance prior to September 2021 when the final sections of the BLA are submitted, it would be acceptable to include your Product Lifecycle Management document including established conditions. However, the Agency recommended that the Sponsor request a CMC pre-BLA meeting to discuss your proposal. However, the Agency recommended that the Sponsor request a CMC pre-BLA meeting to discuss the specific proposal.

The Sponsor asked if the PLCM document would need to incorporate all proposed established conditions from Module 3 or an alternative format such as reference to specific established conditions would be allowed. The Agency stated that a CMC pre-BLA meeting could be used to further discuss a specific proposal in further detail.

Additional Clinical Comments:

1. General: We recommend an additional meeting prior to the BLA submission once frontline data is available. During this meeting, the Agency can further advise the Sponsor on approaches to facilitate review of and improve the overall package. Discussion at that time may include items, such as the Assessment aid and RTOR programs through the Oncology Center of Excellence.

   Discussion:
   The Agency clarified the recommendation for a subsequent pre-BLA meeting to occur following the availability of top-line efficacy and safety data. Further, the Agency stated that the determination of what risk mitigation strategies will be needed, such as a REMS, will be determined during the review. Based on the risk of CRS, the Agency is considering whether a REMS may be needed.

   The Agency requested to use the Assessment Aid to facilitate the review of the mosunetuzumab BLA for patients with FL. For the RTOR program, the Agency will determine whether the BLA can be reviewed under RTOR once top-line efficacy and safety data are available. At the time of top-line results, provide a summary and timeline of the proposed presubmission(s)

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that would occur under RTOR in relation to the anticipated submission of the complete BLA. See the RTOR website for further information https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program.

2. **Efficacy data**
To aid in the FDA's assessment of efficacy and facilitate response adjudication, we recommend that you include the following details regarding efficacy assessments.

a. *Radiology reports*: Submit local radiology reports and IRC eCRFs for any cases where there is a discrepancy between the investigator and IRC for either best overall response or duration of response. If radiology reports were not captured, obtain them from the study site. Submit anonymized PET/CT and CT reports (identified by unique subject ID) preformed as baseline, during study treatment, at end of therapy and follow-up until disease progression or new anti-lymphoma therapy. Organize the radiology reports with informatively named hyperlinks.

b. *Summary response dataset:* Include a dataset that summarizes efficacy per IRC and per investigator, one row per subject. Include a separate column for bone marrow status at baseline (positive, negative, not performed) and an additional column for date of post baseline bone marrow assessment for patients who have radiographic CR. Please include:

USUBJID	Date of First Objective Response IRC	Best Overall Response IRC	Best Overall Response Investigator	BM involvement at baseline	Date of negative BM biopsy, if BM involved at baseline and radiographic CR	Date of Censor for DOR or DOR event IRC *	Reason for Censor IRC	Clinical PD date^

* Please provide corresponding columns for DOR per investigator.
^ This column is used if an investigator detected PD early by non-radiological means. A date is included if it is earlier than the date of radiographic PD. Indicate N/A if not applicable.

c. *Waterfall plot*
- Please include a waterfall plot of best overall response for the FL primary efficacy populations. The waterfall plot should display maximal % tumor reduction per IRC, and include categories for patients who were NE and, separately, patients who had PD by clinical criteria (not radiographically evaluated).
- Submit an analysis dataset that includes all of the information needed to generate this waterfall plot (e.g., columns for SPD at baseline and at best overall response), with 1 patient per row. This information can be included in the "summary response dataset" recommended above. In the dataset, please include all patients with IRC-assessed efficacy who cannot be represented on the waterfall, providing the reason (e.g., radiographically

unevaluable disease). Thus, the dataset should include all patients in the efficacy populations.

Discussion 2 (Efficacy data): Post-Meeting Comment

2a. The request for efficacy response data in the FL patients, (i.e., local versus IRC-assessed radiology reports, etc.) is specifically for discrepancies in the response assessment between the IRC and the investigator. Provide information to facilitate FDA review and adjudication for these patients. The Agency acknowledges that IRC-assessed efficacy data is not part of the eCRF data.

2b. The proposed ADAM datasets for response and bone marrow laboratory data appear acceptable. In addition, the proposal to provide the requested efficacy data as a combined listing in the efficacy section of the CSR is acceptable.

2c. The summary SPD by IRF dataset, as proposed, is acceptable.

3. **Safety Data**
   a. *Laboratory analysis datasets*
      - Include a baseline grade for each row, in addition to the toxicity grade for post-treatment measures.
      - Include laboratory toxicity grading that indicates the directionality of the abnormality at baseline and post-treatment, for example for potassium, "-3" for grade 3 hypokalemia, "3" or "+3" for grade 3 hyperkalemia.
      - Provide a shift column that describes the change from baseline grade to posttreatment grade. For example, for change from grade 1 hyperkalemia to grade 1 hypokalemia post-treatment, the shift column for potassium would specify "+1 to -1", indicating treatment-emergent hypokalemia.
      - Include a baseline flag, and a flag for post-baseline labs obtained within the primary safety analysis window (e.g., within 30 days of last study treatment but before NALT).
      - Include a treatment-emergent flag.
      - An example of a corresponding table of treatment-emergent lab abnormalities is provided below. In this table, a shift from grade 3 to grade 4 would be included in the "Grade ≥3" column, as would a shift from grade < 3 to grade ≥3

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Treatment-emergent laboratory abnormalities							
Parameter	Regimen						
	N evaluable*	Any grade		G ≥ 3		G 4	
		n	%	n	%	n	%
Hematology							
Anemia							
Thrombocytopenia							
Neutropenia							
Chemistry							
Potassium decrease							
ALT increased							
* Generally defined as the number of patients with a baseline and at least one post-baseline assessment for the particular lab.							

b. *AE datasets*
   - Grouped terms: Provide a list or .xpt file of grouped preferred terms. The AE dataset should include flags for AEs that were included in grouped terms and flags for AESIs.
   - Include flags in the ISS and indication-specific AE datasets for treatment-emergent AEs that occur during the primary safety analysis window
   - Treatment-emergent AEs that occur during the primary safety analysis window but prior to initiation of NALT.
   - AEs that occur after NALT

c. *Death summary dataset*: Include an analysis dataset summarizing all reported deaths and the reasons for the ISS. Include columns indicating the study #, regimen, flags for the various subpopulations, time since last study treatment, whether death occurred after disease progression / relapse, whether death occurred after NALT (including consolidative therapy), and the date of NALT.

d. *Exposure:* To facilitate exposure analysis for efficacy and safety, provide a summary exposure analysis dataset having one patient per row that includes: flags for various populations, regimen, starting dose, duration of exposure, relative dose intensity, date of permanent study treatment discontinuation with reason, # of dose delays, date of first dose delay, # of dose reductions, date of first dose reduction.

Discussion 3 (Safety): Post-Meeting Comment

3a. The laboratory shift tables in the CSR should include the specific baseline grade per CTCAE versus "not high" or "low" in order to allow

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confirmation from the associated laboratory datasets.

3d. The Sponsor's proposal to include date of first dose delay due to adverse event, but not other extraneous reasons, such as holidays or rescheduling is acceptable.

Additional Clinical Pharmacology Comments

The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application should be consistent with FDA Guidance for Industry, "*Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products –Content and Format*" (available at: https://www.fda.gov/media/74346/download). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

1. 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.

Discussion 5: Post-Meeting Comment

The proposed plan appears reasonable. Additional sensitivity analysis should be conducted comparing inclusion and exclusion of cases considered not unrelated to the treatment to support decision making and provide justification. A final determination of the adequacy of the submitted data will be assessed during the BLA review.

   b. What are the exposure-response relationships for efficacy, safety and biomarkers?

Discussion 5: Post-Meeting Comment

The Agency do not have specific recommendations on which endpoints should be selected to assess the exposure-response relationship. The Agency recommended that the selection of endpoints should reflect the mechanisms of action and is clinically meaningful with close correlation with efficacy and safety. In the clinical pharmacology package, the Sponsor should provide the rationale supporting the selection of endpoints for exposure-response analysis for the Agency to review. A final determination of the adequacy of the submitted analyses will be assessed during the BLA review.

   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?

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d. What is the impact of immunogenicity on exposure, efficacy and safety?

2. Apply the following advice in preparing the clinical pharmacology sections of the original submission:
    a. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
    b. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate.

3. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
    a. Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
    b. Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.

4. Submit the following for the population pharmacokinetic analysis reports:
    - 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 pharmacometrics 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.

7. Include the purpose of the simulations, assumptions, detailed process of PBPK model building and verification, summary of model input parameters, version of software, simulation results, and conclusions in the study report.

   Provide the study report as PDF files (screenshots can be incorporated if required). Include the model files used to generate the final PBPK simulations. These files should be executable by FDA reviewers using the specified software. Include appropriate supporting documentations such as any special instructions and file definitions.

8. Complete and include the tables (Table 1 - bioanalytical method life cycle information, and Tables 2a-b - summary method performance of each bioanalytical method) in your 351(a) BLA submission to provide the information regarding the bioanalytical methods for pharmacokinetic and/or immunogenicity assessments used in pivotal clinical pharmacology studies and its life-cycle information pertaining to the submission. Do not delete any rows from the tables.

   We recommend that these tables be included as an Appendix in the Summary of Biopharmaceutics located in eCTD 2.7.1. In addition to including in the Appendix, we request you also submit both tables in docx format. Include any other additional bioanalytical information that might be relevant for review in your BLA submission.

Table 1. Summary life cycle information of bioanalytical method(s) used in submission of BLA xxxxxx to measure analyte X in matrix

	Method validation #1	**Method validation #2**	**Clinical Study x**	**Clinical Studies y-z**
Analyte	Drug name	Drug x, Drug y	Drug x, and Drug y	Drug x, Drug z
Validation type	Full	Partial validation of method xx	NA	NA
• CTD ref #	Ref # in eCTD	x0000.0xxxxxx	x0000.0xxxxxx	x0000.0xxxxxx
• method ID	Method ID xx (version)	SOP xxxx or Method xxx (v	SOP xxxx or Method xxx (v	SOP xxxx or Method xxx (v
• BA site	Name of BA test facility	US Lab 1	US lab 1	Other lab

Reference ID: 5700032

• Matrix • Platform • Format	Serum/ Plasma/Urine/ whole blood LC/MS, ELISA, ECL A validated sandwich format using x as capture and y as detection, a bridging format using z as both capture and detection, competitive assay using x as a capture and b as a competitor			
Stock reference & lot	Drug 1, lot 1	Drug 1, lot 2 Drug 2, lot 1		
Calibration range (LLOQ - ULOQ) and levels validated	x- x000 ng/mL (Eg. 2, 5, 50, 250, 1000, 1500, 2000 ng/mL)	x- x000 ng/mL	x- x000 ng/mL	x- x000 ng/mL
Matrix/ study population	Normal or x diseased serum	Normal serum	Normal serum	x Diseased population
Relevant reference and applicable report amendment (s) and links -Amendment 1 -Amendment 2				
Amendment history				

The bioanalytical method performance summary table (**Table 2a**) is recommended in describing PK and/or biomarker methods. Please use one method per analyte per table. This table is not applicable for anti-drug antibody methods. Do not delete any rows or columns from the table. State "not applicable" if certain rows or columns are not applicable. Include any additional bioanalytical data that may be relevant to the submission.

Table 2a. Summary method performance of a bioanalytical method to measure [analyte] in [matrix]

Bioanalytical method validation report name, amendments, and hyperlinks	
Method description	

Reference ID: 5700082

Materials used for calibration curve & concentration			
Validated assay range			
Material used for QCs & concentration			
Minimum required dilutions (MRDs)			
Source & lot of reagents (LBA)			
Regression model & weighting			
Validation parameters	**Method validation summary**		**Source location**
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	x	
	Cumulative accuracy (%bias) from LLOQ to ULOQ Product A Product B and/or Product C	x to y% x to y% x to y%	
	Cumulative precision (%CV) from LLOQ to ULOQ Product A Product B and/or Product C	≤ x% ≤ x% ≤ x%	
QCs performance during accuracy & precision	**<u>Cummulative accuracy (%bias) in 5 QCs</u>** QCs: Product A Product B and/or Product C	 x to y% x to y% x to y%	
	<u>Inter-batch %CV</u> QCs: Product A Product B and/or Product C	 ≤ x% ≤ x% ≤ x%	

Reference ID: 5100002

	Total error QCs: Product A Product B and/or Product C	≤ x% ≤ x% ≤ x%	
Selectivity & matrix effect	Number of total lots tested. Range of observed bias. State any issue		
Interference & specificity	Number of total lots tested. Range of observed bias. State any issue		
Hemolysis effect	Number of total lots tested. Range of observed bias. State any issue		
Lipemic effect	Number of total lots tested. Range of observed bias. State any issue		
Dilution linearity & hook effect	Describe data here		
Bench-top/process stability	Describe data here Product A Product B and/or Product C		
Freeze-Thaw stability	Describe data here Product A Product B and/or Product C		
Long-term storage	Describe data here Product A Product B and/or Product C		
Parallelism	Describe data here		
Carry over	Describe data here		
Method performance in study number **(In addition to the report name, also provide hyperlink to the report)**			
Materials used for calibration curve & QC			
Assay passing rate	(including incurred sample reanalysis (ISR))		
Standard curve performance	• Cumulative bias range: x to y% • Cumulative precision: ≤ x% CV		
QC performance	• Cumulative bias range: x to y% • Cumulative precision: ≤ x% CV • TE: ≤ x% (LBA only)		

Method reproducibility	Incurred sample reanalysis was performed in x% of study samples and x % of samples met the pre-specified criteria	
Study sample analysis/ stability	Describe storage stability coverage for standard/QC and samples	

If the method above was modified, describe the modification(s) and cross-validation results, with any additional information in **Table 2b** below.

Table 2b. Summary of method [x] modification(s) and cross-validation results

Bioanalytical method validation report name and hyperlink			
Changes in method			
New validated assay range if any			
Validation parameters	**Cross-validation performance**		**Source location**
Calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	x to y%	
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ x%	
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	x to y%	
	Inter-batch %CV	≤ x%	
	Percent total error (TE)	≤ x%	
Cross-validation	Numbers of spiked or incurred samples analyzed and result		
List other parameters			

3.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. They Agency recommends an additional meeting prior to the BLA submission once frontline data is available. During this meeting, the Agency can further advise the Sponsor on approaches to facilitate review of and improve the

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overall package. Discussion at that time may include items, such as the Assessment Aid and Real-Time Oncology Review (RTOR) programs through the Oncology Center of Excellence.

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

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan and it was concluded that the determination of what risk mitigation strategies will be needed (risk of CRS), will be determined during the BLA 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 any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2))

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

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

For the latest version of the molecular target list, please refer to FDA.gov.[2]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020, or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

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

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

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

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

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[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information

[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.
-

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

MANUFACTURING FACILITIES

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

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specific manufacturing responsibilities for each facility.

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

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

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

Corresponding names and titles of onsite contact:

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

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[6] and the guidance for industry, "*Identification of Manufacturing Establishments in Applications Submitted" to CBER and CDER Questions and Answers*[7]*."* Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

[6] https://www.fda.gov/media/84223/download

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

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*.[8]"

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[9]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid[10]

[8] https://www.fda.gov/media/85061/download
[9] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[10] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

Reference ID: 5170002

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no actions identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor sent the attached document titled "Response to FDA Preliminary Comments" via email on January 19, 2021, for the meeting with the Agency.

19 Pages have been Withheld in Full as B4(CCI/ TS) Immediately Following this Page

Reference ID: 4709082

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/

NICHOLAS C RICHARDSON
02/18/2021 05:16:56 PM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 120651
Request Receipt Date	April 14, 2020
Product	mosunetuzumab
Indication	The treatment of adult patients with relapsed or refractory follicular lymphoma who have received at least two prior systemic therapies.
Drug Class/Mechanism of Action	Bispecific CD20- directed, CD3 T-cell engager (bispecific antibody targeting both CD20 and CD3)
Sponsor	Genenetch, Inc.
ODE/Division	OOD/DHMII
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	June 13, 2020 (defaults to Friday, June 12, 2020)

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. Briefly describe the indication for which the product is intended:

   Mosunetuzumab is intended for the treatment of adult patients with relapsed or refractory follicular lymphoma who have received at least two prior systemic therapies.

2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?
   ☐ YES ☒ NO

3. Was the BTDR submitted to a PIND? ☐ YES ☒ NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. Consideration of Breakthrough Therapy Criteria:

   a. Is the condition serious/life-threatening[1])? ☒ YES ☐ NO

If 4a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
      ☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
      ☐ Undetermined
      ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b: N/A

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.
   Mosunetuzumab is a humanized IgG1 bispecific antibody targeting both CD3 (on the surface of T cells) and CD20 (on the surface of B cells). It activates T cells by connecting CD3 in the T-cell receptor complex with CD20 on benign and malignant B cells, forming an immunologic synapse, leading to lysis of the B cell.

   Targeting of CD20 by a monoclonal antibody (as with rituximab) is a critical part of B-cell non-Hodgkin lymphoma (B-NHL) treatment, including treatment of follicular lymphoma (FL). There are no bispecific antibodies approved for the treatment of B-NHL.

   Regulatory history: In 10/2019, the Agency provided preliminary BTDR advice for mosunetuzumab for relapsed or refractory FL. The Agency's recommendation was to submit the BTDR after more mature follow-up for duration of response (DOR) and to consider obtaining independent review committee (IRC) evaluation of response rates.

8. Information related to endpoints used in the available clinical data:

   a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

      The primary endpoint is overall response rate (ORR), with DOR as a secondary endpoint. ORR with durability is the main outcome supporting the BTDR, with efficacy based on IRC assessment.

   b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

      - *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
      - *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
      - *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit*.

For patients with FL, ORR with durability is routinely accepted by the Division as a clinically significant endpoint for supporting accelerated approval (an endpoint reasonably likely to predict clinical benefit). Complete remission (CR) rate may be supportive. Progression-free survival (PFS) is the usual accepted primary endpoint for confirmatory trials in FL.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval. N/A

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:
    - *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
    - *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

For patients with relapsed or refractory FL, the following table summarizes the efficacy of mosunetuzumab (expanded upon in the next section) relative to the most relevant approved therapies. The combination of lenalidomide and rituximab (R^2) has regular approval for patients with previously treated FL, whereas three PI3K inhibitors have accelerated approval in patients with FL after at least 2 prior therapies.

Table 1: Efficacy of Mosunetuzumab Compared to Approved Therapies for Relapsed or Refractory FL

	Mosunetuzumab	Lenalidomide + rituximab (R^2) [a]		PI3K inhibitors [b]
		AUGMENT trial (R-sensitive disease only)	MAGNIFY trial	
Number of patients	109	147	186 (177 treated)	62 – 104
Design	Single-arm	Randomized	Randomized [c]	Single-arm
Prior therapies	≥ 2	≥ 1	≥ 1	≥ 2
# of prior therapies Median (range) 1 2 ≥ 3	 3 (2 – 11) 0 34% 56%	 1 53% 17% 30%	 2 (1, 8) 38% 27% 34%	 3 – 4 –
Refractoriness Ritux refractory Ritux + alkylator refractory POD24	 76% 51% 43%	 0 0 33%	 40% 24% 34%	 56 – 100% 43 – 95% --
Efficacy				
ORR (95% CI)	69% (59, 78)	80% (73, 86)	59% (51, 66)	42 – 59%
CR	47% (37, 57)	35% (27, 43)	35% (28, 43)	1 – 17%

		Lenalidomide + rituximab (R^2) [a]		PI3K inhibitors [b]
Median DOR	--	37 mo	NR	10 – 12.2 mo
Median PFS	--	39 mo	30 mo	

Abbreviations: POD24 = progression of disease within 24 months of start of initial therapy; R or Ritux = rituximab; R/R relapsed/refractory

[a] R^2 has regular approval for previously treated FL (after ≥ 1 therapy).
[b] Idelalisib, copanlisib, and duvelisib, all with accelerated approval for patients with relapsed or refractory FL after ≥ 2 therapies
[c] Approval was based on a single-arm evaluation of R2; patients were subsequently randomized to maintenance therapy with either rituximab alone or R2.

Two other relevant regimens have regular approval: bendamustine (an alkylating agent), and the combination of obinutuzumab (an anti-CD20 monoclonal antibody) with bendamustine. However, the patients in the mosunetuzumab trial had relapsed or refractory disease after an alkylator:

- Bendamustine
  - Regular approval for indolent B-NHL that has progressed during or within 6 months of rituximab or rituximab-containing regimen
  - In single-arm study of 100 pts with indolent NHL (62% FL):
    - ORR 74% (95% CI: 64, 82), CR/CRu 17%, median DOR 9.2 mo (95% CI: 7.1, 10.8)
- Obinutuzumab with bendamustine (GB)
  - Regular approval for FL relapsed after, or refractory to, a rituximab-containing regimen
  - In 164 FL patients randomized to GB (41% with 1 prior therapy, 39% with ≥ 2):
    - ORR 79%, CR 15.5%, median PFS not reached

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[2]:

Axicabtagene ciloleucel (Yescarta) is a CD19-directed chimeric antigen receptor (CAR) T-cell therapy, which received BTD for the treatment of adult patients with relapsed or refractory FL after at least 2 prior therapies.

11. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[3], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

b. Include any additional relevant information. Consider the following in your response:
   - *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*

[2] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[3] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*
- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

The Division recommends granting of the BTDR for the proposed indication. The basis of the BTDR is an ongoing, single-arm phase 1 clinical trial, GO29781, of mosunetuzumab in patients with relapsed or refractory (rel/ref) B-cell malignancies (>350 patients treated) that includes 109 patients with relapsed or refractory FL after at least 2 prior systemic therapies (101 with efficacy data). Prior treatment with an anti-CD20 antibody and an alkylating agent was required. The drug is administered intravenously, with gradually increases doses on Days 1, 8, and 15 of Cycle 1, then at a fixed dose on Day 1 of subsequent 21-day cycles, for a maximum of 17 cycles.

As shown in Table 2, patients with FL had a median of 3 prior systemic therapies, with 33% having 4 or more prior therapies. Most (76%) had refractory disease to the last regimen; 51% had "double refractory" disease to both an alkylator and an anti-CD20 agent.

Table 2: Characteristics of Patients with Rel/Ref FL in Study GO298781 (N = 109)

Median age	60
# of prior systemic therapies	
Median (range)	3 (2 – 11)
2	34%
3	30%
4	17%
5 or more	16%
Prior treatment	
Chemoimmunotherapy	99%
Rituximab + lenalidomide	8%
Refractory to last regimen	65%
Refractory to any anti-CD20 regimen	76%
High-risk FL subsets	
"Double refractory" to anti-CD20 + alkylator	51%
POD 24	43%
Refractory to PI3K inhibitor	12%
Prior CAR-T	6%

By IRC assessment, of 101 patients with FL evaluated for efficacy, the ORR was 69% (95% CI, 59-89%) with a CR rate of 47%. Response rates are shown for all patients combined and according to the dose of mosunetuzumab.

Table 3: ORR with Mosunetuzumab in Rel/Ref FL

Response per IRC [a]	All patients with FL (n =101)	< 1/2/60/30 mg (n = 62)	1/2/60/30 mg (prioritized dose) (n = 39)
ORR (95% CI)	69% (59, 78)	68% (55, 79)	72% (55, 85)
CR rate (95% CI)	47% (47, 57) [b]	50% (37, 63)	41% (26, 58)

[a] 2007 International Working Group criteria, CT-based

[b] PET negative CR in all but 1 case

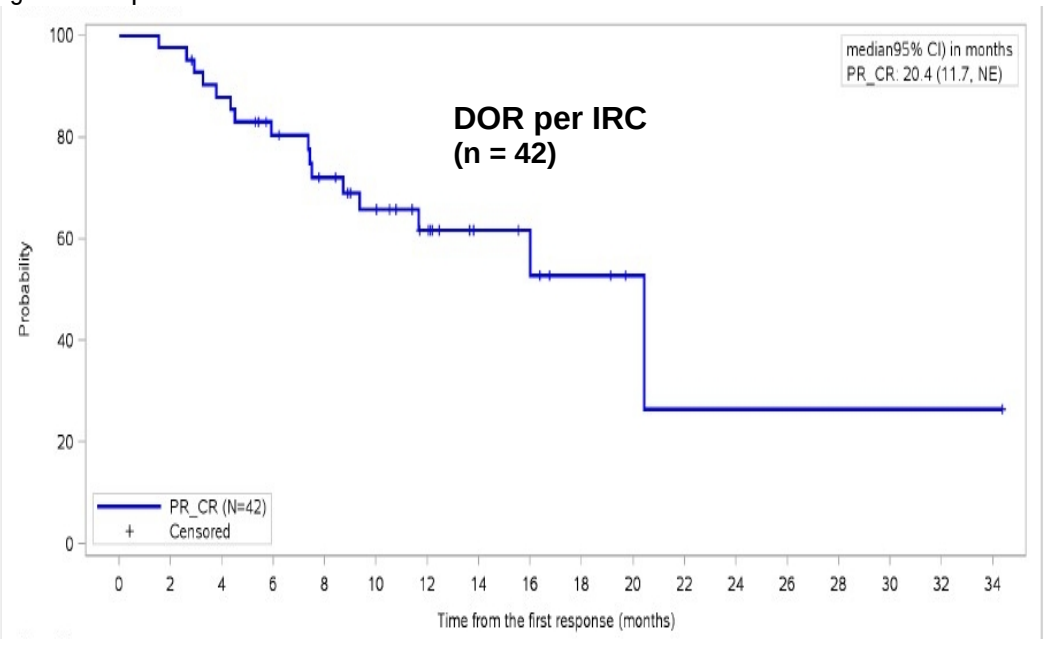
Efficacy was maintained in poor-risk subgroups, including patients with double-refractory disease (n = 51; ORR 67%, CR 47%) and patients refractory to PI3K inhibitors (n = 13; ORR 85%, CR 62%). Of 8 patients who received prior R^2, 4 (50%) achieved a response including 3 (38%) with CR, with DOR lasting from 4.4+ to 12.1+ months, the latter in a patient with 8 prior therapies.

Durability of response is presented for the 62 patients treated at doses less than the intended registrational dose, because of their longer time on study (median time on study, 14.4 months). Of the 42 patients who achieved response, durability of response was demonstrated by 71% having remissions lasting at least 6 months, and 33% having remissions lasting at least 12 months (Table 4 and Figure 1).

Table 4: DOR in Lower-Dose Cohort

DOR per IRC	All responders at doses < 1/2/60/30 mg (n = 42)
Pts with DOR lasting:	
≥ 6 mo	30 (71%)
≥ 12 mo	14 (33%)
K-M estimates (95% CI)	
6-mo DOR	80% (68, 93)
12-mo DOR	97% (90, 100)

Figure 1: Kaplan-Meier Estimate of DOR in Lower-Dose Cohorts



Limitations of efficacy data: An important limitation of these data is that only a minority of patients received R^2, which is available therapy for the proposed indication. The ORR with mosunetuzumab of 69% (95% CI: 59, 78) is similar to that with R^2 in the Magnify trial (ORR 59%; 95% CI 51, 66). However, of the 8 recipients of mosunetuzumab who had prior R^2, half achieved an objective response including several patients with IRC-assessed CR. Thus, there is preliminary evidence that mosunetuzumab has efficacy in patients with relapsed or refractory FL after failure of available therapy. Additionally, mosunetuzumab had clinically meaningful single-agent activity in patients who were heavily pretreated and/or had other poor-risk features.

Another limitation is that the DOR data are from patients treated at lower-dose cohorts. However, the DOR is expected to be comparable, if not better, in patients who receive the higher dose.

Safety: A shared safety concern with T-cell engaging therapies is cytokine release syndrome (CRS). For mosunetuzumab, the gradual step-up dosing was established in order to mitigate CRS. Of 153 patients with NHL treated at the intended registrational dose of mosunetuzumab, CRS developed in 33%, with 2.7% of cases being Grade 3-4. Serious adverse events (AEs) occurred in 42% with fatal AEs in <1%.

Central nervous system neurotoxicity is another safety concern with some T-cell engaging therapies, including mosunetuzumab. The incidence of neurotoxicity was 47%, with most (97%) being Grade 1-2; the predominant manifestations were headache, insomnia, and dizziness for which driving restrictions are in place for higher-risk patients.

These safety issues do not affect the Division's recommendation to grant the BTDR.

12. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

Provide brief summary of rationale for granting:

Based on ORR with demonstration of durability, there is preliminary evidence that mosunetuzumab has clinically meaningful efficacy in patients with relapsed or refractory FL after at least 2 prior therapies, including in patients who have received available therapy. The high CR rates are supportive.

13. Division's next steps and sponsor's plan for future development:

If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

A Type B meeting was held 3/2020 to discuss the registrational pathway for mosunetuzumab in relapsed or refractory FL. The sponsor proposes to use the current, single-arm clinical trial (Study GO29781) to support accelerated approval, based on an expansion cohort of patients with relapsed or refractory FL after at least 2 prior systemic therapies. A randomized phase 3 trial for regular approval may also be considered as the initial registrational approach.

14. List references, if any: None

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

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
06/01/2020 07:54:13 PM

NICHOLAS C RICHARDSON
06/01/2020 09:41:27 PM

NICOLE J GORMLEY
06/02/2020 09:24:42 AM

IND 120651

MEETING MINUTES

Genentech, Inc.
Attention: Jason Puskas, (Hons) BSc, RAC, CCPE
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080-4490

Dear Mr. Puskas:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for mosunetuzumab (BTCT4465A).

We also refer to the teleconference between representatives of your firm and the FDA on March 17, 2020. The purpose of the meeting was to discuss proposed design of the Phase I Expansion Part of Study GO29781 to support accelerated approval of mosunetuzumab in the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies.

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:

- Meeting Minutes

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

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase
Meeting Date and Time:	Tuesday, March 17, 2020; 9:00 AM -10:00 AM (ET)
Meeting Location:	Teleconference
Application Number:	IND 120651
Product Name:	Mosunetuzumab (BTCT4465A)
Indication:	Treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies.
Sponsor Name:	Genentech, Inc.
Meeting Chair:	Nicholas Richardson, DO, MPH
Meeting Recorder:	Wanda Nguyen, PharmD

FDA ATTENDEES

Office of Oncologic Diseases/Division of Hematologic Malignancies II
Nicole Gormley, MD, Acting Director
Nicholas Richardson, DO, MPH, Acting Clinical Team Leader
Yvette Kasamon, MD, Clinical Reviewer

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

Office of Clinical Pharmacology (OCP)/Division of Cancer Pharmacology I
Olanrewaju Okusanya, PharmD, MS, Team Leader
Huiming Xia, PhD, Reviewer

Office of Biostatistics/Division of Biometrics IX
Yu-te Wu, PhD, Team Leader
Laura Fernandes, PhD, Reviewer

SPONSOR ATTENDEES

Genentech, Inc.
Carol O'Hear, MD, PhD, Global Development Leader, Clinical Science
Josephine Ing, Global Regulatory Lead, Regulatory
Chi-Chung Li, PhD, Senior Scientist, Clinical Pharmacology
Brendan Bender, PhD, Scientist, Clinical Pharmacology
Bruce McCall, MD, Group Medical Director, Clinical
Safety Jason Puskas, (Hons) BSc, RAC, Program Manager, Regulatory
Michael Wei, MD, PhD, Medical Director, Clinical Science
Shen Yin, PhD, Clinical Scientist, Clinical Science
Catherine Granier, Principal Statistical Scientist, Biostatistics
Natalie Dimier, PhD, Senior Principal Statistical Scientist, Biostatistics
Antonia Kwan, MD, PhD, Medical Director, Clinical Safety
Hong Wang, PhD, DABT, Director, Toxicology Oncology
Kate Peng, PhD, Associate Director, BioAnalytical Sciences
Iraj Hosseini, PhD, Scientist, Preclinical and Translational PK

1.0 BACKGROUND

Mosunetuzumab is a full-length, fully humanized anti-CD20/CD3 T-cell dependent bispecific antibody of an immunoglobulin (Ig)G1 isotype that is produced in Chinese hamster ovary (CHO) cells using the knobs-into-holes technology. The proposed indication for mosunetuzumab is for treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies.

The purpose of this meeting is to discuss and obtain agreement from the Agency on the following topics in the development program for mosunetuzumab:

- The nonclinical package to support registration of mosunetuzumab;
- The proposed clinical dose/regimen for investigation in the pivotal expansion and for registration of mosunetuzumab in the targeted indication;
- The clinical pharmacology plan to support registration of mosunetuzumab;
- The proposed design of the Phase I Expansion Part of Study GO29781 to support accelerated approval of mosunetuzumab in the target indication;
- The proposed total patient exposure to support registration of mosunetuzumab in the targeted indication;
- The proposed designs of the Phase III confirmatory trials to support continued approval of mosunetuzumab in the target indication.

FDA sent Preliminary Comments to Genentech, Inc. on March 12, 2020.

2.0 QUESTIONS

Question 1: *Does the Agency agree that the completed nonclinical studies support registration of mosunetuzumab?*

FDA Response to Question 1: The nonclinical studies conducted appear sufficient to support the submission of a BLA, but the reproductive risk assessment is incomplete.

As communicated to you in 2018, we agree that reproductive toxicology studies with mosunetuzumab are not needed. However, an integrated summary using a weight-of-evidence (WOE) approach for reproductive risk assessment should be provided with the BLA. We note your reproductive risk assessment included in the briefing document using data from toxicology studies conducted with mosunetuzumab. We consider this assessment incomplete. See the guidance for industry titled Oncology pharmaceuticals: reproductive toxicity testing and labeling recommendations for factors that could be included in a WOE approach https://www.fda.gov/media/124829/download. You may not rely upon product-specific literature for which you do not have right-to-reference, including product labeling or FDA's Summary Basis of Approval, for products submitted under the 351(a) pathway.

Any final decisions on the adequacy of the nonclinical package will be determined during the review of the BLA.

Meeting Discussion: The Agency recommended to remove the list of products for which the Sponsor does not have the right-to-reference. Other components used in the WOE-based reproductive risk assessment of mosunetuzumab appear reasonable to the Agency and can be submitted with the BLA.

Question 2a: *Does the Agency agree with the proposed mosunetuzumab dose and schedule, (Cycle 1 Day 1/8/15 1/2/60 mg; 60 mg on Cycle 2 Day 1; and 30 mg on Day 1 of Cycle 3 and subsequent cycles, q3w) for investigation in the ongoing pivotal expansion and in support of registration?*

FDA Response to Question 2a: The 1/2/60/30 mg dose may be a reasonable dose, however, your dose selection justification as presented in the meeting package does not address the following:

- The reason why AUC_{0-42} was selected over RO% for exposure-response for efficacy as primary evidence to support dose selection for the loading dose, given RO% was proposed to be a better matrix over AUC_{0-42} to support RP2D determination during prior MIDD meeting
- Exposure-response for efficacy based on change in tumor-size from baseline

- Potential detrimental effect on efficacy (response rate and duration of response) by reducing to 30 mg starting from Day 1 of Cycle 3 since AUC_{0-42} based exposure response analysis cannot discriminate the difference between 1/2/60 and 1/2/60/30 dose regimen
- How sensitive baseline factors including tumor burden and leftover anti-CD20 treatment may contribute to the variation of treatment outcome and dose selection
- How the selected dose can cover the majority of patients with various levels of baseline factors
- The reason(s) to support the treatment duration (two doses) of the 60 mg loading dosing

While the selection of 1/2/60/30 mg may be reasonable based on available data, you should continue to re-evaluate your dose selection and validate your exposure response model with emerging data, by using your dose evaluation strategy and the aforementioned points raised by the Agency.

Meeting Discussion: **The Agency stated that the Sponsor's approach is acceptable. The Sponsor clarified the justification for dose selection using AUC_{0-42} supported the exploration of doses higher than 9 mg. The Agency stated that the time course data provided additional information that supported the higher doses (i.e., > 13.5 mg). The Agency acknowledged the Sponsor's response regarding the use of the 60 mg dose. The Agency noted that the time course data for the 1/2/60/30 mg regimen was informative, but the sample size was small and encouraged the sponsor to continue to collect these data and incorporate them in their analysis. The Agency stated that this data could be supportive in understanding the impact of the higher doses (30 mg vs. 60 mg then 30 mg) on the rate and duration of response. The Agency also asked the Sponsor to evaluate if *a prior* knowledge of baseline tumor load was feasible in the clinical trials or in practice, and if it could be incorporated in selecting a loading dose for those specific patients. The Sponsor acknowledged the Agency's recommendation and will take this into consideration.**

Question 2b: *Does the Agency agree that the proposed clinical pharmacology plan supports registration of mosunetuzumab?*

FDA Response to Question 2b: Your proposed clinical pharmacology plan appears acceptable. The final decision will be made during filing of your BLA submission.

Submit your QT evaluation report along with datasets and codes used for analysis for FDA QT-IRT to review. When you submit your QT evaluation report, please include a completed version of the "QT Evaluation Report Submission Checklist" located at the IRT website (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/interdisciplinary-review-team-cardiac-safety-studies-formerly-qt-irt).

Question 3: *Does the Agency agree that the proposed design of the GO29781 expansion cohort is appropriate to support the following indication under accelerated approval:*

Mosunetuzumab is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies.

In particular, does the Agency agree with:

- *the studied population;*
- *the primary endpoint and secondary endpoints;*
- *the sample size and inclusion of supportive data with longer duration of follow up from a lower-dose interim expansion cohort;*
- *the timing of the efficacy analysis?*

FDA Response to Question 3: In general, trials in patients with relapsed or refractory FL that are not randomized and have a primary endpoint reasonably likely to predict clinical benefit may be used to support accelerated approval. Considerations of accelerated approval include the magnitude and durability of the treatment effect, the safety profile, the overall benefit/risk, and the other requirements for accelerated approval, such as providing meaningful advantage over available therapies for this indication. The determination of available therapies is made at the time of regulatory action, and thus could include agents that are not presently approved. Demonstrating an improvement over available therapy can be challenging in a field with multiple ongoing development programs. Therefore, a randomized clinical trial with a primary PFS endpoint is recommended as the initial registrational approach for patients with relapsed or refractory FL.

For the proposed single-arm trial, we have the following comments:

a. Study population: Your intended population (FL failing ≥ 2 systemic therapies) contains patients for whom available therapy exists, such as lenalidomide + rituximab. For a single-arm registrational trial, you would need to demonstrate an advantage over available therapy. You need to either evaluate a more heavily pretreated patient population, including patients failing lenalidomide + rituximab, or demonstrate a higher overall response rate than current available therapy.

   The eligibility criterion “no available therapy expected to improve survival” should be removed because it lacks specificity.

   Refer also to “Additional Comments” regarding eligibility criteria.

   Meeting Discussion: The Sponsor provided further information regarding the characteristics of the study population treated with mosunetuzumab and inquired whether patients with relapsed or

refractory FL who have received at least 2 prior systemic therapies is appropriate for potential registration under the accelerated approval pathway. The Agency reiterated that a randomized controlled trial is the recommended approach for initial registration. The Agency noted that it will be challenging to demonstrate a substantial improvement over available therapy in the proposed patient population. Ultimately, it is at the Sponsor's risk and discretion to pursue initial registration using a single arm trial.

b. Treatment plan: In a potentially registrational trial, it is important that the regimen be uniform, so that an adequate number of patients are evaluable at the dose-schedule intended for marketing. However, the protocol specifies 8 cycles, with an **option** for 17 cycles based on ongoing clinical benefit. For the primary efficacy cohort, standardize the number of cycles to allow consistent application to all eligible patients

Meeting Discussion: The Agency acknowledges the Sponsor's clarification of the treatment regimen based on response and requested that the protocol language be assessed to ensure consistency regarding the treatment plan.

c. Timing of efficacy analysis: The proposed timing of the efficacy analysis (≥ 6 months after initiation of treatment in all of the FL expansion cohort) is premature, because both the magnitude and durability of response are key determinants of efficacy. In the primary efficacy cohort (n = 80), all patients who achieve response should be followed for DOR for a minimum of 9 months, with follow-up measured from the date of first objective response (rather than date of treatment initiation) until the date of last adequate (IRC-assessed) disease assessment or next anti-lymphoma therapy (NALT). The longer follow-up in the lower-dose expansion cohort does not reduce the minimum follow-up duration expected in the higher-dose cohort.

Meeting Discussion: The Agency recommends at least 9 to12 months of duration of response follow up to support an adequate assessment of durability with the dose and regimen intended for registration.

d. Endpoints: For a single-arm trial, we agree with the proposed primary endpoint of IRC-assessed CR and secondary endpoints that include DOR, however PFS should be an exploratory, rather than secondary, endpoint.

For registrational purposes, if an intermediate endpoint other than overall response rate is selected as the primary endpoint for a single-arm trial in patients with relapsed or refractory FL. You will need to provide data to justify the selected intermediate endpoint, such as CR rate, is reasonably likely to predict clinical benefit in your intended population.

Time-to-event endpoints such as PFS and OS are difficult to interpret in a single arm study and cannot be used for labelling claims, because it is unclear to what extent the outcomes can be attributed to the treatment effect versus to disease and patient characteristics.

e. Sample size: A sample size of 100 treated patients is recommended to support a BLA. However, a larger efficacy population may be needed to demonstrate that efficacy (e.g. response rate with 95% CI) with mosunetuzumab is better than that of available therapy. Refer also to above comments regarding the initial registration approach.

Meeting Discussion: The Sponsor and the Agency had a discussion regarding an appropriate sample size, based on the magnitude of treatment effect, to support potential demonstration of substantial improvement over available therapy. The Agency noted the changing FL landscape and the challenges with demonstrating improvement over available therapy.

f. Analysis population: A primary efficacy population based on all enrolled patients at the intended registrational dose appears acceptable.

Question 4: *Does the Agency agree that the proposed total patient exposure would be adequate for registration of mosunetuzumab in the targeted population?*

FDA Response to Question 4: The planned safety database appears reasonable. However, the adequacy of the safety data to support a BLA will be a review issue.

Question 5: *Does the Agency agree that either of the two potential Phase III studies proposed below would be an acceptable confirmatory trial to verify the clinical benefit of mosunetuzumab and to support continued approval of mosunetuzumab monotherapy in patients with relapsed or refractory follicular lymphoma who have received at least two prior systemic therapies?*

1. *A global randomized Phase III trial of mosunetuzumab plus lenalidomide versus rituximab plus lenalidomide in adult patients with relapsed or refractory follicular lymphoma after one or more lines of systemic therapy.*

2. *A global randomized Phase III trial of mosunetuzumab versus rituximab in adult patients with previously untreated follicular lymphoma who are elderly or unfit to receive immunochemotherapy.*

FDA Response to Question 5: Questions regarding the acceptability of the proposal are premature in the absence of a detailed protocol and analysis plan. A

randomized comparison of mosu+len vs. rituximab+len, with a PFS primary endpoint, appears reasonable.

The second proposal may also be viable but has limitations. We have the following comments:

- More information about the safety and tolerability of mosunetuzumab in elderly patients would be necessary.
- Given the toxicities of mosunetuzumab in general and the ~2-year median PFS with rituximab alone as initial therapy, further justification would be necessary to evaluate mosunetuzumab in the first-line setting.
- Further discussion would be needed to determine an appropriate patient population, especially given that the toxicities of mosunetuzumab may exceed those of some standard chemotherapy regimens.
- A larger study than that proposed would likely be necessary.

The Agency is open to further discussion in a separate pre-phase 3 meeting.

Meeting Discussion: There was no discussion.

Post-Meeting Comment: The Agency is open to further discussion on the proposed Phase 3 trials. For a subsequent discussion, the Agency recommends submission of a separate meeting request. To facilitate the discussion, a detailed trial synopsis and rational for each proposed trial is requested.

ADDITIONAL COMMENTS:

1. Eligibility criteria: Because treatment with an anti-CD20 antibody may lead to downregulation or loss of tumor CD20 expression, we recommend to revise the eligibility criteria to require histologically proven relapsed or refractory lymphoma, with documentation of continued CD20 expression on the most recent biopsy indicative of relapsed or persistent disease.

   Meeting Discussion: There was no discussion.

   Post-Meeting Comment: Given the potential risks of mosunetuzumab, the Agency recommends confirmation of relapsed/persistent disease that demonstrates CD20 expression by local assessment; however, for eligibility purposes, the biopsy need not be of the most recent relapse/progression.

2. Clinical pharmacology: Provide a summary of the available Clinical Pharmacology information in all milestone and clinical pharmacology meeting packages and protocol submissions using the attached Tables 1 and 2.

Table 1: Highlights of Clinical Pharmacology

General Information		
Chemical structure and major physical and chemical properties		• Include log P, pKa, solubility (in water and buffers at different pH levels) if oral drug product • Include chemical structure and molecular weight
Indication		• Include the proposed indication • Include other relevant indications under different INDs
Route of administration and formulation type and strengths		• Specify if oral, IV, SC or topical administration • Specify tablet, capsule, intravenous solution or lyophilized powder • List which formulation used in each clinical trial and provide a comparability or bioavailability data for the different products
Mechanism of action		• List proposed mechanism of action for this indication • List proposed mechanism of action for other indications if relevant
Dose and Adverse Events		
Therapeutic dose and exposure		• List proposed clinical dosing regimen for this indication • List proposed clinical dosing regimen for other indications • Provide mean (%CV) C_{max} and AUC at the maximum administered single dose • Provide mean (%CV) C_{max} and AUC at steady state following the administration of the proposed clinical dose
Maximum tolerated dose		• List MTD or OBD identified in clinical trials • Provide the HNSTD or NOAEL
Major adverse events		• List most common adverse events • List dose limiting adverse events • Describe dose or exposure related adverse events • Provide the median time to first and subsequent dose modifications and the reason for these modifications
Pharmacokinetic (PK) Features		
Dose or exposure range tested in clinical trials	Single Dose	• Dose range • Mean (%CV) Cmax and AUC range
	Multiple Dose	• Dose range, dosing interval and duration • Mean (%CV) C_{max} and AUC
Range of linear PK		• Linear dose range • Non-linear dose range
Accumulation at steady state		• Dose range, dosing interval and duration • Mean (%CV) for parent and clinically relevant metabolites
Metabolites		• List relevant (active or major) metabolites • Describe safety and activity (e.g., receptor binding)

Absorption	Bioavailability	• Mean (%CV)
	T_{max}	• Median (minimum, maximum) for parent • Median (minimum, maximum) for metabolites
Distribution	Vd/F or Vd	• Mean (%CV)
	Protein binding (%)	
	Blood to plasma ratio	
Elimination	Route	• Summarize findings of mass balance study in nonclinical and clinical studies • Specify primary route and percentage dose eliminated (parent, metabolites). • List other routes
	Half-life	• Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	• Mean (%CV)
Metabolism	• by CYP ☐ Yes ☐ No ☐ NA, if yes, specify • by Phase II enzymes ☐ Yes ☐ No ☐ NA • by other enzyme systems ☐ Yes ☐ No ☐ NA, if yes, specify • Inhibits CYP ☐ Yes ☐ No ☐ NA, if yes, specify and provide Ki or IC50. • Inhibits Phase II enzymes ☐ Yes ☐ No ☐ NA, if yes specify and provide Ki or IC50. • induces CYP ☐ Yes ☐ No ☐ NA, if yes specify	
Transporters	• by major transporters ☐ Yes ☐ No ☐ NA, if yes, specify • Inhibits major transporters ☐ Yes ☐ No ☐ NA, if yes, specify and provide Ki or IC50. • induces major transporters ☐ Yes ☐ No ☐ NA, if yes specify	
Intrinsic Factors	Age	Geriatric patients: • Age range • Mean changes in C_{max} and AUC
		Pediatric patients: • Age range/pediatric subpopulations • Mean difference in C_{max} and AUC
	Sex	• Mean difference in C_{max} and AUC
	Race	• Mean difference in C_{max} and AUC
	Hepatic impairment	• Mean difference in C_{max} and AUC
	Renal Impairment	• Mean difference in C_{max} and AUC
	Weight	• Mean changes in C_{max} and AUC

Extrinsic Factors	Drug interactions (including gastric acid reducing agents)	• List DDI studies with geometric mean ratio for C_{max} and AUC of parent, metabolites or total analyte
	Food effects	• Geometric mean ratio for C_{max} and AUC • Specify meal type (i.e., high-fat, standard, low-fat)
Population PK Analyses		• Provide data source listing • Summarize results

Pharmacodynamic (PD) Features	
PD Studies: e.g.: QT effect, receptor occupancy, biomarkers	
Analyses for E-R relationships	
Other Studies	
e.g., Genotyping	

Table 2: Completed /Ongoing/ Planned Clinical Pharmacology Studies (for this IND):

Study No.	Study Title	Study Objectives	Study subjects	Study Design	Current Status
			N= Age= Gender= Healthy/Disease=		☐ Completed ☐ Ongoing ☐ Planned

Meeting Discussion: There was no discussion.

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.[2]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request

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

receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult FDA's Guidance on Formal Meetings Between the FDA and Sponsors or Applicants[3] 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.[4]

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.[5]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,[6] 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 are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[7] 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.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide

[3] See the guidance for industry *"Formal Meetings Between the FDA and Sponsors or Applicants."*
[4] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[5] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[6] https://www.fda.gov/media/88173/download
[7] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

versions and associated implementation dates.

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 started on or 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 FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.[8] For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide[9] (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.[10] When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[11]

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

[8] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[9] https://www.fda.gov/media/88173/download
[10] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[11] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

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* (February 2018) and the associated *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*.[12]

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

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

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.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

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

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[13]: In general, the data submission should be fully CDISC-compliant to

[13] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program

facilitate efficient review.
- AssessmentAid[14]

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.

21 Pages have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[14] 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/

NICHOLAS C RICHARDSON
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