CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761324Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 135659

MEETING MINUTES

Genmab US, Inc.
Attention: Donghui Ni
Director, Regulatory Affairs
777 Scudders Mill Road
Bldg, 2, 4th Floor
Plainsboro, NJ 08536

Dear Mr. Ni:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GEN3013.

We also refer to the telenconference between representatives of your firm and the FDA on December 8, 2021. The purpose of the meeting was to discuss the content and structure of the registration dossier.

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

If you have any questions, call Natasha Kormanik, Senior Regulatory Project Manager, at (240) 402-4227.

Sincerely,

{See appended electronic signature page}

Nicholas Richardson, DO, MPH
Clinical Team Lead
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.

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance

Meeting Date and Time: December 8, 2021; 12:00 PM – 1:00 PM (ET)
Meeting Location: Teleconference

Application Number: IND 135659
Product Name: GEN3013 (epcoritamab)
Indication: (b) (4) [redacted]

Sponsor Name: Genmab US, Inc.
Regulatory Pathway: 351(a) of the Public Health Service Act

Meeting Chair: Nicholas Richardson, DO, MPH
Meeting Recorder: Natasha Kormanik, MSN, RN, OCN

FDA ATTENDEES

Office of Oncologic Diseases (OOD)
Maitreyee Hazarika, MD – Acting Associate Director for Safety
Elizabeth Everhart, MSN, RN, ACNP – Associate Director for Labeling
Felicia Diggs, MSN, RN – Acting Safety Regulatory Project Manager

OOD/ Division of Hematologic Malignancies II
Nicole Gormley, MD – Director
Nicholas Richardson, DO, MPH – Clinical Team Leader
Yvette Kasamon, MD – Clinical Team Leader
Pamela Seam, MD – Clinical Reviewer

OOD/ Division of Hematology, Oncology, Toxicology
Brenda Gehrke, PhD – Supervisory Pharmacologist/Toxicologist
Ramadevi Gudi, PhD – Pharmacology/Toxicology Reviewer

Office of Biostatistics/ Division of Biometrics IX
Qing Xu, PhD – Statistical Team Leader
Wenjuan (Jessie) Gu, PhD – Statistical Reviewer

Office of Clinical Pharmacology (OCP)/ Division of Cancer Pharmacology I
Nan Zheng, PhD – Clinical Pharmacology Team Leader
Ankit Shat, PhD, DABT – Clinical Pharmacology Reviewer

Office of Regulatory Operations/ Division of Regulatory Operations for Oncologic Diseases
Theresa Carioti, MPH – Chief, Project Management Staff
Natasha Kormanik, MSN, RN, OCN® – Senior Regulatory Health Project Manager

SPONSOR ATTENDEES

Genmab
Claire Blanchette – Vice President, Compound Development Team Lead
Claudia Corrado, MD – Vice President, Head Medical Hematology
Brian Elliott, MD – Senior Director, Medical Science
Mariana Sacchi, MD – Senior Director, Medical Monitor
Dena DeMarco, BSN – Senior Director, Team Lead, Clinical Research Scientist
Huaibao Feng, PhD – Director, Biostatistics
Tommy Li, PhD – Associate Director, Pharmacology
Steven Xu, PhD– Senior Director, Pharmacology
Frederikke Lihme Egerod, PhD – Director, Non-Clinical Safety & Toxicology
Rima Nassar, PhD – Vice President, Head of Regulatory Affairs
Donghui Ni, MSc – Director, Regulatory Affairs
Jessica Wang, PharmD – Director, Regulatory Affairs
Tahi Ahmadi, MD, PhD – Executive vice president, CMO

AbbVie
Jill Kadam, BS, MBA – Asset Strategy Lead, Program Strategy
Mariana Cota Stirner, MD, PhD – Executive Medical Director, Oncology
Jun Wu, MD, MS – Senior Medical Director, Oncology
Minh Dinh, MD – Senior Medical Director, Oncology
Thomas Doerr, MSc – Senior Scientific Director, Oncology
Apurvasena Parikh, PhD – Director, Clinical Pharmacology & Pharmacometrics
Magdalena Uhart, MD – Product Safety Team Leader
Jerry Ping, PhD– Director, Biostatistics
David Ipe, MS – Director, Biostatistics
William Palo, MS – Director, Safety Statistics
Bruce Trela, PhD, DABT – Senior Director, Preclinical Safety
Thomas Podsadecki, MD – Vice President, Regulatory Affairs, Oncology
Naomi Raviv, MSc – Director, Regulatory Affairs, Oncology
Claire Devlin, BSc – Associate Director, Regulatory Affairs, Oncology
Jinrong Liu, PhD, MBA – Associate Director, Regulatory Affairs, Oncology
Laura Navarre, BSc – Director, Regulatory Affairs, Oncology
David Ross, Pharm. D, MBA – Senior Director, Regulatory Affairs, Oncology

1.0 BACKGROUND

Epcoritamab is a bispecific antibody targeting CD3 and CD20. On October 14, 2021, the Sponsor requested a meeting to discuss the content and structure of the registration dossier. The Sponsor is proposing an indication (b) (4)

FDA sent Preliminary Comments to Genmab US, Inc. on December 3, 2021.

2.0 DISCUSSION

Question 1: *Does the Agency agree that the nonclinical toxicology package is adequate to support the BLA filing?*

FDA Response to Question 1: The nonclinical toxicology package appears sufficient to support the filing of the BLA for epcoritamab in the proposed indication. Any final decisions on the adequacy of the nonclinical package will be determined during the BLA review.

Discussion: No discussion occurred.

Question 2: *Does the Agency agree that the clinical data package is adequate to support the initial BLA filing?*

FDA Response to Question 2: The clinical data package appears reasonable. However, the adequacy of the content to support filing will be determined during the filing review.

We have the following request:

1. Provide an update on the status of the of the GCT3013-05 trial evaluating epcoritamab versus an investigator's choice of BR or R-GemOx in patients with relapsed or refractory large B-cell lymphoma. As able, provide an estimate of the timing of full enrollment and the primary analysis.

Discussion: No discussion occurred.

Question 3: *Does the Agency agree with the planned analyses and data presentation in the Summary of Clinical Efficacy (SCE)?*

FDA Response to Question 3: It is acceptable to submit a Summary of Clinical Efficacy (SCE) in lieu of an Integrated Summary of Effectiveness as long as the SCE provides a comprehensive evaluation of efficacy of epcoritamab in patients with relapsed or refractory large B-cell lymphoma after 2 lines of prior systemic therapy within the SCE requirements. In general, the proposed presentation of the efficacy data

in the SCE is acceptable.

Discussion: **No discussion occurred.**

Question 4: *Does the Agency agree with the planned analyses and data presentation in the Summary of Clinical Safety (SCS) and Integrated Summary of Safety (ISS)?*

FDA Response to Question 4: The planned analysis and data presentation in the SCS and ISS are reasonable and should provide a comprehensive evaluation of safety of epcoritamab in patients with R/R LBCL after 2 lines of systemic therapy within requirements of the SCS and ISS.

Discussion: **No discussion occurred.**

Question 5: *Does the Agency agree with the datasets and programs planned to be submitted with the BLA?*

FDA Response to Question 5: The current plan for the submission of datasets and programs appears reasonable.

In addition, the CRS and neurotoxicity datasets should include the following:

For a CRS dataset: See the information in Additional Clinical Comment #3.

For neurotoxicity (NT) dataset: Please include the following information with one row assigned to each unique subject ID. Please include the NT timing in relation to CRS (predating CRS, concurrently with CRS, following onset of CRS and isolated toxicity), CTCAE grade for neurotoxicity, study day of onset, study day of maximal neurotoxicity grade and study day of resolution, administration of steroids, tocilizumab, additional intervention and investigator identified NT (Yes or No).

Discussion: **The Agency acknowledged that ICANS events were graded by ASTCT criteria rather than CTCAE criteria and other neurologic events were graded using CTCAE. For neurologic events not reported as ICANS, the Agency acknowledged the use of investigator-assessed relatedness to epcoritamab. To facilitate the evaluation of neurologic toxicity, the Agency requested that a dataset flag be used to identify whether neurologic adverse events occurred during an ICANS event using the MedDRA hierarchy, such as neurologic high-level group terms. In addition, for events that are not classified as ICANS by investigators, the Agency stated that the Sponsor should evaluate whether the neurologic event as recorded per CTCAE meets the definition of ICANS per ASTCT to ensure identification of all ICANS events. For these events, the Agency stated they should be recoded using ASTCT criteria.**

Question 6: *Does the Agency agree with the proposed approach for submission of subject narratives and individual case report forms (CRFs)?*

FDA Response to Question 6: The proposed approach for submission of subject narratives and individual CRFs appears reasonable.

We also have the following recommendations:

1. Include any death occurring within 90 days of study treatment as opposed to death due to TEAE or unknown cause, unless occurring after initiation of NALT.
2. 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.
3. To better inform the tolerability of the regimen, provide a table that briefly explains the following:
    a. Study drug action (interrupted, modified, discontinued)
    b. If discontinued, the reason for study drug discontinuation if other than AEs or inefficacy.
    c. Duration of the event and its outcome
    d. If available, any rechallenge information
    e. 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, CRS, NT, 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

Discussion: **The Sponsor proposed to provide narratives for all deaths that occur within 60 days of last dose of study treatment or until start of NALT, which ever occurs earlier. Also, narratives for serious adverse events deemed related to epcoritamab between 61 and 90 days by the investigator following last dose of epcoritamab will be provided. The Agency stated that the proposal appears reasonable and that further information may be requested during the BLA review.**

Question 7: *Does the Agency agree with the sponsor's proposal of MedDRA high-level group term classifications for the neurological events requiring safety narratives?*

FDA Response to Question 7: The Agency utilizes two analysis methods to define neurologic toxicity.

1. Method 1 as defined by Topp et al 2015.
    a. Topp MS, Gokbuget N, Stein AS, Zugmaier G, O'Brien S, Bargou RC, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. Lancet Oncol 2015;16 (1):57-66
2. Method 2 (Broad definition) as defined by the Agency which uses the MedDRA system organ class (SOC) of psychiatric disorders and nervous system disorders excluding the following high-level group terms (HLGT): sleep disorders and disturbances, and peripheral neuropathies.

For safety narratives, the proposed HLGTs listed in the meeting package appears reasonable.

Discussion: **No discussion occurred.**

Question 8: *Does the Agency agree with the proposed plan for submission of the Summary of Clinical Pharmacology (SCP) and population PK and exposure-response analysis as listed?*

FDA Response to Question 8: The proposed plan for summary of clinical pharmacology, population PK, and exposure-response and immunogenicity analyses appears acceptable to support the characterization of the clinical pharmacology properties of epcoritamab. 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" for more detailed information regarding the submission of clinical pharmacology information.

Please note, sufficient dose justification is a critical component to support the registration of epcoritamab. We have significant concerns regarding the adequacy of the data to support the optimized dose regimen selection for epcoritamab. As described in the advice provided during multiple prior meetings (EOP1 meeting dated 05/18/2020, EOP2 meeting/pre-Phase 3 meeting dated 03/16/2021, 07/13/2021, and preliminary BTDR advice meeting dated 11/08/2021), from the Agency's perspective, the optimization of the RP2D is still considered ongoing. Until the requested data is provided, it is premature to agree with your dose selection strategy based on the safety, efficacy, and PK/PD data from studies GCT3013-01 and GCT3013-04 conducted in patients with aNHL, iNHL, and MCL.

Discussion: **No discussion occurred.**

Question 9: *For the planned initial BLA under the AA registration pathway, does the Agency agree with the sponsor's approach to contextualize the benefit-risk profile of epcoritamab based primarily on the GCT3013-01 aNHL cohort in the context of historical data?*

FDA Response to Question 9: To support accelerated approval, the data must support that epcoritamab provides a meaningful therapeutic benefit over available therapies. Available therapies include agents with regular approval or regimens that are commonly administered per the standard of care or treatment guidelines. Therefore, you will need to provide a comparative summary of epcoritamab in the context of available therapies, including regimens that may be commonly administered to patients with relapsed or refractory LBCL, to support potential accelerated approval. Additionally, the determination of available therapy is made at the time of regulatory action and may include additional therapies that are approved after your initial submission.

Discussion: No discussion occurred.

Question 10: *Does the Agency agree to the proposed eCTD content for the epcoritamab BLA?*

FDA Response to Question 10: The propose eCTD content appears reasonable.

Discussion: No discussion occurred.

Question 11: *Does the Agency agree with the sponsor's plan to submit a BLA for epcoritamab monotherapy* (b) (4) (b) (4) *based on the proposed data package from the R/R iNHL cohort of trial GCT3013-01?*

FDA Response to Question 11: No. A data package of 60 patients with indolent NHL with adequate follow-up is not sufficient to support a BLA for the proposed indication in patients with indolent forms of NHL. Further, submission of updated efficacy data during the BLA review is not acceptable. At the time of BLA submission, it is expected that efficacy data be robust and complete, including sufficient follow-up for duration of response. For patients with indolent NHL, it is recommended that all responders have 12 months of follow-up. We recommend submission of a subsequent meeting request to discuss your approach for initial registration using a single-arm trial and your overall development in patients with indolent NHL.

Discussion: No discussion occurred.

Question 12: *Does the Agency have any advice on the proposed plan to submit a BLA for epcoritamab monotherapy* (b) (4) (b) (4)

FDA Response to Question 12: See FDA response to Question 11.

Discussion: No discussion occurred.

Additional Comments

Clinical

1. We recommend submitting an additional pre-BLA meeting request once the topline data is available.
2. The proposed indication includes patients with HGBL, PMBCL, and Grade 3b FL. There is limited data in the listed histologies and whether the data support inclusion in a potential indication will be a review issue.
3. The current management of epcoritamab-induced CRS includes use of tocilizumab. Tocilizumab is indicated for the treatment of CAR T-cell-induced severe or life-threatening CRS and has not been approved for CRS induced by T-cell engaging bispecific antibodies. Therefore, (b) (4) (b) (4) you will need to provide data from multiple trials evaluating epcoritamab to inform the use of tocilizumab (TCZ) for the mitigation of CRS. We have the following additional comments.
    a) Since additional datasets will be required given incorporation of multiple studies, you should provide a proposed ISS along with the respective datasets for review.
    b) To facilitate analysis of the use of tocilizumab in the treatment of CRS in patients treated with epcoritamab, include a detailed summary of the reason(s) tocilizumab was indicated and administered (i.e., persistent hypotension, etc.) for the corresponding CRS grade.
    c) For patients with CRS that was not treated with TCZ, include a detailed summary of symptoms (hypotension, need for supplemental oxygen) and the corresponding CRS grade similar to the granularity requested in (b)(ii) for those patients receiving TCZ.
    d) Include in the BLA a document summarizing the initial CRS management instructions and each modification over the life of Study GCT3013-01, and serial changes in CRS grading and management instructions in the epcoritamab Investigator's Brochure. This can be a free-standing document or an appendix to the SCS/ISS.
    e) Include in the BLA a document summarizing the initial ICANS management instructions and each modification over the life of Study GCT3013-01, and serial changes in ICANS management instructions in the epcoritamab Investigator's Brochure. This can be a free-standing document or an appendix to the SCS/ISS.
    f) For the analyses of safety of use of tocilizumab, include in the SAFSAP or SCS/ISS how you ascertained AEs for tocilizumab from the dataset submitted (e.g., state the data file and variable or a description of the algorithm that you used to identify AEs due to tocilizumab).
    g) For the analyses of efficacy of tocilizumab for treatment of CRS, include in the SAFSAP or SCS/ISS the definition of response, and the data file and variable used to determine the date of the response. If you are using a derived

variable to determine the data of response, ensure that the define file has an explanation of the derivation.

h) Ultimately, whether any agreed upon data package would support the proposed CRS management instructions in labeling will be a review issue.

i) Plan to provide in the epcoritamab BLA submission a custom xpt data file for all cases of CRS or suspected CRS in all studies included in the Integrated Summary of Safety (ISS) using an algorithmic approach to identify potential CRS cases based on the criteria in the following table:

Criteria	Domain	Variable	Value
CRS per investigator	ADAE	PT	Cytokine release syndrome
	ADAE	PT	Cytokine storm
≥ 1 of these (fever)	ADAE	PT	Pyrexia
	ADAE	PT	Febrile neutropenia
	VS/ADVS	Temperature	• *any value ≥ 38.0 degrees C*
≥ 1 of these (hypotension)	ADAE	PT	Hypotension
	ADAE	HLGT	Decreased and nonspecific blood pressure disorders and shock
	ADCM	MED	• *any vasopressor medication*
	VS/ADVS	Systolic Blood Pressure	• *any value < 90 mm Hg for ages ≥ 10 years* • *see Pediatric Advanced Life Support Guidelines for ages 8-10 years*
≥ 1 of these (hypoxia or respiratory symptoms)	ADAE	PT	Hypoxia
	ADAE	PT	Oxygen saturation decreased
	ADAE	PT	Respiratory distress
	ADAE	PT	Respiratory arrest
	ADAE	PT	PO2 decreased
	ADAE	PT	Dyspnoea
	ADAE	HLT	Respiratory failures (excl neonatal)
	ADCM	MED	• *any oxygen value (oxygen, O2, etc)*
	VS/ADVS	O2SAT	• *any value < 90%*

j) Include cases within a prespecified number of days from the last dose of study drug that are:
   - Called CRS per the investigator AND/OR
   - Have a fever criterion plus (a hypotension criterion AND/OR a respiratory criterion)

k) Provide a brief narrative for each case. If you do not conclude that the event is CRS, describe the data (e.g., blood culture results) that support an alternate etiology of fever, hypotension and hypoxia.

l) Submit a custom data file ("ADCRS") with the following information for each episode identified by the algorithm:

ADCRS (one row per CRS episode)
CRS Start Date
CRS Study Relative Start Day
CRS End Date
CRS Study Relative End Day
CRS Duration
Cycle number
CRS Cycle Relative Start Day
Maximal ASTCT CRS Grade
ASTCT Grade ≥ 3 CRS Start Date
ASTCT Grade ≥ 3 CRS relative Start Day
Hospitalization for CRS Start Date (if treated as an outpatient)
Hospitalization for CRS Relative Start Day (if treated as an outpatient)
ICU Start Date
ICU Relative Start Day
ICU Duration
Date of last dose of study drug before start of CRS event
Action taken with study drug
Earliest date study drug interrupted, dose reduced, or withdrawn for this event
Con Med - Toci Flag
Con Med - Steroids Flag
Con Med - Pressors Flag
Con Med - Oxygen Flag
Con Med - Anti-Seizure Flag
Con Med - Anti-IL-1 Flag
Con Med - Anti-IL-6 Flag
Con Med - Other Flag
CRS Symptom - Cardiovascular Flag
CRS Symptom - Coagulopathy Flag
CRS Symptom - Constitutional Flag
CRS Symptom - Fever Flag
CRS Symptom - Gastrointestinal Flag
CRS Symptom - Hepatic Flag
CRS Symptom - Hypotension Flag
CRS Symptom - Hypoxia Flag
CRS Symptom - Neurologic Flag
CRS Symptom - Renal Flag
CRS Symptom - Respiratory Flag
CRS Symptom - Skin Flag
CRS Symptom - Other Flag
CRS Symptom - Other describe
Procedure - Dialysis/HF Flag
Procedure - Ventilator Support Flag
Procedure - Other Flag
Procedure - Other describe
Sponsor's adjudication if CRS event (yes/no)
Sponsor's alternative etiology if not a CRS event

m) Include also the following modifications to the standard CDISC files for the ISS:

ADSL (one row per subject)

Flag for patients with CRS
Max ASTCT grade CRS
Flag for patients with ICANS
Max ASTCT ICANS grade

ADAE (one row per event)
Flag for Cytokine Release Syndrome term or CRS sign/symptom
Flag for ICANS term or Neurotoxicity sign/symptom

ADCM (one row per drug use)
Flag for CRS prophylaxis drug
Flag for CRS treatment drug
Flag for ICANS prophylaxis drug
Flag for ICANS treatment drug
Flag for vasopressor
Flag for oxygen
Flag for systemic corticosteroid
Flag for anti-cytokine
Add dose of tocilizumab used (mg/kg)
Flag for variable identifying reason for tocilizumab administration

n) Include in the Reviewer's Guide where to find cytokine and CRP data for all epcoritamab-treated patients with CRS, and the tocilizumab PK data for epcoritamab-treated patients with CRS who received tocilizumab.

Discussion:

CRS Trial Data

The Sponsor proposed to include CRS data from all epcoritamab-treated patients in studies GCT3013-01 and GCT3013-04. To support an evaluation of the use of tocilizumab in the mitigation of epcoritamab-induced CRS, the Agency stated that further information is required on the number of patients from the -01 and -04 study who experienced CRS and how many received tocilizumab. The Sponsor stated they could provide information on the proportion of patients across epcoritamab trials with CRS who received tocilizumab and importantly, those who did not receive tocilizumab for the Agency to review. The Agency stated that if the data provided is limited in the number of patients who received tocilizumab, inclusion of data from additional studies as able is recommended to allow for an adequate assessment on the use of tocilizumab in the mitigation of epcoritamab-induced CRS. The Agency stated that ultimately, the adequacy of the data to support inclusion of tocilizumab in potential labeling for epcoritamab will be a review issue.

Tocilizumab Safety

To support the analysis of safety of use of tocilizumab, the Sponsor proposed to provide narratives for SAEs and listings for all treatment-emergent adverse events within 7 days following tocilizumab administration. The Agency stated the proposal appears reasonable.

Tocilizumab Response

To define response to tocilizumab, the Sponsor proposed that patients are considered responders if CRS resolved within 14 days of the first dose of tocilizumab, if no more than 2 doses of tocilizumab were needed, and if no drugs other than tocilizumab and corticosteroids were used for treatment. The Agency stated that the definition of response should be the timing of CRS resolution based on the natural history of CRS resolution without tocilizumab in the setting of epcoritamab treatment. In addition, if corticosteroid use is initiated or escalated following administration of tocilizumab, that would be considered a failure. The Agency stated that the Sponsor should provide an updated definition of response with appropriate justification. The Agency noted that the definition should be at least less than 5 days to ensure a clinically meaningful effect. The Agency noted that the determination of response to tocilizumab and the clinical meaningfulness will be a review issue. To gain a full understanding, the Agency also requested the time to resolution for each patient with CRS regardless of treatment with tocilizumab.

CRS Event Identification

To identify all potential CRS events, the Sponsor proposed to include all cases of fever plus hypotension and/or respiratory criteria within 3 days following any dose of epcoritamab. The Agency recommend a timeframe of 7 days since epcoritamab is administered every 7 days for cycles 1-3. The Sponsor agreed to a timeframe of 7 days.

Hospitalization Data

The Agency acknowledged that ICU start day and duration would not be provided. The Agency requested clarification on whether procedure data was collected, such as ventilator support. The Sponsor stated that procedural data was collected as part of the CRF.

Clinical Pharmacology

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.
    b) What are the exposure-response relationships for efficacy, safety and biomarkers in the target patient population?
    c) How do extrinsic (e.g., other drugs) and intrinsic factors (such as sex, race, body weight, organ dysfunctions, and disease) influence the exposure, efficacy, or safety of your drug? What dose modifications are recommended?
    d) What is the impact of immunogenicity on exposure, efficacy and safety?

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.
    c) Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
        - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
        - Identify individual subjects with dosage modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dosage modifications in the datasets.
2. Submit a study report describing the population pharmacokinetic analyses and exposure-response analyses. Refer to Guidance for Industry for population PK, exposure-response relationships, and pharmacometric data and models submission guidelines.
3. Use the laboratory analysis dataset (adlb.xpt) for the laboratory-based adverse reactions and the adverse event analysis dataset (adae.xpt) for the non-laboratory-based adverse reactions (individual and pooled terms as appropriate) to evaluate the exposure-response relationship for safety and the effect of intrinsic and extrinsic factors on safety based on the maximum toxicity grade compared to baseline.
4. Include a variable that identifies the maximum toxicity grade compared to baseline for laboratory-based adverse reactions in laboratory analysis dataset (adlb.xpt) and for non-laboratory-based adverse reactions (individual or pooled where applicable) in adverse event analysis dataset (adae.xpt) to support these analyses. A description of the pooled non-laboratory-based adverse reactions should be provided in the reviewer guide and consistent with common pooled terms used to inform labeling if applicable.
5. 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*". 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.

Statistical

The future NDA submission should include following:

- All raw as well as derived variables in .xpt format. FDA strongly recommends submission of datasets using CDISC standards.
- SAS programs used to create the derived datasets for the efficacy endpoints and the SAS programs used for efficacy data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs.
- SAS programs for derived datasets and the analyses which are associated with the results presented in the proposed package insert as well as any interim analysis if performed.
- A mock-up define file to show the variables which will be included in the derived datasets for the primary and key secondary efficacy analyses including, but not limited to, the variables for reasons of censoring, dates of IRC determined event or censoring and variables for subgroup analyses, etc. Variables used for sensitivity analysis of the statistical analysis plan (SAP) should also be included.

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 receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric

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

product development, please refer to FDA.gov.[3]

ADVANCING ONCOLOGY DECENTRALIZED TRIALS

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

For details please refer to: https://www.fda.gov/about-fda/oncology-center-excellence/advancing-oncology-decentralized-trialsb

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues discussed.

5.0 ACTION ITEMS

No action items identified.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor's response to preliminary comments.

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

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/s/

NICHOLAS C RICHARDSON
12/10/2021 07:31:57 AM

IND 135659

MEETING MINUTES

Genmab US, Inc.
Attention: Donghui Ni
Director, Regulatory Affairs
777 Scudders Mill Road
Building 2, 4th Floor
Plainsboro, NJ 08536

Dear Mr. Ni:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GEN3013.

We also refer to the teleconference between representatives of your firm and the FDA on March 16, 2021. The purpose of the meeting was to discuss (b) (4) (b) (4)

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

If you have any questions, call Natasha Kormanik, Senior Regulatory Project Manager, at (240) 402-4227.

Sincerely,

{See appended electronic signature page}

Yvette Kasamon, MD
Clinical Team Lead
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.

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/s/

YVETTE L KASAMON
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