

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761400Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 138791

MEETING MINUTES

Regeneron Pharmaceuticals, Inc.
Attention: Smita Abbi, PhD
Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

Dear Dr. Abbi:¹

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for REGN5458.

We also refer to the video conference between representatives of your firm and the FDA on October 18, 2023. The purpose of the meeting was to discuss the proposed content and format of the planned REGN5458 BLA submission for treatment of patients with relapsed or refractory multiple myeloma (RRMM) (b) (4)

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

If you have any questions, call Laura Wall, Senior Regulatory Project Manager, at 301-796-2237.

Sincerely,

{See appended electronic signature page}

Bindu Kanapuru, MD
Supervisory Associate Director for Therapeutic
Review
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: B
Meeting Category: Pre-BLA

Meeting Date and Time: October 18, 2023 from 12:30 PM (ET) to 1:30 PM (ET)
Meeting Location: Videoconference

Application Number: IND 138791
Product Name: REGN5458
Indication: proposed for treatment of patients with relapsed or refractory multiple myeloma (RRMM) (b) (4)
Sponsor Name: Regeneron Pharmaceuticals, Inc.
Regulatory Pathway: 351(a) of the Public Health Service Act

Meeting Chair: Bindu Kanapuru, MD
Meeting Recorder: Laura Wall, MS, BSN, PHNA-BC

FDA ATTENDEES

Office of Oncologic Diseases/Division of Hematologic Malignancies II

Nicole Gormley, MD, Director
Nicholas Richardson, DO, MPH, Deputy Director
Bindu Kanapuru, MD, Supervisory Associate Director for Therapeutic Review
Patrick DeMoss, MD, Clinical Reviewer
Deepti Telaraja, MD, Clinical Reviewer

Office of Oncologic Diseases

Shan Pradhan, MD, Associate Director for Safety
Jessica Kim, PharmD, Safety Regulatory Project Manager

Office of Regulatory Operations/Division of Regulatory Operation for Oncologic Diseases

Theresa Carioti, MPH, Chief Project Management Staff
Laura Wall, MS, BSN, PHNA-BC, Senior Regulatory Project Manager
Megan Sybeldon, PharmD, Regulatory Project Manager
Andrea Babb, PharmD, Regulatory Project Manager

Office of Biostatistics/Division of Biometrics IX

Qing Xu, PhD, Statistical Team Leader
Mingyu Xi, PhD, Statistical Reviewer

OOD/Division of Hematology Oncology Toxicology

Brenda Gehrke, PhD, Pharmacology/Toxicology Supervisor

Simon Williams, PhD, Pharmacology/Toxicology Reviewer

Office of Clinical Pharmacology/Division of Cancer Pharmacology I

Xiling Jiang, PhD, Clinical Pharmacology Team Leader

Sriram Subramaniam, PhD, Clinical Pharmacology Reviewer

Office of Biotechnology Products (OBP)

Chana Fuchs, PhD, OBP Team Leader

Ralph Bernstein, PhD, OBP Reviewer

Kristine Leahy, RPh, Senior Regulatory Project Manager

Office of Surveillance and Epidemiology

Laura Zendel, PharmD, BCPS, Division of Risk Management Deputy Division Director

Naomi Boston, Division of Risk Management Team Leader

Till Olickal, Division of Risk Management Analyst

Candido Alicea, PhD, OSE Regulatory Project Manager

Center for Devices and Radiological Health/Office of In Vitro Diagnostics (OIR)

Ying (Katelin) Mao, PhD, Chief, Immunology and Flow Cytometry Branch

Jacqueline Cleary, BS MT(ASCP), Immunology and Flow Cytometry Branch Lead
Reviewer

SPONSOR ATTENDEES

Ned Braunstein, MD, Executive Vice President, Regulatory Affairs

Anand Achanta, PhD, Vice President, Regulatory Affairs

Joanna Pols, PhD, Executive Director, Regulatory Affairs

Smita Abbi, PhD, Director, Regulatory Affairs

Danish Iqbal, PhD, Manager, Regulatory Affairs

Andres Sirulnik, MD, PhD, Senior Vice President, Translational & Clinical Sciences,
Hematology

Karen Rodriguez Lorenc, MD, Vice President, Global Program Head, Translational &
Clinical Sciences, Hematology

Glenn Kroog, MD, Executive Director, Translational & Clinical Sciences, Hematology

Yariv Houvras, MD, PhD, Senior Director, Translational & Clinical Sciences,
Hematology

John Davis, PhD, Vice President, Clinical Pharmacology

Anasuya Hazra, PhD, Senior Director, Clinical Pharmacology

Sameer Upadhyay, MD, Executive Director, Global Patient Safety

Martha Makaratzis, MD, Director, Global Patient Safety

Jyotirmoy Dey, PhD, Senior Director, Biostatistics

Aurora Breazna, PhD, Associate Director, Biostatistics

Michelle DeVeaux, PhD, Senior Manager, Biostatistics

U.S. Food and Drug Administration

Silver Spring, MD 20993

www.fda.gov

Anita Boyapati, PhD, Senior Director, Precision Medicine
Jennifer Hamilton, PhD, Vice President, Precision Medicine
Jennifer McNay, PhD, Senior Vice President, CMC Regulatory Affairs & Industrial Affairs

Anne Pirozzi, PhD, Senior Director, CMC Regulatory Sciences
Hayley Mattice, MS, Senior CMC Regulatory Sciences Specialist
Sarah Sidnam, PhD, CMC Senior Staff Scientist
Patricia Longo, PhD, CMC Staff Scientist
Kellie Taylor, PhD, Executive Director, CMC Regulatory Affairs
Zhenzhen Liu, PhD, Director, CMC Regulatory Affairs
Crystal Cicchino, BS, Manager, CMC Regulatory Affairs

1.0 BACKGROUND

The purpose of the pre-BLA meeting was to discuss the proposed content and format of the planned REGN5458 BLA submission for the treatment of patients with relapsed or refractory multiple myeloma (RRMM) (b) (4)

and to discuss the available data package.

2.0 DISCUSSION

2.1. Efficacy and Safety

Question 1: *Does the Agency agree that the efficacy data from Study 1826 are adequate for the assessment of benefit of linvoseltamab to support initial accelerated approval for the proposed application?*

FDA Response to Question 1:

1. We reiterate our concerns regarding the use of a single arm trial to support accelerated approval in multiple myeloma and challenges with the interpretation of results in the absence of a control arm.

You have requested an indication for the treatment of adult patients with relapsed or refractory multiple myeloma (b) (4)

However, we note that there are currently approved therapies for this population. Additionally, available therapies are determined at the time of regulatory action on the BLA. The definition of available therapy may change over time given the evolving treatment landscape for multiple myeloma.

We recommend you conduct a randomized clinical trial to support the initial registration for linvoseltamab for patients with multiple myeloma.

2. If you decide to pursue an initial marketing application based on the results of a single arm trial, the magnitude of the treatment effect and the durability of the response are critical components to establish efficacy.
- At the time of application submission, the expectation is that the duration of response (DoR) follow-up is complete and robust. All patients should have a minimum of 9 to 12 months of follow-up from the onset of first response (PR or better) to allow for an adequate assessment of durability of response and safety. The adequacy of the follow-up and the rate of early censoring will be an important aspect of the benefit-risk assessment during the review process.
 - Additionally, the confirmatory trial should be well underway and will be an important component of the benefit-risk determination to support approval. Whether the proposed confirmatory trial is deemed “well underway” will be a review issue.
 - The time-to-event endpoint PFS is not interpretable in a single-arm study, because it is unclear to what extent the outcomes can be attributed to the treatment effect vs. the underlying disease. Therefore, the analysis result of PFS will be considered exploratory.
 - Whether the data is sufficient to support the benefit-risk of lincoseltamab for the proposed patient population will be determined during the review process.

See also response to Question 10 #1 regarding the Module 3 information required at the time of the initial BLA submission.

Discussion: No discussion occurred.

Question 2: *Does the Agency agree that the safety data from Study 1826 are adequate for the assessment of lincoseltamab safety profile in support for the proposed application?*

FDA Response to Question 2:

The Agency does not agree to the adequacy of the safety database in advance. The adequacy of the safety database will be determined during review of the BLA.

Regarding your pooling strategy, the proposal to pool patients who received the 200 mg full dose (N=12 in Phase 1 and N=105 in Phase 2) may be reasonable if there are not any major differences between phase 1 and 2 including but not limited to the patient population, duration of follow-up, efficacy, and safety assessments.

Discussion: No discussion occurred.

Question 3: *Does the Agency agree with the proposed content and presentation of clinical data within the Summary of Clinical Efficacy (SCE, Module 2.7.3) and proposed plan not to submit an Integrated Summary of Clinical Efficacy (ISE)?*

FDA Response to Question 3:

Your proposal for the SCE appears reasonable. However, we do not agree with your proposal not to submit an ISE.

In general, the SCE should provide a data summary consisting mostly of narrative summaries with tables and figures incorporated as needed. Given you plan to submit supportive efficacy data from multiple cohorts that include patients treated at different dose levels, you should also include a separate ISE. The ISE should be in Module 5 and should contain a more detailed, in-depth analysis, including integrated analyses, appendices, datasets, and summaries of all relevant data. The ISE datasets should include flags to indicate the primary and supportive efficacy populations and different dosing regimens.

Discussion: The Agency stated that the Sponsor's proposal for an integrated summary of clinical efficacy appears reasonable. The Agency reiterated that Phase 2 Cohort 2 should also be reported separately in the CSR.

Question 4: *Does the Agency agree with the proposed content and presentation of clinical data within the Summary of Clinical Safety (SCS, Module 2.7.4) and proposed plan not to submit an Integrated Summary of Clinical Safety (ISS)?*

FDA Response to Question 4:

Your proposal for the SCS appears reasonable. However, we do not agree with your proposal not to submit an ISS.

Your submission should include a separate ISS. In general, the SCS should provide a data summary consisting mostly of narrative summaries with tables and figures incorporated as needed. The ISS should be in Module 5 and should contain a more detailed, in-depth analysis, including integrated analyses, appendices, datasets, and summaries of all relevant data. The SCS should also include information on the use of tocilizumab or other supportive medications in relation to CRS and ICANS.

Discussion: The Agency stated that the Sponsor's proposal for an integrated summary of clinical safety appears reasonable. The Agency reiterated that Phase 2 Cohort 2 should also be reported separately in the CSR.

Question 5: *Does the Agency agree that minimal residual disease (MRD) results generated from a lab-developed (b) (4) test (LDT), validated according to the FDA Guidance for Industry on submissions for Hematologic MRD, may be used to*

supplement missing data from the primary (b) (4) test for Study 1826 in the BLA submission to support a more complete MRD data package?

FDA Response to Question 5:

We have insufficient information to agree with the proposed methodology and description of performance characteristics of the (b) (4) assay for MRD assessment, especially regarding the variability of LLOD and LLOQ.

We have the following comments.

1. You state on page 36, (b) (4)
(b) (4)
2. You state on page 36, (b) (4)
(b) (4)

You should submit the below information to the Agency to assess the analytical validation for the assay used in the proposed trial.

- a. A statement of intended use including the analyte(s) being measured, specimen types (anticoagulants), the indications for use (i.e., diseases), whether the test is qualitative, semi-quantitative, and or quantitative. Please provide a detailed device description including what steps are semi-automated versus manual operation.
- b. The specific test method or standard operating procedure (SOP) including instruments, reagents, and specimen handling that will be used by the operator to perform the (b) (4) MRD assay should be provided.
- c. Confirmation that the lab has a process in place for reagent control for the critical reagents used in the (b) (4) MRD assay.
- d. An analytical validation protocol including detailed study designs for each

- specimen type including the gating strategy methods for analysis, pre-analytical sample requirements, number of total number of events collected, and the interpretation of the result for the (b) (4) MRD (b) (4) assay. It is important that consistent result reporting criteria are applied to all reported results.
- e. Analytical validation data for the (b) (4) MRD assay, including the line data in Excel format.
 - f. Summary of the detailed study designs for your analytical validation of the assay and performance for accuracy, precision, linearity, reagent and sample stability, interferences (specificity) and Limit of Detection (sensitivity).
3. Be advised that the assay protocols and methods for analyzing the (b) (4) MRD assay data should be fully specified and locked down prior to the use of this assay in the proposed clinical trial.
 4. It is also important that consistent result reporting criteria are applied to all reported results. For example, you would need to decide on the specific method (i.e., manual and automated) used for each of the steps described in your device procedure and provide analytical validation performance for each method separately.
 5. You proposed (b) (4)
 6. Whether or not the MRD results are sufficiently robust to inform the benefit-risk for (b) (4) will be assessed during the review process.

Discussion: The Agency expressed concerns (b) (4)
The Agency
discussed the limitations of the data in the validation report for the (b) (4) assay submitted to the Agency and stated that the Sponsor should request a meeting with CDRH to discuss the proposed (b) (4) assay. Ultimately whether the MRD results are sufficiently robust to support a benefit risk determination of their product will be determined during the review of the submission.

2.2. Clinical Pharmacology

Question 6: *Does the Agency agree with the proposed content and format of Summary of Clinical Pharmacology (Module 2.7.2)?*

FDA Response to Question 6:

Yes. Also, refer to the Clinical Pharmacology Additional Comment #1 below.

Discussion: No discussion occurred.

Question 7: *Does the Agency agree that the proposed population pharmacokinetic and exposure-response analyses are adequate to support the BLA filing?*

FDA Response to Question 7:

Yes. In general your proposed plan appears reasonable. However, the following recommendations should be addressed in the BLA submission:

1. Provide justification with supporting data for the measurement of total linvoseltamab, given that the free drug is the active component and should be the driver for popPK and E-R analyses.
2. Investigate immune response status (ADA) as a potential covariate in popPK analysis. Also, we recommend investigating time-varying ADA status.
3. In addition to the exposure metrics listed in the modeling and simulation plan (i.e, trough concentrations (C_{trough}) and maximum concentrations (C_{max}) at week 4 Day 1 or at week 16 Day 1, average concentration (C_{avg}) over the period of 16 weeks at relevant dosing intervals, and C_{max} at weeks 1- 4), include C_{max}, C_{avg}, and C_{trough} at the last full dose of the QW dosing period and at the last full dose of the Q2W dosing period in the proposed E-R analysis.
4. Provide PK, PD, efficacy, and safety data to support that a less frequent dosing of linvoseltamab (i.e., 200 mg Q2W and Q4W) will not result in a loss of efficacy for patients with RRMM as this will impact the benefit-risk of linvoseltamab.

In addition to datasets, SAS programs and documentation files will need to be provided for population PK and exposure-response analyses.

Also, refer to the Clinical Pharmacology Additional Comments #2-8 below.

Discussion: No discussion occurred.

2.3. Risk Mitigation/Labeling

Question 8: *We are aware that 3 bispecific T-cell engagers for RRMM that recently received accelerated approval all required a REMS with ETASU. However, there are important differences between those products and linvoseltamab, including the route of administration, step-up dosing regimen and, for Talvey, the tumor antigen. We would like to understand the considerations that the Agency will focus on in its review of our BLA to determine if a REMS with or without ETASU will be required. It is our assessment, the safety information and safety management guidance planned for inclusion in the label and medication guide are adequate to ensure safe and*

effective use of linvoseltamab and hence, a REMS is not warranted. A justification of the Sponsor's position is provided below, and the Sponsor will provide a final no-REMS justification in the BLA. At this stage, we are interested in understanding the Agency's thinking on this topic as the medical community gains more experience with risk management with this class of agents and the specific safety profiles of each individual agent, acknowledging that any final decision will be a review issue.

FDA Response to Question 8:

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

Discussion: The Agency reiterated that the decision regarding the need for a REMS will be determined during the review of the application. The Agency will communicate the need for REMS as appropriate during the review process.

2.4. Regulatory

Question 9: *Does the Agency agree that the efficacy and safety data from Study 1826 are adequate to evaluate the benefit-risk profile of linvoseltamab to support the review of the BLA under accelerated approval pathway for the target indications in RRMM and that linvoseltamab data are sufficiently differentiated from profiles of products with accelerated approval such that linvoseltamab could receive accelerated approval if one of the currently approved products under accelerated approval (likely to be teclistamab in our assessment) receives full approval for this indication before the action date for linvoseltamab?*

FDA Response to Question 9:

Accelerated approval is reserved for drugs that treat a serious condition, provide a meaningful advantage over available therapies, and demonstrate an effect on a surrogate or intermediate clinical endpoint. Whether the product meets criteria to support accelerated approval is made at the time of regulatory action. We recommend you conduct a randomized clinical trial with a PFS endpoint supported by OS to support the initial registration for linvoseltamab.

Discussion: The Agency reiterated that whether a product meets criteria to support accelerated approval is made at the time of regulatory action. The Agency encouraged the Sponsor to prioritize enrollment and completion of their proposed randomized trial. The sponsor stated that they have an ongoing RWD study and questioned whether this could be helpful to the agency during its review of this single arm trial. The Agency stated that

there are significant limitations with the use of RWD as an external control but are willing to engage in further discussion with the sponsor regarding any proposed uses of RWD.

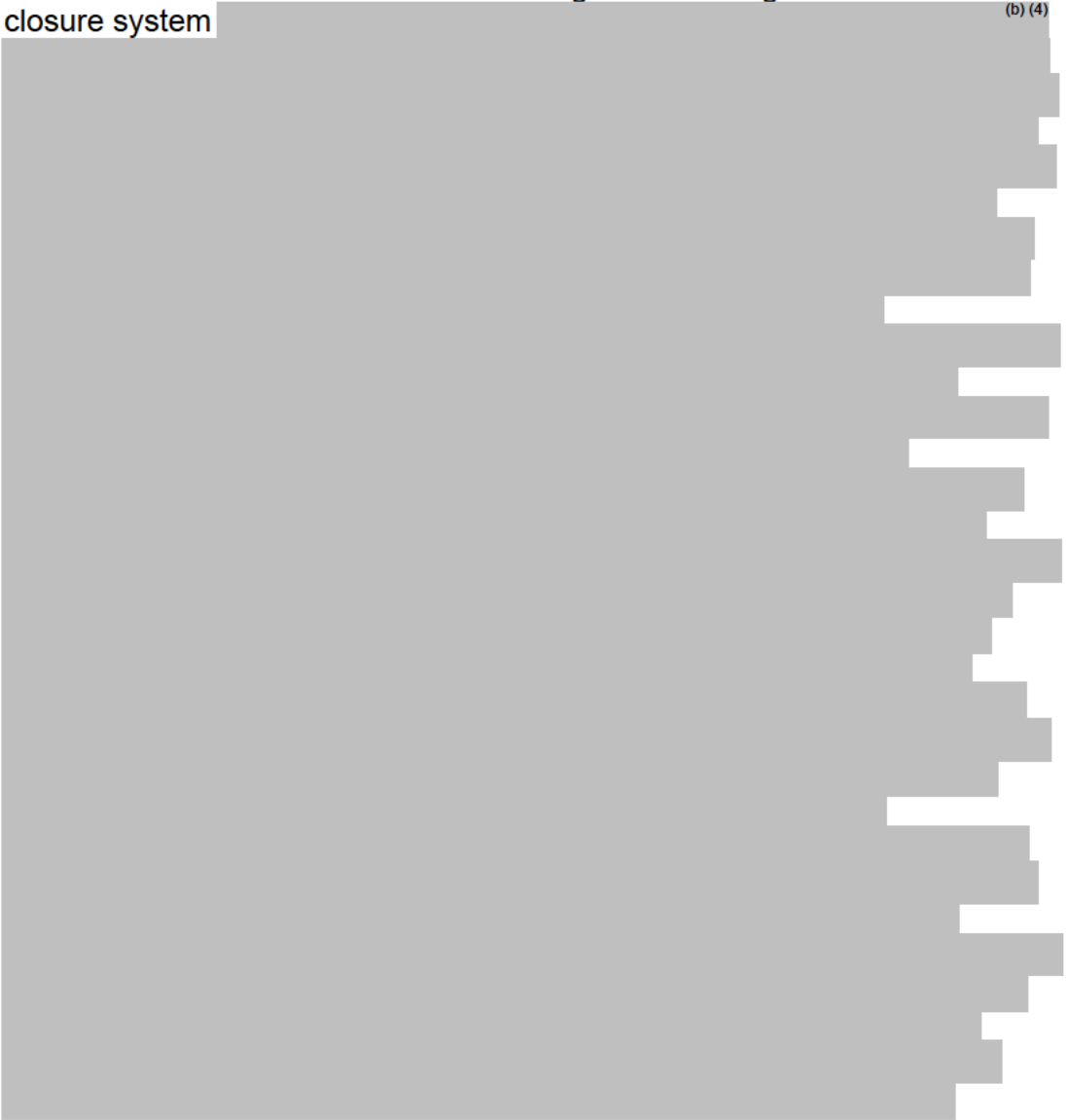
Question 10: Does the Agency agree with the proposed eCTD table of contents for the planned BLA as well as the content and structure of the electronic submission datasets and analysis datasets as described in the Study Data Standardization Plan?

FDA Response to Question 10:

No. We have the following comments.

1. Regarding contents of module 3 of the BLA:
 - a. The commercial DP is described as a 5mg and a 200mg DP in a container closure system

(b) (4)



(b) (4)

A complete Module 3 is expected at the time of application submission. Additional stability data can be submitted if requested by FDA (i.e., solicited amendment) during the review cycle.

Additional sponsor questions and clarifications from the responses and slides emailed on 17 Oct 2023

- 1) Does the Agency agree that the (b) (4) mg/mL (b) (4) lot and 2 mg/mL (b) (4) lots can be accepted as primary batches?

Discussion: The Agency stated

(b) (4)

Whether the data are sufficient to support that (b) (4) lots can be accepted as primary batches will be a BLA review issue.

- 2) If yes, does the Agency agree that the proposed stability dataset supported by comparability reports would meet the expectation for a complete Module 3 at the time of BLA submission?
- 3) Does the Agency agree that simple stability data updates to the BLA can be made during the review period, without requiring a solicited amendment?

Discussion: No. A simple stability update that is submitted without a solicited amendment may be submitted during the first 30 days after BLA submission if agreed upon, however this was not discussed or agreed upon during the meeting. After that timeline any stability update will have to be requested by FDA.

- b. Section 3.2.S.2.5 of Appendix 3 of the meeting package identifies that validation of a (b) (4) process (b) (4)

will be provided. This strategy is not acceptable. We also note that this validation plan was not mentioned or

discussed in the Type C CMC meeting package for this product (WRO dated 5/15/2023).

See additional Sponsor questions and clarifications from the responses and slides emailed on 17 Oct 2023.

The following is a post-meeting comment addressing the Sponsor's clarification:

The Agency appreciates the information provided

(b) (4)



- c. In section 3.2.S.5 for Reference Standards or Materials, include the protocol(s) (e.g. SOPs) for a new ref std. The protocol(s) could be included in this section or in section 3.2.R.

Discussion: No discussion occurred.

- d. Include detailed information on visual inspection, defects, defect rates, and a post VI statistical evaluation in Section 3.2.P.3.5. This was not included in the information to be provided for this section in appendix 3.

Discussion: No discussion occurred.

- e. To facilitate the Agency's review of the drug substance (DS) and drug product (DP) manufacturing processes for REGN5458 provide the information for

process parameters and in-process controls, as applicable, in the following tabular format. Please provide a separate table for each unit operation. The tables should summarize information from module 3 and may be submitted either to module 3.2.R or module 1.

Process Parameter/ Operating Parameter/ In-Process Control	Proven Acceptable Range/ Control Limits/ Targets ¹ for the Commercial Manufacturing Process	Criticality Classification ²	Characterized Range/ Control Limits/ Targets ¹ tested in Process Development Studies	Manufactured Ranges for Clinical Study Lots	Manufactured Ranges from Process Validation	Justification of the Proposed Commercial Acceptable Range ³	Comment ⁴
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As applicable.

²For example, critical process parameter, key process parameter, non-critical process parameter, as described in module 3.

³This could be a brief verbal description and/or links to the appropriate section of the eCTD.

⁴Optional.

Please note that the requested summary information will not substitute requirements for detailed information and adequate data from process characterization and process validation studies in sections 3.2.S.2.5, 3.2.S.2.6, 3.2.P.2 and 3.2.P.3.5 to support the commercial manufacturing process.

Discussion: No discussion occurred.

- f. To facilitate the Agency's review of the control strategy for REGN5458 provide information for quality attributes and process- and product-related impurities for the DS and the DP in the following tabular format. The tables should summarize information from module 3 and may be submitted either to module 3.2.R or module 1.

Quality Attributes and Process and Product Related Impurities for DS and DP	Criticality Classification ¹	Impact ²	Source ³	Analytical Method(s) ⁴	Proposed Control Strategy ⁵	Justification of the Proposed Control Strategy ⁶	Comment ⁷
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For example, critical quality attribute or non-critical quality attribute.

²What is the impact of the attribute, e.g. contributes to potency, immunogenicity, safety, efficacy.

³What is the source of the attribute or impurity, e.g. intrinsic to the molecule, fermentation, protein A column.

⁴List all the methods used to test an attribute in-process, at release, and on stability. For example, if two methods are used to test identity then list both methods for that attribute.

⁵List all the ways the attribute is controlled, for example, in-process testing, validated removal, release testing, stability testing.

⁶This could be a brief verbal description and/or links to the appropriate section of the eCTD.

⁷Optional.

Discussion: No discussion occurred.

- g. To facilitate the Agency's assessment of the adequacy of the proposed commercial release specifications of REGN5458 DS and DP, provide information for each release specification in the tabular format provided below. Please provide a separate table for REGN5458 DS and DP, as described below. Each release specification should be described in a separate row. Add additional rows for additional release specifications, as needed. In general, include footnotes for each column of grouped results to indicate which lot numbers were used for each calculation of minimum-maximum range, and provide the number of batches or lots used (n=?) in the table as well.

Release Specification for REGN5458 Drug Substance							
Attribute	Analytical method	Proposed commercial release acceptance criteria	Release results for non-GMP DS batches ¹ (n=?) (min-max)	Release results for non-PPQ GMP clinical DS batches using the clinical manufacturing process ² (n=?) (min-max)	Release results for non-PPQ GMP clinical DS batches using to-be-marketed manufacturing process ³ (n=?) (min-max)	Release results for DS PPQ batches ⁴ (n=?) (min-max)	Justification of specification (e.g. clinical experience, manufacturing capability, etc.)
¹ List all non-GMP DS batches included in the range calculation. ² List all non-PPQ GMP clinical DS batches using the clinical process included in the range calculation. ³ List all non-PPQ GMP clinical DS batches using the to-be-marketed process included in the range calculation. ⁴ List all PPQ DS batches included in the range calculation.							

Release Specification for REGN5458 Drug Product							
Attribute	Analytical method	Proposed commercial release acceptance criteria	Release results for non-clinical and developmental DP lots ¹ (n=?) (min-max)	Release results for non-PPQ clinical DP lots using clinical formulation ² (n=?) (min-max)	Release results for non-PPQ clinical DP lots using to-be-marketed formulation ³ (n=?) (min-max)	Release results for DP PPQ lots ⁴ (n=?) (min-max)	Justification of specification (e.g. clinical experience, manufacturing capability, etc.)
¹ List all non-clinical and developmental DP lots included in the range calculation. ² List all non-PPQ clinical DP lots using clinical formulation included in the range calculation. ³ List all non-PPQ clinical DP lots using to-be-marketed formulation included in the range calculation. ⁴ List all PPQ DP lots included in the range calculation.							

Discussion: No discussion occurred.

- h. If you will be submitting protocols to qualify a new reference standard (RS), to facilitate the Agency's review, provide justifications for each of your proposed acceptance criteria used for the qualification of the new RS with

relation to how each is sufficient to maintain the function that the RS provides in each assay as well as to prevent product drift

The information may be provided in a table to include:

Method	Purpose of the method ¹	Reference Standard/Material Use ²	Proposed Control Strategy	Justification of the Proposed Control Strategy ³

¹ e.g. purity, identity, charge heterogeneity, potency, glycan profile, etc.

²What is the use in the assay, including how its run (e.g. run in beginning and end of a chromatography and required to be comparable to a representative profile, or conform to some %RSD for specific peaks) and the criteria required within the assay (e.g. shape of a dose response 4PL fit, and r^2 value, slope, EC50 range).

³ how the RS acceptance criteria proposed will meet the need of each assay based on the manner in which the RS is used.

Discussion: No discussion occurred.

- i. The BLA submission should include a copy of the protocols/SOPs used for DS and DP release assays, in addition to the method summary that is included in section 3.2.S.4.2. These protocols are needed in order to appropriately assess the assay validation reports and reference standard qualification protocols. The protocols may be submitted in sections 3.2.R or in the analytical procedures sections 3.2.S.4.2 and 3.2.P.5.2, as relevant for the assay.

Discussion: No discussion occurred.

2. The proposed Table of Contents contains the Other Pharmacokinetic Studies in M4.2.2.27. This should be placed in M4.2.2.7.
3. Also, ensure that any files associated with 3.2.P.2 Pharmaceutical Development are placed under M3.2.P.2 and not placed in any sub folder (M3.2.P.2 should not contain any sub folders)
4. Regarding submission of the datasets.
 - a. The analysis datasets should be sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation.
 - b. Include 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. Note: please provide detailed comments for the SAS programs.

c. Include 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. Note: please provide detailed comments for the SAS programs.

d. Include 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 SAP should also be included.

Additional Clinical Comments:

1. Include efficacy results based on refractory status of patients to prior therapies in the CSR and include flags in the datasets to indicate this information.
2. Include a dataset that includes the following information for all responders:

Subject	Disease assessment at screening*	Disease assessment at baseline (prior to treatment)*	Adjudicated best response*	Disease assessment at progression*	Study day of progression
0001					
...					

* Include results of serum and urine protein electrophoresis, immunofixation, free light chain analysis, imaging, bone marrow aspirate and biopsy.

3. The case narratives should be generated or reviewed/edited by trained personnel with medical knowledge and should include the following information: study day of onset (not calendar date), day from last dose of study drug, basic demographic information (age, sex, underlying diagnosis), predisposing risk factors/comorbidities, description of the event including signs, symptoms and relevant laboratory values/diagnostic tests leading to diagnosis, treatment for the event, information related to study drug action (interrupted, modified, discontinued, etc.), duration of the event, event outcomes, re-challenge/de-challenge information (if available), and investigator and sponsor assessment regarding the causality of the event to either the investigational drug or an alternative etiology.
4. To enhance retrieval of narratives, your submission should include a hyperlinked table tracking subject narratives by category, like the example below:

Subject	DLT	Death	SAE	Discontinuation	CRS	Neurotoxicity	...
0001	Y		Y	Y			
0002		Y			Y		
...							

5. Additional narratives may be requested during the review process if needed.
6. For assessment of neurologic adverse events, we recommend grouping of related preferred terms. Use a broad grouping of terms, which may include terms that map outside of the Nervous System and Psychiatric Disorder System Organ Classes. (e.g., gait disturbance under General Disorders, muscle rigidity under Musculoskeletal Disorders, etc.). We have provided an example below; however, it is expected that the list would include different/additional terms based on the adverse events collected in Study 1826.
 - Encephalopathy: agitation, apathy, aphasia, confusional state, delirium, depressed level of consciousness, disorientation, dyscalculia, hallucination, lethargy, memory impairment, mental status changes, somnolence.
 - Motor dysfunction: cogwheel rigidity, dysgraphia, dysphonia, gait disturbance, hypokinesia, muscle rigidity, muscle spasms, muscular weakness, peroneal nerve palsy, psychomotor hyperactivity, tremor, VIth nerve paralysis.
 - Sensory neuropathy: dysesthesia, hypoesthesia, hypoesthesia oral, neuralgia, paresthesia, paresthesia oral, peripheral sensory neuropathy, sciatica, vestibular neuronitis.
7. Include Yes/No flags for cytokine release syndrome (CRS) and neurotoxicity (NT) in the ADAE and ADSL datasets. The CRS and NT Yes/No flags should be a subject level flag and not an adverse event (AE) level flag.
8. Submit separate datasets for CRS and neurotoxicity. The dataset(s) should incorporate the following:

CRS Dataset

- Each row assigned to a unique subject with CRS diagnosis.
- Key elements of CRS: fever, hypotension, hypoxia.
- CRS treatment: oxygen, vasopressors, tocilizumab, corticosteroids, ventilator support, ICU stay, other interventions (e.g., other IL-6 inhibitors), if used.
- Details of treatment: For example, number of vasopressors and type of oxygen delivery (e.g., low-flow nasal cannula, facemask, etc.), need to be captured to grade CRS accurately by the proposed ASTCT (American Society for Transplantation and Cellular Therapy) grading criteria. Other treatment details should also be provided – for example, dose of steroids and start/stop dates for each intervention.
- Date and day of study treatment and start and end dates and study days for CRS to capture timing of CRS onset and duration.
- Maximum CRS grade based on ASTCT consensus grading system
- Organ dysfunction (SOC and PT) grade based on CTCAE seen in association with CRS.

- CRS grading by Lee criteria to enable comparison of toxicity profile across products.
- Flag for subjects in CRS dataset that develop neurotoxicity concurrently with CRS, with maximum grade.

Neurotoxicity Dataset

- Each row assigned to a unique subject.
 - NT timing in relation to study treatment and in relation to CRS (e.g. preceding CRS, occurring concurrently with CRS, following CRS, or an isolated event).
 - Date and day of study treatment and start and end dates and study days for NT to capture timing of NT onset and duration.
 - Therapeutic intervention with details/outcome.
 - Outcome: e.g., resolution, worsening, unchanged but ongoing.
 - Maximum grade of ICANS (immune effector cell-associated neurotoxicity syndrome) based on ASTCT consensus grading system
 - NT symptoms/signs not included under ICANS, such as tremor and dysarthria should be graded with CTCAE.
 - Both Neurologic and Psychiatric SOC adverse events should be captured in the NT dataset
9. To support the BLA submission for REGN5458 and inform the use of tocilizumab (TCZ) for the mitigation of CRS, we recommend that your submission includes the following information:
- a. To facilitate analysis of the use of TCZ in the treatment of CRS in patients treated with REGN5458, include a detailed summary of the reason(s) TCZ was indicated and administered (i.e., persistent hypotension, etc.) for the corresponding CRS grade.
 - b. 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.
 - c. Include a summary of the initial CRS grading and management instructions and each modification over the life of the study, and serial changes in CRS grading and management instructions in the Investigator's Brochure.
 - d. Include a summary of the initial ICANS grading and management instructions and each modification over the life of study, and serial changes in ICANS grading and management instructions in the Investigator's Brochure.

10. Regarding the use of TCZ in patients with CRS, provide the following in tabular summary format based both on events of CRS and based on maximum severity in patients:
 - a. Time to first dose of TCZ in relation to onset of CRS by Grade.
 - b. Time from TCZ dose to resolution of CRS by Grade.
 - c. List of CRS events by Grade that lasted longer than 5 days in patients that received TCZ compared to those who did not.
 - d. Time to next REGN5458 dose in patients who developed CRS and received TCZ compared to those patients who did not.
 - e. Duration of CRS in those patients who received TCZ compared to those who did not.
 - f. Rate of dose interruption or dose skips for CRS in patients who received TCZ compared to those patients who did not.
 - g. Rate of patients who received steroids concurrently with TCZ and time to resolution of CRS.
 - h. Rate of patients who received steroids after failure of TCZ and time to resolution of CRS.
 - i. Rate of patients who received steroids only for treatment of CRS and time to resolution of CRS.
 - j. The definition of CRS resolution.
11. Include the following information regarding requirements for hospitalization for REGN5458 in your BLA submission:
 - a. Details regarding requirements for hospitalization specified in the protocol with respect to priming dosing, treatment dosing, and for patients after specified events of cytokine release syndrome (CRS), neurotoxicity (NT), and infusion-related reactions (IRRs).
 - b. Include a summary of the initial hospitalization requirements and each modification over the life of study, and serial changes in hospitalization requirements in the Investigator's Brochure.
 - c. Provide details in table format regarding the timing and duration of hospitalization for REGN5458 administration for patients treated at the RP2D by dose (i.e., priming dose 1, priming dose 2, initial treatment dose, and any subsequent doses) and after occurrence of specified events of CRS, NT, and IRRs.

Clinical Pharmacology Additional Comments

1. 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.
2. Address the following questions in the Summary of Clinical Pharmacology:

- a. What is the basis for selecting the doses and dosing regimen used in the registration trials to support your marketing application? Identify individuals who required dose modifications and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.
 - b. What are the exposure-response relationships for efficacy, safety and biomarkers?
 - c. How do extrinsic (e.g., other drugs) and intrinsic factors (such as sex, race, body weight, organ dysfunctions, and disease) influence the exposure, efficacy, or safety of your drug? What dose modifications are recommended?
 - d. What is the impact of immunogenicity on exposure, efficacy and safety?
3. Apply the following advice in preparing the clinical pharmacology sections of the original submission:
 - a. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials. If multiple bioanalytical methods or multiple sites were using a method were used for study sample analyses, submit cross-validation data.
 - b. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean $\pm$ standard deviation) and median with range as appropriate.
 - c. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The patients' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
 - i. 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 patients that have been excluded from the analysis should be flagged and maintained in the datasets.
 - ii. Identify individual patients with dosage modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dosage modifications in the datasets.
4. Submit the following for the population pharmacokinetic analysis reports:
 - a. Standard model diagnostic plots
 - b. Individual plots for a representative number of patients. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
 - c. Model parameter names and units in tables.
 - d. Summary of the report describing the clinical application of modeling results. Refer to the pharmacometric data and models submission guidelines.
5. Submit the following information and data to support the population pharmacokinetic analysis:
 - a. SAS transport files (*.xpt) for all datasets used for model development and validation

- b. A description of each data item provided in a Define.pdf file. Any concentrations or patients that have been excluded from the analysis should be flagged and maintained in the datasets
- c. 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 safety) relationships in the targeted patient population.
7. Refer to Guidance for Industry for population PK, exposure-response relationships, and pharmacometric data and models submission guidelines. Use the laboratory analysis dataset (adlb.xpt) for the laboratory-based adverse

ADDITIONAL CMC COMMENTS

1. Regarding the comparability data to be submitted in section 3.2.P.2.3 (Appendix 3) and the information previously provided in your email of 30 June, 2023 in response to the CMC type C WRO comments of 15 May 2023, the newly proposed condition of 45 °C to be included in the comparability study appears to be more appropriate than the originally proposed conditions to assess drug product comparability. Regarding Regeneron's proposal to submit the 0, 1, and 2 months stability data at 25 °C with the initial BLA submission and update the BLA with the 3 and 6 months data and comparability analysis during the BLA review, as the initial data timepoints up to 3 months at 25 °C have already been shown to not detect changes in product quality, the 6 months datapoints submitted late in the review cycle may delay CMC assessment and conclusions regarding the comparability of the DP manufactured by the (b) (4) commercial process and the DP manufactured by the (b) (4) clinical process, data from the 6 months timepoint will be needed for a final assessment and conclusion on comparability and therefore we agree that they should be submitted during the BLA review and as soon as they become available.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

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

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

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

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that 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 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

² <https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>

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

Information⁴ and Pregnancy and Lactation Labeling Final Rule⁵ 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*.

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

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>

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 specific manufacturing responsibilities for each facility.

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

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 356h⁶ 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>

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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:

- RTOR⁹: In general, the data submission should be fully CDISC-compliant to

⁸ <https://www.fda.gov/media/85061/download>

⁹ <https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program>

facilitate efficient review.

- Assessment Aid¹⁰

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.

RACE AND ETHNICITY DIVERSITY PLANS

Refer to FDA Draft Guidance "*Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials- Guidance for Industry*" at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/diversity-plans-improve-enrollment-participants-underrepresented-racial-and-ethnic-populations>, for recommendations on the approach to develop and submit a Race and Ethnicity Diversity Plan to enroll representative numbers of participants from underrepresented racial and ethnic populations in the United States, in clinical trials during the development of your product. The Diversity Plan should be developed and discussed with FDA early in clinical development, preferably before initiation of any trials intended to support registration.

¹⁰ <https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project>

Although this draft Guidance specifically focusses on race and ethnicity Diversity Plans for the enrollment of members of racial and ethnic populations that have historically been underrepresented in clinical trials, FDA encourages sponsors to consider expanding the Diversity Plan to also account for other underrepresented populations (e.g., based on other demographic characteristics such as sex, age, gender, etc.).

Submit the Diversity Plan under eCTD Module 1.6 if included in meeting background package, otherwise submit under Module 2.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues require further discussion.

5.0 ACTION ITEMS

No action items.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor sent the attached response documents to the Agency's Meeting Preliminary Comments via email on October 16 and 17, 2023.

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/

BINDU N KANAPURU
11/06/2023 01:39:43 PM



IND 138791

MEETING MINUTES

Regeneron Pharmaceuticals, Inc.
Attention: Hui Wang, PhD
Associate Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

Dear Dr. Wang:¹

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for REGN5458.

We also refer to the teleconference between representatives of your firm and the FDA on August 23, 2022. The purpose of the meeting was to discuss the proposed design of phase 3 study R5458-ONC-2245 to support a regular approval and label expansion of REGN5458 in patients with multiple myeloma (MM) who have received an immunomodulatory agent and a proteasome inhibitor (PI).

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 Laura Wall, Senior Regulatory Project Manager at 301-796-2237.

Sincerely,

{See appended electronic signature page}

Bindu Kanapuru, MD
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-Phase 3

Meeting Date and Time: August 23, 2022 from 2:00 PM (ET) to 3:00 PM (ET)
Meeting Location: Teleconference

Application Number: IND 138791
Product Name: REGN5458
Indication: Proposed for the treatment of patients with multiple myeloma (MM) who have received an immunomodulatory agent and a proteasome inhibitor (PI)

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

Meeting Chair: Bindu Kanapuru, MD, Clinical Team Leader
Meeting Recorder: Laura Wall, MS, BSN, APHN-BC

FDA ATTENDEES

Office of Oncologic Diseases (OOD)/Division of Hematologic Malignancies II

Nicole Gormley, MD, Director
Bindu Kanapuru, MD, Clinical Team Leader
Andrea Baines, MD, Clinical Reviewer
Patrick DeMoss, MD, Clinical Reviewer

Office of Regulatory Operations/Division of Regulatory Operations for Oncologic Diseases

Theresa Carioti, MPH, Chief Project Management Staff
Laura Wall, MS, BSN, APHN-BC, Senior Regulatory Health Project Manager

OB/Division of Biometrics IX

Xing Xu, PhD, Biometrics Team Leader
Mingyu Xi, PhD, Biometrics Reviewer

Office of Clinical Pharmacology, Division of Cancer Pharmacology I

Olanrewaju Okusanya, PharmD, Deputy Director
Xiling Jiang, PhD, Clinical Pharmacology Team Leader
Justin Collazo, PharmD, MS, Clinical Pharmacology Reviewer

SPONSOR ATTENDEES

Ned Braunstein, MD, PhD, Executive Vice President, Regulatory Affairs & Global Patient Safety
Anand Achanta, PhD, Vice President, Regulatory Affairs
Joanna Pols, PhD, Executive Director, Regulatory Affairs
Hui Wang, PhD, Associate Director, Regulatory Affairs
Andres Sirulnik, MD, PhD, Senior Vice President, Translational & Clinical Sciences, Hematology
Karen Rodriguez Lorenc, MD, Vice President, Global Program Head
Glenn Kroog, MD, Executive Director, Clinical Sciences Oncology
Yariv Houvras, MD, PhD, Director, Clinical Sciences Oncology
Thomas DiCioccio, PhD, Vice President, Pharmacometrics
Jenn Visich, PhD, Senior Director, Clinical Pharmacology
Sameer Upadhyay, MD, Executive Director, Global Patient Safety
Martha Makaratzi, Director, Global Patient Safety
Jing-ou Liu, PhD, Executive Director, Biostatistics
Jyotirmoy Dey, PhD, Senior Director, Biostatistics
Pourab Roy, PhD, Manager, Biostatistics
James Harnett, PhD, Executive Director, Health Economics & Outcomes Research
Lei Chi, PhD Director, Health Economics & Outcomes Research

1.0 BACKGROUND

The purpose of the Pre-Phase 3 meeting is to discuss the proposed design of the phase 3 study R5458-ONC-2245 and selection of the recommended phase 2 dose (RP2D) of REGN5458 based on data from the ongoing phase 1/2 study R5458-ONC-1826, and the proposed strategy for an accelerated approval of REGN5458 monotherapy in patients with multiple myeloma who have received an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody, based on data from the ongoing phase 1/2 study R5458-ONC-1826.

2.0 DISCUSSION

2.1. Clinical Question for Dose Selection

Question 1: *Given the totality of the available safety, efficacy, drug and total ligand exposure data over the range of doses tested in the phase 1/2 study 1826, does the Agency agree with the Sponsor's choice of the registrational dose of 200 mg REGN5458 (following a step-up dose of 5 and 25 mg) administered as an intravenous (IV) infusion?*

FDA Response to Question 1:

No, we have the following comments.

Registrational Dose

You have not provided adequate data to support the proposed registrational dose of 200 mg REGN5458.

- You should evaluate the PK, PD, efficacy and safety of the REGN5458 5/25/200 mg dosing regimen in at least 20 patients with at least 3 months of follow up in Study 1826 and submit this data to the Agency.
- You should provide detailed information regarding the incidence of ICANS and updated CRS data in patients who received 5/25/50 mg, 5/25/200 mg, 5/25/400 mg and 5/25/800 mg dosing regimens in Study 1826 and the two cases of Grade 4 CRS in patients who received the 5/25/50 mg or 5/25/200 mg step-up dosing regimen in as reported in Table 14.3.2.5.4 in the meeting background materials.
- You should pool and evaluate all available PK, PD, efficacy, safety, and tolerability data from all dose levels and conduct integrated analyses including dose-response and exposure-response analyses to inform the selection of optimal dosing regimen (i.e., RP2D) of REGN5458.

Refer to the Additional Clinical Pharmacology Comment 1 for the information that you should provide to obtain the Agency's agreement on the proposed REGN5458 RP2D.

Decreased frequency beyond Cycle 6

We have concerns regarding your proposal

(b) (4)

in the proposed phase 3 study R5458-ONC-2245. You should provide information

(b) (4)

Discussion: No discussion occurred.

2.2. Regulatory Question for Accelerated Approval Strategy

Question 2: *Does the Agency agree with the Sponsor's proposed strategy to pursue an accelerated approval of REGN5458 200 mg full dose monotherapy in patients with multiple myeloma who have received an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody, based on the results from Study 1826, depending upon the magnitude and duration of responses?*

FDA Response to Question 2:

No, we do not agree. Refer to the FDA Response to Question 1.

In addition, we reiterate our concerns regarding seeking accelerated approval based on a single arm trial. We have significant concerns regarding your proposal to seek registration for REGN5458 based on the results of Study 1826, a single arm trial, given the challenges with interpretation of data from a single arm trial. The baseline expected response rate and adverse event rates can be difficult to ascertain in a single arm trial. To meet criteria for accelerated approval, in addition to treating a serious or life-threatening illness, the therapy must provide meaningful therapeutic clinical benefit to patients in the context of available therapies in the proposed patient population based on an intermediate endpoint. We note that there are currently approved therapies for the population of patients with multiple myeloma (MM) who have received a PI, an immunomodulatory agent and an anti-CD38 mAb. Additionally, available therapies are determined at the time of regulatory action and the definition of available therapy may change over time given the evolving treatment landscape for MM.

We also have concerns with the limited duration of follow-up proposed. For MM, to allow for an adequate assessment of durability of response and safety, the results would need to be based on at least 9-12 months of follow-up from the time of response.

In addition, for therapies requesting accelerated approval under 21 CFR §314 Subpart H, postmarketing studies should usually already be well underway. However, we note that you do not have an agreed upon trial ongoing to confirm clinical benefit of REGN5458.

We continue to recommend you consider a randomized trial to support the initial registration of REGN5458.

Discussion: The Agency reiterated their comments and concerns about the Sponsor's proposed approach to seek initial accelerated approval of their product based on a phase 2 single arm trial. The Agency reiterated that the confirmatory trial should be well underway at the time the Sponsor requests accelerated approval.

2.3. Clinical Questions for the Proposed Phase 3 Study 2245

Question 3: *Does the Agency agree with the proposed patient population and the inclusion/exclusion criteria for Study 2245?*

FDA Response to Question 3:

Refer to the FDA Response to Question 1.

We have the following comments for future consideration:

- The proposed population of patients who have received at least (b) (4) prior therapies including a PI and lenalidomide and 1 to 4 prior lines of therapy for Study 2245 may be reasonable.
- We note that your proposed criteria for measurable disease are not consistent with the IMWG consensus definition. You should use criteria that are consistent with the consensus definition of measurable disease, especially considering that you propose to include an early line patient population.
- The final indication will reflect the patient population enrolled on the study, considering the number of patients receiving specific lines of therapy prior to study entry, as well as efficacy results within the subgroups based on prior therapies.

Additional comments may be provided upon review of the full protocol.

Discussion: The Sponsor requested clarification regarding which aspect of the proposed criteria for measurable disease in the Study 2245 synopsis was not consistent with the IMWG consensus definition. The Agency noted (b) (4)

The Sponsor stated that they would discuss further internally and address this in the revised protocol. The Agency stated that the Sponsor should either revise the protocol to use the standard threshold or include justification for use of the lower threshold in the protocol.

Question 4: Does the Agency agree with the proposed control arm of Study 2245?

FDA Response to Question 4:

The selection of a control arm is at your discretion; however, the use of a triplet-drug comparator arm appears reasonable.

Discussion: No discussion occurred.

Question 5: Does the Agency agree with the proposed primary endpoint (PFS) and key secondary endpoints for Study 2245?

FDA Response to Question 5:

Refer to the FDA Response to Question 1.

We have the following comments for future consideration:

- a) In general, PFS has been used as an endpoint to support regular approval for MM. However, a statistically significant result of PFS alone may not be sufficient to support approval. FDA interprets PFS results in the context of the observed magnitude of effect, safety, and overall benefit-risk. The proposed phase 3 study should be designed with additional opportunities to evaluate patient safety. There

should be a high likelihood that when the study is completed it can demonstrate an acceptable benefit-risk profile, which includes an evaluation of the impact on overall survival (OS) as both a safety and efficacy metric.

The protocol and SAP should address the following:

- Specify the hierarchical testing order and plan for multiplicity adjustment for the proposed key secondary endpoints and provide power calculations and estimated data maturity at both interim and final analysis of PFS for the key secondary endpoints in the protocol.
 - Provide a detailed OS analysis plan. The final analysis timing for OS should be event-driven and not based on calendar time. Include a table summarizing the information that will be available at different event-driven analysis timepoints for OS, including but not limited to, the target number of OS events, estimated information fraction, futility/safety boundaries (all interim and final analyses). Provide justification for the proposed values.
 - Prospectively detail the primary censoring rule for PFS and corresponding sensitivity/supplementary analyses. Refer to the Guidance for Industry <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trial-endpoints-approval-non-small-cell-lung-cancer-drugsand-biologics> for additional details.
- b) Regarding the proposed key secondary endpoint of MRD-negativity rate, the protocol should include details regarding the proposed analysis of MRD-negativity, including details of the assay that will be used to assess MRD.

We also refer you to the following FDA Guidance for further information regarding assessment of MRD in clinical trials: “*Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment*,” available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/hematologic-malignancies-regulatory-considerations-use-minimal-residual-disease-development-drug-and-biologics>.

Discussion: No discussion occurred.

Question 6: Does the Agency agree with the proposed (b) (4) in Study 2245?

FDA Response to Question 6:

The selection of (b) (4) is at your discretion; however, given your study does not include (b) (4) you should provide further justification for this. In addition, you should provide justification for use of a (b) (4)

(b) (4)

Discussion: The Sponsor provided justification for the proposed (b) (4)
(b) (4) The Agency stated that if the Sponsor chooses (b) (4)
(b) (4) should be included in
the protocol and SAP to assess the internal consistency of the results. The
Agency indicated that (b) (4)
(b) (4)
(b) (4) should be conducted to assess the robustness of the efficacy
results.

Question 7: Does the Agency agree (b) (4)
(b) (4)
(b) (4)

FDA Response to Question 7:

No. (b) (4)
(b) (4)
(b) (4)

(b) (4)

Discussion: No discussion occurred.

2.4. Statistical Question for the Proposed Phase 3 Study 2245

Question 8: Does the Agency agree with the statistical considerations and interim analysis plan for the design of the proposed open-label phase 3 Study 2245?

FDA Response to Question 8:

No, we do not agree. We have the following comments:

- a) We have concerns with your proposal (b) (4)
(b) (4)
(b) (4)
(b) (4)

(b) (4)

- b) Your sample size calculation was based on (b) (4)
- c) We are unable to verify the number of events needed for the sample size calculation based on the parameters you provided. Provide details of your sample size calculation, including the program or version of the software and a screenshot of the calculation, if applicable. The calculation should also account for the planned interim analyses.
- d) Provide detailed censoring rules for the PFS and OS analyses. Refer to FDA guidance on general rules on censoring and sensitivity analyses:
<https://www.fda.gov/downloads/drugs/guidances/ucm259421.pdf>

The Agency will provide additional comments when the full protocol with updated information is submitted for review.

See also response to Question 1.

Discussion: No discussion occurred.

2.5. Regulatory Question for the Proposed Phase 3 Study 2245

Question 9: Does the Agency agree that the open-label phase 3 Study 2245 as designed is adequate to support a regular approval of REGN5458 for the proposed draft indication (b) (4)

FDA Response to Question 9:

No, it is premature to comment on the adequacy of the proposed phase 3 Study 2245 to serve as the confirmatory trial for REGN5458. Refer to the FDA responses to Questions 1, 2, 5, and 8.

Discussion: No discussion occurred.

Additional Comments

Clinical

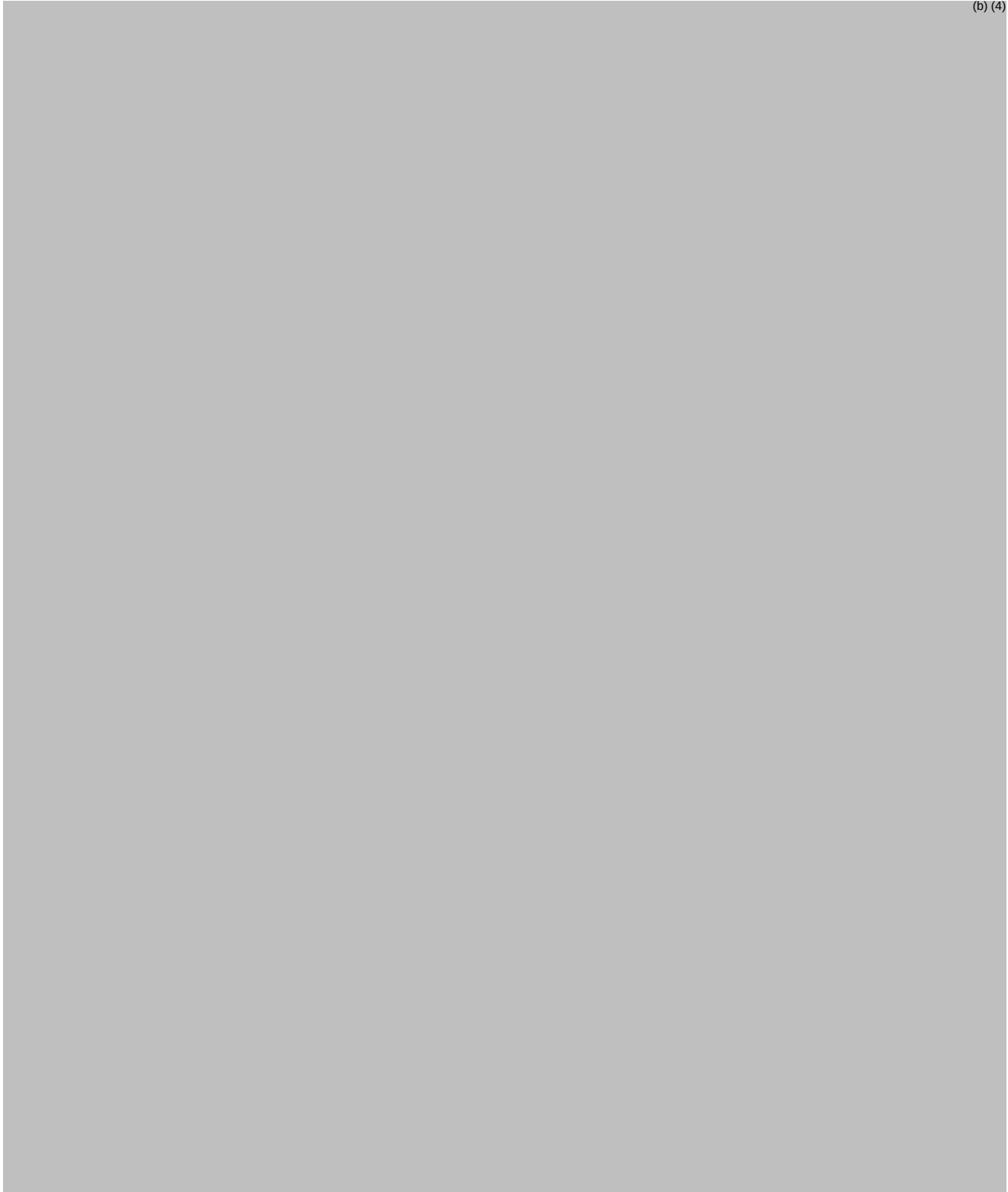
The following comments pertain to the proposed phase 3 Study 2245:

(b) (4)



Clinical Pharmacology

(b) (4)



3.0 OTHER IMPORTANT MEETING 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

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

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](https://www.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

² <https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>

the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

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

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.⁴

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*, as well as email access to the eData Team (cdereadata@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 page⁵ 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 versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the

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

⁴ <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>

⁵ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

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. 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 (Section 7.3 eCTD Sample Submission pg. 44) 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. 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.⁶

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled

⁶ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

Study Data Standards Resources⁷ and the CDER/CBER Position on Use of SI Units for Lab Tests website.

PATIENT-FOCUSED ENDPOINTS

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

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

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

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

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

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

⁷ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

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:

- RTOR⁸: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid⁹

RACE AND ETHNICITY DIVERSITY PLANS

Refer to FDA Draft Guidance “*Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials- Guidance for Industry*” at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/diversity-plans-improve-enrollment-participants-underrepresented-racial-and-ethnic-populations>, for recommendations on the approach to develop and submit a Race and Ethnicity Diversity Plan to enroll representative numbers of participants from underrepresented racial and ethnic populations in the United States, in clinical trials during the development of your product. The Diversity Plan should be developed and discussed with FDA early in clinical development, preferably before initiation of any trials intended to support registration.

⁸ <https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program>

⁹ <https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project>

Although this draft Guidance specifically focuses on race and ethnicity Diversity Plans for the enrollment of members of racial and ethnic populations that have historically been underrepresented in clinical trials, FDA encourages sponsors to consider expanding the Diversity Plan to also account for other underrepresented populations (e.g., based on other demographic characteristics such as sex, age, gender, etc.).

Submit the Diversity Plan under eCTD Module 1.6 if included in meeting background package, otherwise submit under Module 2.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

5.0 ACTION ITEMS

No action items.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor submitted the attached response document to the Agency's Meeting Preliminary Comments via email dated August 19, 2022.

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/

BINDU N KANAPURU
08/31/2022 09:47:53 AM