CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761345Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 133940

MEETING MINUTES

Pfizer, Inc.
Attention: Robert Schaum, PhD
Director, Global Regulatory Affairs
445 Eastern Point Road
Groton, CT 06340

Dear Dr. Schaum:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PF-06863135 (elranatamab).

We also refer to the video conference between representatives of your firm and the FDA on December 16, 2022. The purpose of the meeting was to discuss the adequacy of the C1071003 safety and efficacy data to support a Biologics License Application (BLA) submission.

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 Natasha Kormanik, Senior Regulatory Project Manager, at (240) 402-4227.

Sincerely,

{See appended electronic signature page}

Bindu Kanapuru, MD
Acting Deputy Division Director
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:	December 16, 2022, at 9:00 AM (ET)
Meeting Location:	Video Conference
Application Number:	IND 133940
Product Name:	PF-06863135 (elranatamab)
Indication:	Treatment of adult patients with relapsed or refractory multiple myeloma who have received at least (b) (4) prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody
Sponsor Name:	Pfizer, Inc.
Regulatory Pathway:	351(a) of the Public Health Service Act
Meeting Chair:	Bindu Kanapuru, MD
Meeting Recorder:	Natasha Kormanik, MSN, CRNP, OCN

FDA ATTENDEES

Office of Oncologic Diseases (OOD)
Dianne Spillman, BS – Associate Director, Global Regulatory Outreach
Tina Macaulay - Regulatory Information Specialist
Lauren Hotaki, PharmD – Senior Regulatory Health Project Manager
Yinghua Wang, PharmD, MPH – Senior Regulatory Health Project Manager

OOD/ Division of Hematologic Malignancies II
Nicole Gormley, MD – Division Director
Bindu Kanapuru, MD – Acting Division Deputy Director, Clinical Team Leader
Andrea Baines, MD, PhD – Clinical Reviewer
Rachel Ershler, MD, MHS – Clinical Reviewer
Monica Schmitt, MSN, CRNP – Clinical Reviewer
Patrick DeMoss, MD – Clinical Reviewer

Office of Biostatistics/ Division of Biometrics IX
Qing Xu, PhD – Team Leader
Jing Zhang, PhD – Reviewer
Jay Zhao, PhD – Reviewer

Office of Clinical Pharmacology (OCP)/ Division of Cancer Pharmacology I
Olanrewaju Okusanya, PharmD, MS – Acting Deputy Division Director
Nan Zheng, PhD – Team Leader
Ankit Shah, PhD, DABT – Reviewer
Lili Pan, PhD - Reviewer

Office of Pharmaceutical Quality (OPQ)/Office of Biotechnology Products
Frances Namuswe, PhD – Team Leader

Office of Oncologic Diseases (OOD)/Division of Hematology, Oncology, Toxicology
Haleh Saber, PhD, MS – Deputy Director
Brenda Gehrke, PhD – Team Leader
Daniela Torres, PhD – Reviewer

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

SPONSOR ATTENDEES

Pfizer, Inc.
Nathalie Bouxin, PhD – Medicine Team Lead
Akos Czibere, MD, PhD – Vice President Multiple Myeloma Clinical Group Leader
Andrea Viqueira, MD – Global Clinical Lead (C1071003)
Anne Hickman, DVM, PhD – Safety Risk Lead
Jane White, ScD – Statistics Group Lead for Hematologic Malignancies
Mohamed Elmeliegy, PhD – Global Clinical Pharmacology Lead
Diane Wang, PhD – Clinical Pharmacology Unit Head
Caroline Henesey, PhD – Global Regulatory Portfolio Lead, Heme Malignancies
Robert Schaum, PhD – Global Regulatory Lead (C1071003)
Eric Leip, PhD – Statistics Lead
Kimberly Kaighn, MBA, PMP – Project Management Lead
Linda Gustavson, PhD – Vice President Regulatory Affairs Oncology
Greg Finn, PhD – Global Clinical Lead (C1071005)
Elizabeth VanAlphen, MS – Global Regulatory Lead (C1071005)

1.0 BACKGROUND

PF-06863135 (elranatamab) is a heterodimeric humanized full-length bispecific IgG2 kappa mAb derived from two mAbs, the anti-BCMA mAb (PF-06863058) and the anti-CD3 mAb (PF-06863059).

The Sponsor requested a type B, pre-BLA meeting to seek Agency feedback and concurrence on the adequacy of the C1071003 safety and efficacy data (including

duration of follow-up) obtained from the October 14, 2022, data cut to support the BLA submission. A pre-BLA content and formatting meeting was held on October 21, 2022.

FDA sent Preliminary Comments to Pfizer, Inc. on December 9, 2022.

2.0 DISCUSSION

Question 1: *Does the Agency agree that the available data support the submission of an initial BLA for elranatamab for the proposed indication for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least* (b) (4) *prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody?*

FDA Response to Question 1: We have concerns with your proposal due to the limited duration of follow-up (median follow-up 9.5 months, range 2.4 to 18.5 months) among responders. We recommend that all patients 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. In single arm trials, 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.

Interpretation of time-to-event endpoints such as PFS is challenging in single-arm trials because it is unclear to what extent the outcomes can be attributed to the treatment effect vs. the underlying disease and patient characteristics. Results from time-to-event endpoints are considered as exploratory and would not support an efficacy claim.

- We reiterate that the confirmatory trial should be well-underway at the time of BLA submission and note that agreement has not yet been reached regarding the proposed dosing of elranatamab + daratumumab in the proposed phase 3 confirmatory trial.

- We also reiterate our concerns, as previously stated in the January 14, 2022, and October 21, 2022, Type C Meetings, regarding the limitations of use of a single arm trial to support accelerated approval.

DISCUSSION: The Sponsor provided additional safety data from 30 patients in Arm B of Study C1071005 Part 2 with a longer follow up and exposure data to justify the RP3D of elranatamab and daratumumab (see attached document). The Agency noted the high rate of dose interruptions (70%) of both products, the limitations of the exposure data and reiterated their concerns with the overlapping toxicity with the elranatamab and daratumumab combination. The Agency recommended that the Sponsor consider evaluation of a lower elranatamab dose level or alternate schedules (e.g., 44 mg QW, 76 mg Q2W) in

combination with daratumumab in a randomized dose finding study in a sufficient number of patients with at least 3-months of follow-up to support the dosage regimen(s) for elranatamab in combination with daratumumab in the phase 3 part of Study C1071005.

The Agency stated that it is acceptable to proceed with US enrollment in the Phase 3 trial as designed, and reiterated the importance of having adequate representation of the US patient population. The Agency recommended that the Sponsor consider adding a separate cohort to the Phase 3 study to evaluate a lower dosing regimen or alternate schedule.

Question 2: *The Sponsor is currently evaluating* (b) (4) *Does the Agency have any suggestions around subsequent discussions regarding this topic in light of BTD designation?*

FDA Response to Question 2: (b) (4) You may request a meeting for further discussion with the FDA if you have specific questions (b) (4)

DISCUSSION: No discussion occurred.

Question 3: *Does the Agency agree with the proposed timing of submission of the complete application for the initial BLA for elranatamab on 19 Dec 2022, under Rolling Review?*

FDA Response to Question 3: We recommend that the BLA include all available data for FDA to review to allow for an adequate assessment of benefit-risk and recommend that the BLA include data with a longer duration of follow-up than currently proposed. Refer to the FDA response to Question 1.

DISCUSSION: No discussion occurred.

3.0 OTHER IMORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our September 30, 2022, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program"

under PDUFA VII. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[2]

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The content of a complete application was discussed. The final portion of the applicant's rolling BLA submission is expected on December 19, 2022.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan. Sponsor stated their plans to include a REMS in the BLA submission.
- 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

[2] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

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.[3]

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

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.[4]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[5] and Pregnancy and Lactation Labeling Final Rule[6] 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

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

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

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

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

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

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

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

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

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* 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.[7]

ONCOLOGY PILOT PROJECTS

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

- RTOR[8]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- Assessment Aid[9]

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

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

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.

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 issued identified.

5.0 ACTION ITEMS

The Division will provide an update on the status of Project Orbis participation in January 2023.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor's response to the Agency's preliminary comments and the December 6, 2022, safety data document are appended.

18 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

BINDU N KANAPURU
12/16/2022 01:15:49 PM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 133940
Request Receipt Date	August 30, 2022
Product	Elranatamab (PF-06863135)
Indication	For the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least (b) (4) classes of prior therapies, including a proteasome inhibitor (PI), an immunomodulatory agent, and an anti-CD38 monoclonal antibody.
Drug Class/Mechanism of Action	Biologic/Elranatamab is a bispecific B cell maturation antigen (BCMA)-directed CD3 T-cell engager.
Sponsor	Pfizer
ODE/Division	DHMII
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	October 29, 2022

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthrough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes and** will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR)**.** Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

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

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

   Proposed Indication: For the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least (b) (4) classes of prior therapies, including a proteasome inhibitor (PI), an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

   Revised Indication: For the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior lines of therapy, including a proteasome inhibitor (PI), an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

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

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

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

4. **Consideration of Breakthrough Therapy Criteria:**

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

If 4a is checked "No," please provide the rationale in a brief paragraph below, and send the completed BTDDRT to Miranda Raggio for review so that the BTDR can be denied without MPC review. Once reviewed and cleared by Miranda this BTDR will be removed from the MPC calendar and you can skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined
☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

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

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

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

Deny Breakthrough Therapy Designation ☐

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

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

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

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Multiple myeloma (MM) is a hematologic malignancy characterized by clonal expansion of malignant plasma cells in the bone marrow and overproduction of monoclonal immunoglobulins, leading to impaired hematopoiesis and immunity, bone destruction, and kidney injury. MM accounts for 1.8% of all cancers and 2% of all cancer deaths. In 2022, it is estimated that there will be 34, 470 new cases and 12,640 deaths due to MM in the U.S. The median age at diagnosis is 69 (SEER 2015-2019) and the 5-year relative survival is 57.9% (SEER 2012-2018).

Despite the availability of multiple approved therapies for newly diagnosed and relapsed/refractory MM (RRMM), including agents within the three major classes of anti-myeloma therapies – proteasome inhibitors (PIs), immunomodulatory agents (IMiDs), and anti-CD38 monoclonal antibodies (mAb) – and the option of autologous stem cell transplantation (ASCT) for patients who are eligible, MM remains incurable. Prognosis is poor for patients whose MM becomes refractory to available therapies, including patients who are triple-class refractory (i.e., refractory to a PI, an IMiD, and an anti-CD38 mAb).

Elranatamab (PF-06863135) is a bispecific mAb directed against B cell maturation antigen (BCMA) on B cells and cluster of differentiation 3 (CD3) on T cells. Binding of elranatamab to BCMA on MM cells and CD3 on T cells leads to T cell-mediated cytotoxicity directed against MM cells.

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

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

In the phase 2 trial being used to support BTD in patients with RRMM, Study C1071003, the primary efficacy endpoint is the overall response rate (ORR), defined as the rate of partial response (PR) or better by the International Myeloma Working Group (IMWG) response criteria, as assessed by blinded independent central review (BICR). Secondary efficacy endpoints include ORR by investigator, complete response (CR) rate, duration of response (DOR), time to response (TTR), progression-free survival (PFS), overall survival (OS), minimal residual disease (MRD)-negativity, safety, and PK.

The clinical development plan for elranatamab also includes a proposed a phase 3 confirmatory trial, C1071005, which is an ongoing, open-label, 3-arm, multicenter, randomized study to evaluate elranatamab monotherapy. and elranatamab + daratumumab vs daratumumab + pomalidomide + dexamethasone in (DPd) in patients with RRMM who have received at least 1 prior line of therapy, including lenalidomide and a PI, with a primary endpoint of PFS.

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

ORR, supported by DOR data, is an intermediate endpoint that has been used to support accelerated approval for MM. The Division considers PFS an acceptable endpoint for confirmatory trials in patients with MM.

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

MRD-negativity is not a currently accepted endpoint to support approval, but in the future, may be deemed likely to predict clinical benefit in patients with MM.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population.

The following table includes anti-myeloma therapies that are approved for the population of patients who have received at least 4 prior lines of therapy, including a PI, an IMiD and an anti-CD38 mAb. Selinexor + dexamethasone (highlighted in yellow) is the only relevant comparison because belantamab mafodotin remains under accelerated approval and the two CAR T-cell products (idecabtagene vicleucel and ciltacabtagene autoleucel) are not included in the Division's consideration of available therapy due to the requirement for patient-specific manufacturing and the toxicity profile of these products, which preclude many patients with RRMM from being candidates.

Drug(s)	Approval	Indication	Endpoint	Trial Design/Results
Selinexor + dexamethasone	Accelerated (2019)/Regular (2020)	≥4 prior lines, refractory to 2 PIs, 2 IMIDs, and anti-CD38 mAb	ORR	Single arm trial (N=83) ORR 25.4%; mDOR 3.8 months
Belantamab mafodotin	Accelerated (2020)	≥4 prior lines, including PI, IMID, anti-CD38 mAb	ORR	Single arm trial (N=97) ORR 31%; mDOR NR
Idecabtagene vicleucel	Regular (2021)	≥4 prior lines, including PI, IMID, anti-CD38 mAb	ORR, CR	Single arm trial (N=100) ORR 72%, sCR 28%; mDOR 11 months
Ciltacabtagene autoleucel	Regular (2022)	≥4 prior lines, including PI, IMID, anti-CD38 mAb	ORR, CR	Single arm trial (N=97) ORR 97.9%, sCR 78.4%; mDOR 21.8 months

Abbreviations: PI=proteasome inhibitor, IMiD=immunomodulatory agent, mAb=monoclonal antibody, ORR=overall response rate, mDOR=median duration of response, NR=not reached.

The following table includes anti-myeloma therapies that are approved for patients with 3 prior lines of therapy. Many regimens are approved for patients who have had 3 prior lines of therapy, although most of the trials supporting these approvals did not include patients who had received prior anti-CD38 mAb therapy.

Drug(s)	**Approval**	**Indication**	**Endpoint**	**Trial Design/Results**
KRd	Regular (2015)	1-3 prior lines	PFS	Randomized trial: KRd vs. Rd PFS: 26.3 vs. 17.6 months (HR= 0.69)
Kd	Regular (2016)	1-3 prior lines	PFS	Randomized trial: Kd vs. Vd PFS: 18.7 vs. 9.4 months
Pd	Regular (2015)	≥2 prior lines, Len and PI	PFS/OS	Randomized trial: Pd vs. dex PFS: 3.6 vs. 1.8 months (HR=0.45); OS: 12.4 vs. 8.0 months (HR=0.70)
IRd	Regular (2015)	≥1 prior line	PFS	Randomized trial: IRd vs Rd PFS: 20.6 vs. 14.7 months
Dara-IV	Regular (2015)	≥3 prior lines, PI and IMiD	ORR	Single-arm trial ORR: 29%
DRd	Regular (2016)	≥1 prior line	PFS	Randomized trial: DRd vs. Rd PFS: 45 vs. 17.5 months (HR=0.37); ORR: 91.3%
DVd	Regular (2016)	≥1 prior line	PFS	Randomized trial: DVd vs. Vd PFS: NE vs. 7.2 months (HR = 0.39); ORR: 79.3%

DPd	Regular (2017)	≥2 prior lines, Len and PI	ORR	Single-arm trial ORR: 59.2%
ERd	Regular (2015)	1-3 prior lines	PFS	Randomized trial: ERd vs. Rd PFS: 19.4 vs. 14.9 months (HR=0.70)
EPd	Regular (2018)	≥2 prior lines, Len and PI	PFS	Randomized trial: EPd vs. Pd PFS: 10.3 vs. 4.7 months (HR= 0.54)
SVd	Regular (2020)	≥1 prior line	PFS	Randomized trial: SVd vs. Vd PFS: 13.9 vs. 9.5 months (HR=0.70)
DKd	Regular (2020)	1-3 prior lines	PFS	Randomized trial: DKd vs. Kd PFS: NR vs. 15.8 months (HR=0.63)
Dara-SC	Regular (2020)	≥3 prior lines, PI and IMiD	ORR	Non-inferiority trial: SC vs. IV ORR: 41% vs. 37%
Isa-Pd	Regular (2020)	≥2 prior lines, Len and PI	PFS	Randomized trial: Isa-Pd vs. Pd PFS: 11.5 vs. 6.5 months (HR=0.59)
Isa-Kd	Regular (2021)	1-3 prior lines	PFS	Randomized trial: Isa-Kd vs. Kd PFS: NR vs. 20.3 months (HR=0.55)

Abbreviations: K=carfilzomib, R=lenalidomide, d=dexamethasone, P=pomalidomide, I=ixazomib, Dara/D=daratumumab, E=elotuzumab, S=selinexor, Isa=isatuximab. PI=proteasome inhibitor, IMiD=immunomodulatory agent, ORR=overall response rate, PFS=progression-free survival, OS=overall survival, HR=hazard ratio, NR=not reached.

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

Teclistamab is a BCMA-directed CD3 T-cell engager that was granted BTD on May 26, 2021, for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least (b) (4) prior lines of therapy and whose disease is refractory to a proteasome inhibitor (PI), an immunomodulatory agent (IMiD), and an anti-CD38 monoclonal antibody. BLA 761291 for teclistamab is currently under review in DHMII. Talquetamab, a CD3 T-cell engager directed against a different target on MM cells (GPRC5D) was granted BTD on June 24, 2022, for the treatment of adult patients with relapsed or refractory multiple myeloma, who have previously received at least 4 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody.

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

11. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR:

Trial	Study Design	Population	Treatment	Endpoint	Results
C1071003 (MagnetisMM-2)	Phase 2, open-label, multicenter trial	Cohort A (N=123): RRMM, refractory to PI, IMiD, and anti-CD38 mAb, no prior BCMA-directed therapy Cohort B (N=64): RRMM, refractory to PI, IMiD, and anti-CD38 mAb, and received prior BCMA-directed therapy (ADC or CAR T-cell therapy)	Elranatamab 12/32/76 mg IV on C1D1, C1D4, C1D8, followed by 76 mg IV QW; switch to Q2W dosing if achieve ≥PR for 2 months after at least 6 cycles of QW dosing	ORR by BICR	ORR 61% (95% CI 51.8, 69.6) mDOR NR*

*Median follow-up 6.8 months

The request for BTD is based on preliminary results from the ongoing phase 2, open-label, multicenter, trial, Study C1071003.

The data supporting the BTDR comes from 123 patients in Cohort A. In this cohort, the median age was 68 (range 36 to 89), patients received a median of 5 prior lines of therapy (range 2 to 22), 96% of patients had 3 or more prior lines, 79% had 4 or more prior lines, 100% were triple-class exposed (prior PI, IMiD, and anti-CD38 mAb), 97% were triple-class refractory, and 42% were “penta-refractory” (refractory to 2 PIs, 2 IMiDs, and an anti-CD38 mAb).

With a median follow-up of 6.8 months, the ORR was 61% (95% CI: 51.8, 69.6), the complete response (≥CR) rate was 20.3% (95% CI: 13.6, 28.5), and the median DOR was not reached; among responders, the probability of a response ≥6 months was 90.4% (95% CI 79.9, 95.6).

b. Include any additional relevant information:

A comparison of the efficacy of elranatamab to the approved therapies for similar populations of patients with RRMM is summarized in the table above in Section 9. The ORR of 61% and DOR (median not reached with median follow-up 6.8 months) of elranatamab represent a clinically meaningful improvement compared to the relevant available therapy of selinexor + dexamethasone.

Experience with the safety of elranatamab at the RP2D includes 187 patients treated in the pivotal trial, including 123 patients from Cohort A. In Cohort A, all patients had at least one treatment-emergent adverse event (TEAE), including serious TEAEs in 63.4% of patients, Grade 3-4 TEAEs in 74.8%, fatal TEAEs in 13.8% and TEAEs leading to permanent discontinuation in 10.6%.

The key safety concerns for elranatamab are CRS and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS) and peripheral neuropathy. CRS occurred in 57.7% of patients, all events were Grade 1 or 2, and 34% of patients with CRS received tocilizumab. ICANS occurred in 4.9% of patients and all events were Grade 1 or 2. Peripheral neuropathy occurred in 17% of patients and included two Grade 3 events. Overall, the

safety profile is consistent with what is expected based on the mechanism of action and the 2-step up dosing regimen appears to have mitigated the risk of CRS.

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

☒ GRANT:

Provide brief summary of rationale for granting:

MM is a serious condition, and ORR, supported by DOR data, is an acceptable endpoint for accelerated approval in this disease setting. The data submitted in support of the BTDR is sufficient to be considered as preliminary clinical evidence of improvement over available therapies for patients with triple-class refractory MM. The ORR of 61% with the median DOR not reached with a median of 6.8 months of follow-up observed with elranatamab in this refractory patient population suggests a substantial improvement in comparison to selinexor + dexamethasone. In addition, the depth of response (≥CR rate 20.3%) also represents a substantial improvement over available therapy.

Although the Division is not formally considering the BCMA-directed CAR T-cell products as available therapy, the ORR and ≥CR rates observed with elranatamab are similar to that of idecabtagene vicleucel. Additionally, while elranatamab has the advantage of being an off-the-shelf product, and the observed rates and severity of CRS and ICANS generally appear lower with elranatamab and other anti-BCMAxCD3 bispecific antibodies compared to BCMA-directed CAR T-cell products.

Overall, elranatamab is a bispecific BCMA-directed CD3 T cell engager with a novel mechanism of action compared to other approved anti-myeloma therapies, an acceptable safety profile based on preliminary clinical experience, and preliminary clinical evidence that it may demonstrate substantial improvement on a clinically significant endpoint in MM over available therapies. Because the triple-class refractory population of patients with MM represents an area of unmet medical need, the Division recommends granting BTD for the revised indication: "For the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior lines of therapy, including a proteasome inhibitor (PI), an immunomodulatory agent, and an anti-CD38 monoclonal antibody."

☐ DENY:

Provide brief summary of rationale for denial:

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

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

The Sponsor plans to submit the results from the C1071003 trial from patients treated with elranatamab in Cohort A (N=123), with supportive data from Cohort B (N=64), with an endpoint of ORR as the basis of an application for accelerated approval. The Division has concerns regarding the Sponsor's plan to seek accelerated approval based on data from a single-arm trial. A pre-BLA teleconference to discuss content/format of the proposed BLA is scheduled for October 21, 20222 and a pre-BLA teleconference to further discuss topline efficacy and safety results is scheduled for December 16, 2022. The Sponsor's plans for a confirmatory phase 3 trial, C1071005, comparing elranatamab as monotherapy and in combination with daratumumab-SC vs. a DPd control arm was recently discussed at an End-of-Phase 1 teleconference on July 22, 2022; however, agreement has not been reached regarding the proposed dosing regimen for the elranatamab + daratumumab arm and aspects of the statistical analysis plan.

The Division plans to continue to provide guidance to the Sponsor regarding the planned BLA submission and confirmatory trial.

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

14. List references, if any:

National Cancer Institute Cancer Stat Facts: Multiple Myeloma. Retrieved from https://seer.cancer.gov/statfacts/html/mulmy.html

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

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

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

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

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

/s/

ANDREA C BAINES
10/25/2022 11:19:06 AM

BINDU N KANAPURU
10/25/2022 11:29:40 AM

NICOLE J GORMLEY
10/25/2022 05:19:36 PM

IND 133940

MEETING MINUTES

Pfizer Inc.
Attention: Robert Schaum, PhD
Director, Global Regulatory Affairs
445 Eastern Point Road
Groton, CT 06340

Dear Dr. Schaum:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PF-06863135 (elranatamab).

We also refer to the video conference between representatives of your firm and the FDA on August 21, 2022. The purpose of the meeting was to discuss the format and content of the biologics license application (BLA) planned for elranatamab in November - December 2022, supported by the phase 2 study C1071003.

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 Natasha Kormanik, Senior Regulatory Project Manager, at (240) 402-4227.

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:	C
Meeting Category:	Guidance – BLA Format and Content
Meeting Date and Time:	October 21, 2022 at 3:30 PM (ET)
Meeting Location:	Video Conference
Application Number:	IND 133940
Product Name:	PF-06863135 (elranatamab)
Indication:	Treatment of adult patients with relapsed or refractory multiple myeloma who have received at least (b)(4) prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody
Sponsor Name:	Pfizer Inc.
Regulatory Pathway:	351(a) of the Public Health Service Act
Meeting Chair:	Bindu Kanapuru, MD
Meeting Recorder:	Natasha Kormanik, MSN

FDA ATTENDEES

Oncology Center of Excellence (OCE)
Donna Rivera, PharmD – Associate Director, Real World Evidence

Office of Oncologic Diseases (OOD)
Shan Pradhan, MD – Acting Associate Director for Safety
Stacie Woods, PharmD- Safety Regulatory Project Manager

OOD/ Division of Hematologic Malignancies II
Nicole Gormley, MD – Director
Bindu Kanapuru, MD – Clinical Team Leader
Andrea Baines, MD, PhD – Clinical Reviewer

Office of Biostatistics/ Division of Biometrics IX
Qing Xu, PhD – Statistical Team Leader
Jay Zhao, PhD – Statistical Reviewer

Office of Clinical Pharmacology (OCP)/ Division of Cancer Pharmacology I
Xiling Jiang, PhD – Acting Clinical Pharmacology Team Leader
Lili Pan, PhD – Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality (OPQ)/Office of Biotechnology Products
Frances Namuswe, PhD – Team Leader
Jun Liu, PhD – Product Quality Reviewer
Kelly Ballard, MS – Regulatory Business Process Manager

Office of Surveillance and Epidemiology (OSE)/ Division of Medication Error Prevention and Analysis
Hina Mehta, PharmD – Team Leader
Nicole Iverson, PharmD, BCPS – Analyst
Frances Fahnbulleh, PharmD – Safety Regulatory Project Manager

OSE/ Division of Risk Management (DRISK)
Naomi Boston, PharmD – Team Leader
Robert Pratt, PharmD – Risk Management Analyst

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

SPONSOR ATTENDEES

Pfizer Inc.
Nathalie Bouxin, PhD – Medicine Team Lead
Akos Czibere, MD, PhD – Vice President Hematology Clinical Franchise Leader
Andrea Viqueira, MD – Global Clinical Lead
Anne Hickman, DVM, PhD – Safety Risk Lead
Jane White, ScD – Statistics Group Lead for Hematologic Malignancies
Mohamed Elmeliegy, PhD – Global Clinical Pharmacology Lead
Diane Wang, PhD – Clinical Pharmacology Unit Head
Caroline Henesey, PhD – Global Regulatory Portfolio Lead, Hematologic Malignancies
Robert Schaum, PhD – Global Regulatory Lead
Eric Leip, PhD – Statistics Lead
Kim Kaighn, MBA, PMP – Portfolio and Project Management Lead
Louise Dowling, PhD – Global CMC Lead
Joy Thompson, BS, PMP – Co-Development Lead
Linda Gustavson, PhD – Vice President Regulatory Affairs Oncology
Jamie Wilkins, Pharm D – Head, Risk Management Center of Excellence
Wei Shen, MS – Statistical Programming
Bohdan Wolosiuk, MS – Group Lead, Data Analysis and Reporting
Marco DiBonaventura, PhD – Value and Evidence Lead

1.0 BACKGROUND

On August 3, 2022, the Sponsor requested a Type C meeting to discuss the format and content of the proposed biologic licensing application (BLA) they plan to submit for elranatamab in November-December 2022, based on the phase 2 study C1071003.

The applicant proposes a rolling BLA submission for elranatamab.

FDA sent Preliminary Comments to Pfizer Inc. on October 17, 2022.

2.0 DISCUSSION

Question 1: *Does the Agency agree with Pfizer's revised proposal for the presentation of efficacy information in the Summary of Clinical Efficacy (SCE)?*

FDA Response to Question 1: In general, your proposal to include participants enrolled in Cohort B (N=64) and data from participants treated at the RP2D of 76 mg SC QW from studies C1071001 and C1071009 as supportive data in the SCE appears reasonable.

However, we need additional clarification regarding the proposed primary efficacy analysis population. (b) (4) However, the current statistical analysis plan (SAP) version 8 dated on July 8, 2022, only includes the first 90 participants enrolled in Cohort A in the primary efficacy analysis. Clarify the primary efficacy analysis population for your proposed BLA and submit a revised SAP as applicable.

We have the following additional comments:

- We reiterate that for regulatory purposes the efficacy decision considerations would be based on the lower limit of the 95% confidence interval exceeding a clinically relevant response rate.

- Additionally, to allow for an adequate assessment of durability of response and safety, we recommend at least 9-12 months of follow-up from the time of response for all responders.

DISCUSSION: The Sponsor (b) (4) **provided additional information regarding the projected duration of follow-up for the planned BLA submission (see attachment). The Agency stated that the primary efficacy analysis population should be clearly defined in the SAP. The efficacy evaluation will be based on the primary efficacy analysis population. The Agency reiterated that they recommend a minimum of 9-12 months of follow-**

up from the time of response for all responders to allow an adequate assessment of durability of response and benefit-risk. The Agency stated that efficacy data is expected to be complete and robust at the time of BLA submission.

Question 2: *Does the Agency agree with the proposed CRS and NT data sets to be included in the BLA?*

FDA Response to Question 2: We agree with your proposal to include CRS and NT flags in the ADSL/ADAE datasets. The ADAE dataset should also include flags for ICANS and flags for events that the investigator considered to be symptoms of CRS or ICANS (if captured in the eCRF).

We do not agree with your proposal to create the CRS and NT datasets at the event level. The CRS and NT datasets should be modeled after the ADAE dataset and allow for assessment of patient-level data in addition to event-level data. The datasets should also include information on the use of tocilizumab and other supportive therapies in relation to CRS, NT, and ICANS. FDA may request additional information regarding CRS and NT during review of the BLA. See the Additional Clinical Comments below for information regarding CRS and NT that should be included.

DISCUSSION: The Sponsor stated that the datasets would be modeled after ADAE. The Agency stated that the Sponsor's approach appears reasonable, and that additional information may be requested following review of the data.

Question 3: *Does the Agency agree that the safety profile of elranatamab does not warrant a Risk Evaluation and Mitigation Strategy (REMS) Program?*

FDA Response to Question 3: There are significant concerns with the risk of CRS and neurologic toxicity, including ICANS, with elranatamab. A REMS may be warranted. If you think a REMS is necessary to ensure the benefits of elranatamab outweigh its risks, a REMS proposal should be submitted with the BLA. If you choose not to submit a REMS, include in your submission your rationale for why a REMS is not necessary to ensure the benefits of elranatamab outweigh its risks.

The determination of whether a REMS is necessary, and the adequacy of the proposed REMS will be determined during review of the BLA.

DISCUSSION: The Agency acknowledged the information submitted by the Sponsor regarding a possible REMS (see attachment). The Agency stated that in general the approach is reasonable. The Agency reiterated that a determination of whether a REMS is needed, and the adequacy of the proposed REMS would be determined during review of the BLA submission.

The Agency stated that the REMS should be submitted as a standalone document, including the REMS materials that will support the communications and training elements proposed to relevant stakeholders. Additionally, a REMS Supporting Document that includes an assessment plan of the REMS program should also be included. The Risk Management Framework should be included in the REMS Supporting Document.

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

FDA Response to Question 4: In general, FDA (b) (4) FDA continues to recommend a randomized controlled trial and believes it is feasible and ethical. Overall, (b) (4) particularly in a disease setting where a controlled trial is feasible, may not be justified or reasonable.

(b) (4)

DISCUSSION: The Agency stated [redacted] (b) (4) **to support the application, the Sponsor should submit the study protocol and SAP for Agency review prior to conducting the real world data study and including this data in the BLA submission.**

Question 5: *Does the Agency agree with the proposal for submission and review of portions of an application (rolling review) for the initial BLA for elranatamab?*

FDA Response to Question 5: The proposed BLA may be eligible for rolling review given the fast-track designation for elranatamab; however, you will need to submit a formal request for rolling review that includes a proposed timeline, for the Agency's review and agreement. A determination to grant rolling review will be made following review of the formal request. Note that the existing mechanisms for rolling review in which, generally, complete modules (e.g., the complete clinical module) are submitted prior to a complete application submission, differ from RTOR, which is intended to facilitate earlier submission of critical efficacy and safety data and may involve submission of components of individual modules (e.g., parts of the clinical module, etc.) at separate times.

DISCUSSION: The Sponsor provided details regarding their plan to submit a request for rolling review (see attachment). The Agency reiterated that the determination to grant a rolling review will be made following review of the formal request.

Question 6: *Does the Agency agree that the planned BLA could be a candidate for participation in RTOR, with the proposed list of components and the corresponding scheduled timeline?*

FDA Response to Question 6: It is premature to comment on your proposed list of components and timeline. At the time top-line results of Study C1071003 are available, and the database has been locked, you may submit a formal request to apply for review under RTOR. You should include the top-line results and a written justification explaining how your application demonstrates that it is appropriate for RTOR.

We reiterate our previous comments from the meeting on January 14, 2022 that, in general, submissions that may be considered for RTOR should:

- Demonstrate substantial improvement over available therapy which may include drugs previously granted breakthrough therapy designation for the same or other indications.
- Have a straightforward study design.
- Have endpoints that can be easily interpreted.

Refer also to the *FDA Real-Time Oncology Review (RTOR) Guidance for Industry*, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-time-oncology-review-rtor.

DISCUSSION: No discussion occurred.

Question 7: *Does the Agency consider that the planned BLA could be a candidate for participation in Project Orbis?*

FDA Response to Question 7: In general, your proposal to participate in Project Orbis may be reasonable**.** However, in order to assess the interest from the Project Orbis Partners (POPs), you should submit a Global Submission Plan (GSP; see attached) that provides details and timelines for submission to the other regulatory authorities, including the proposed approval pathway(s) and clinical trials supporting the proposed indication, along with any other relevant information. The GSP should be submitted within a week after the Sponsor meeting (or earlier) so that POPs can be alerted to a potential application and allocate resources if necessary.

DISCUSSION: No discussion occurred.

Additional Comments

Clinical Pharmacology

1. In the BLA submission package, provide information to support that a less frequent dosing of elranatamab (i.e., Q2W) in patients who received QW dosing for at least 6 cycles and have achieved an IMWG response category of PR or better persisting for at least 2 months will not result in a loss of efficacy for such patients as this will impact the benefit-risk of elranatamab.

Statistics

2. Ensure that the define files contain sufficient comments, adequate bookmarks, and hyperlinks to facilitate FDA's review.
3. Provide the SAS programs as well as format library files used for efficacy data analysis. If the SAS programs use any SAS macro, provide all necessary macro programs.
4. Provide 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 indicating dates of determined event or censoring, reasons for censoring, variables for subgroup analyses, etc. Variables used for sensitivity analysis of the SAP should also be included.

Clinical

5. We have concerns with your proposal to submit an initial BLA for accelerated approval for elranatamab based on the results of a single arm trial.

- We reiterate our comments previously stated in the meeting on January 14, 2022. As previously stated, we recommend that you consider a randomized clinical trial to support the initial registration of elranatamab.
- If you decide to proceed with a BLA submission, note that for therapies requesting accelerated approval under 21 CFR §314 Subpart H, postmarketing studies should usually be already well underway. We reiterate the comments from the meeting on July 22, 2022, regarding Study C1071005 and note that agreement has not been reached on the proposed confirmatory trial.

6. We have the following additional comments regarding the efficacy and safety analyses and datasets:
   a) 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.
   b) Include a dataset that includes the following information for all responders:

Patient ID	Disease assessment at screening*	Disease assessment at baseline (prior to treatment)*	Adjudicated best response*	Disease assessment at progression*	Study day of progression

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

   c) Investigator attribution should not be used to assess neurotoxicity rates.
   d) For assessment of neurologic adverse events, we recommend grouping of preferred terms. Use broad grouping of terms that includes relevant terms that may 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 a few examples below, however, it is expected that the list may include additional terms based on adverse events collected in the trial.

      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.

DISCUSSION: **The Sponsor requested clarification regarding the grouping of PTs for neurologic toxicity. The Agency recommended that the Sponsor consider the revised grouping approach as described in the preliminary comments and stated that it is at the Sponsor's discretion to perform analyses based on alternative PT groupings.**

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

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

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

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

pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

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

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

FDARA REQUIREMENTS

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

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

[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

you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

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

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

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

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*

[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

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*.[6]

ONCOLOGY PILOT PROJECTS

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

- RTOR[7]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- Assessment Aid[8]

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*

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

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.

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.

NONPROPRIETARY NAME

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

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

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

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

The Agency sent preliminary comments on October 17, 2022 and the Sponsor provided response document on October 20, 2022, which is appended to these meeting minutes.

17 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

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11/01/2022 02:41:38 PM

IND 133940

MEETING MINUTES

Pfizer Inc.
Attention: Robert Schaum, PhD
Director, Regulatory Affairs
445 Eastern Point Road
Groton, CT 06340

Dear Dr. Schaum:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PF-06863135 (elranatamab).

We also refer to the teleconference between representatives of your firm and the FDA on January 14, 2022. The purpose of the meeting was to discuss the format and content for a planned biologic licensing application.

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

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

Sincerely,

{See appended electronic signature page}

Bindu Kanapuru, MD
Clinical Team Lead
Division of Hematologic Malignancies II
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

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

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance

Meeting Date and Time: January 14, 2022 at 2:30 PM (ET)
Meeting Location: Teleconference

Application Number: IND 133940
Product Name: PF-06863135 (elranatamab)
Indication: Relapsed and refractory multiple myeloma
Sponsor Name: Pfizer Inc.
Regulatory Pathway: 351(a) of the Public Health Service Act

Meeting Chair: Bindu Kanapuru, MD
Meeting Recorder: Natasha Kormanik, MSN, RN, OCN®

FDA ATTENDEES

Office of Oncologic Diseases (OOD)/ Division of Hematologic Malignancies II
Nicole Gormley, MD – Director
Bindu Kanapuru, MD – Clinical Team Leader
Elizabeth Hill, MD – Clinical Reviewer
Andrea Baines, MD, PhD – Clinical Reviewer

OOD
Felicia Diggs, MSN, RN – Safety Regulatory Project Manager

Office of Clinical Pharmacology (OCP)/ Division of Cancer Pharmacology I
Xiling Jiang, PhD – Team Leader
Ankit Shah, PhD, DABT – Reviewer

Office of Biostatistics/ Division of Biometrics IX
Qing Xu, PhD – Team Leader
Jay Zhao, PhD – Reviewer

Office of Product Quality (OPQ)/ Office of Biotechnology Products/ Division of Biotechnology Review and Research
Frances Namuswe, PhD – Team Leader
Jun Liu, PhD – Product Quality Reviewer
Rabiya Haider, PharmD – Sr. Regulatory Business Process Manager

Office of Product Quality (OPQ)/ /Office of Pharmaceutical Manufacturing Assessment
Virginia Carroll, PhD – Team Leader
Maria Scott, PhD – Reviewer

eDATA and eSUB
Lina Cong – Regulatory Information Specialist

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

SPONSOR ATTENDEES

Pfizer Inc.
Nathalie Bouxin, PhD – Medicine Team Lead
Akos Czibere, MD, PhD – Vice President Hematology Clinical Franchise Leader
Andrea Viqueira, MD – Global Clinical Lead
Anne Hickman, DVM, PhD – Safety Risk Lead
Umberto Conte, PharmD – Oncology Clinical Lead
Vassiliki Papadimitrakopoulou, MD – Vice President Clinical Development Oncology
Mohamed Elmeliegy, PhD – Global Clinical Pharmacology Lead
Diane Wang, PhD – Clinical Pharmacology Unit Head
Jane White, ScD – Statistics Group Lead for Hematologic Malignancies
Eric Leip, PhD – Statistics Lead
Matthew Smith, MS – Statistical Programming Group Lead
Ann Subashi, MA – Global CMC Team Lead
Louise Dowling, PhD – Global CMC Lead
Joy Thompson, BS, PMP – Large Molecule Co-Development Team Leader
Linda Gustavson, PhD – Vice President Regulatory Affairs Oncology
Caroline Henesey, PhD – Global Regulatory Portfolio Lead, Hematologic Malignancies
Robert Schaum, PhD – Global Regulatory Lead
Kim Kaighn BS, MBA – Project Management Lead, Oncology

1.0 BACKGROUND

On November 16, 2021, the Sponsor requested a content and format meeting in preparation for a BLA submission. Elranatamab (PF-06863135) is a heterodimeric humanized full-length bispecific IgG2 kappa mAb derived from two mAbs, the anti-BCMA mAb (PF-06863058) and the anti-CD3 mAb (PF-06863059). The Sponsor is proposing a BLA submission for elranatamab for the treatment of relapsed and refractory multiple myeloma.

FDA sent Preliminary Comments to Pfizer, Inc. on January 7, 2022.

2.0 DISCUSSION

Preamble

We have significant concerns regarding your proposal to seek registration for elranatamab based on the results of Study C1071003, 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 triple class refractory MM. 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.

For therapies requesting accelerated approval under *21 CFR §314 Subpart H*, postmarketing studies should usually be already underway. However, we note that you do not have an agreed upon trial ongoing to confirm clinical benefit of elranatamab at this time.

We recommend a randomized trial with a primary endpoint of PFS as the initial registration approach for elranatamab in multiple myeloma.

DISCUSSION: The Agency reiterated their concerns regarding the Sponsor's proposal to seek initial registration for elranatamab based on a single arm trial.

The Agency acknowledged the Sponsor's request for a EOP1 meeting in May 2022 to discuss the revised design of their Phase 3 study. The Agency reiterated that if the Sponsor decides to submit a BLA (b) (4) the confirmatory trial should be well underway at time of submission. The Agency recommended that the Sponsor expedite the initiation of such trial.

Question 1: Does the FDA agree that clinically meaningful ORR and DOR in Study C1071003 would support a BLA filing (b) (4)

FDA Response to Question 1: *No, we have concerns with your proposal to submit a BLA for elranatamab for accelerated approval based on the results of a single arm trial. Refer to the preamble.*

We also have concerns with the limited duration of follow up. For multiple myeloma, 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. This information should be provided at the time of the initial BLA submission.

(b) (4)

DISCUSSION: No Further discussion

Question 2: Does the Agency agree that the analytical comparability plan and resulting data package is sufficient to support the transition from Puurs to Kalamazoo as the drug product commercial manufacturing site?

FDA Response to Question 2: *No. Based on the limited information provided, we do not agree that the proposed analytical comparability plan and resulting data package are sufficient to support the transition from Puurs to Kalamazoo (KZO) as the drug product (DP) commercial manufacturing site. In the briefing package, you described that the analytical comparability assessment for transition to KZO was submitted in the IND 133940 amendment sequence number (SN) 0106 on September 10, 2021. However, the DP comparability assessment submitted in amendment SN 0106 is insufficient to support that the DP lots manufactured from KZO are comparable to the historical DP lots because you only compared one KZO DP lot with historical DP lots in terms of the DP release and additionally generated cell-based bioassay testing. Moreover, in the briefing package you further described that a comprehensive analytical comparability was conducted which includes the assessment of release, stability, and "heightened" characterization testing between the pre- and post-change materials. However, you provided neither detail information for this comparability plan nor comparability study results to support the transition from Puurs to KZO as the DP commercial manufacturing site. In order to ensure that DP lots manufactured from KZO are comparable with the historical DP lots and support KZO as a commercial DP manufacturing site, we highly recommend that you submit a detail analytical comparability plan prior to a BLA submission.*

We have the following additional recommendations:

- *At least three KZO DP lots using the proposed commercial process should be used to support comparability.*

- *The comparability plan should include pre-established and justified comparability acceptance criteria for the quality attributes assessed in your analytical comparability study. The comparability acceptance criteria should be based on the available historical manufacturing and clinical experience.*
- *In addition to the DP lot release comparison, additional characterization comparison for the quality attributes (e.g., sub-visible particles (b) (4) µm, oxidation, deamidation, etc.), which might be potentially impacted by the DP manufacturing process should be carefully selected and included in your comparability study. Regarding the comparative stability assessment, you did not provide information on the stability condition(s) to support that the pre-change and post-change DP lots have the similar degradation profiles (including degradation rates and species) for the stability indicating quality attributes. The stability comparison of the pre-change and post-change materials should be conducted for an appropriately selected length of time under conditions that could provide meaningful incremental changes for the stability indicating quality attributes over time. If changes to the stability degradation profiles are not expected under the proposed stability condition(s), a stability study under more stringent conditions, e.g., using forced degradation condition under a higher temperature and/or longer time with at least 3-4 time points, should be conducted to clearly capture the degradation profiles (rate and degradation species). This is especially important if limited data will be provided under long term storage conditions. Any differences in stability degradation profiles between the pre-change and post-change materials should be adequately addressed.*

DISCUSSION: **The Sponsor acknowledged the Agency's communication in granting the CMC meeting request. The Sponsor stated that an updated meeting package would be provided within a week. The Agency encouraged the Sponsor to submit the updated information as soon as possible to accommodate review process. The Agency will reach out to the Sponsor if there are any changes to the meeting date.**

Question 3: Does the FDA agree with the overall scope of clinical data and table of contents planned for the initial submission of elranatamab monotherapy for the treatment of patients with RRMM?

FDA Response to Question 3: *Refer to the preamble.*

In general, your proposed CDSIC dataset packages are reasonable. Additionally, you should provide the following information:

1. Ensure that the define files contain sufficient comments, adequate bookmarks, and hyperlinks to facilitate FDA's review.
2. Provide the SAS programs as well as format library files used for efficacy data analysis. If the SAS programs use any SAS macro, provide all necessary macro programs.

3. Provide a mock-up define file to show the variables which will be included in the derived datasets for the primary analyses. Variables used for sensitivity analysis of the SAP should also be included.

DISCUSSION: No Further discussion

Question 4: Does the FDA agree with the proposed clinical pharmacology analyses for the BLA and the proposal for a mapping ISI?

FDA Response to Question 4: *In general, your proposed plan for the clinical pharmacology analyses and the proposal for a mapping ISI appears reasonable. A final determination of the adequacy of the clinical pharmacology package will be determined at the time of BLA review. Refer to "Additional Clinical Pharmacology Comments" for more detailed information regarding the submission of clinical pharmacology information.*

In the proposed meeting for dose-selection, you should provide adequate PK, PD, efficacy and safety data and conduct integrated dose-response and exposure-response analyses based on all available information to obtain the Agency's agreement on key aspects related to elranatamab dose/dosage regimen selection and justification.

Regarding the immunogenicity assays, in the briefing package you described that bioanalytical assays to measure ADA (anti-drug antibody) and Nab (Neutralizing antibody) are either developed or are currently being developed and validated. We remind you that your immunogenicity assays should be fully validated with multi-tiered testing approach (e.g., ADA screening assay, confirmatory assay, titer assay, neutralizing assay etc.) prior to testing clinical samples from pivotal clinical studies in accordance with the Guidance for Industry: Immunogenicity Testing of Therapeutic Protein Products – Developing and Validating Assays for Anti-Drug Antibody Detection (January 2019).

DISCUSSION: No Further discussion

Question 5: Does the Agency agree with Pfizer's proposal for the presentation of efficacy information in the Summary of Clinical Efficacy (SCE) and Integrated Summary of Efficacy (ISE)?

FDA Response to Question 5: *Refer to the preamble.*

Additional Comments:

- *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.*

- *Provide a pooled analysis of efficacy for Cohort A and Cohort B.*

DISCUSSION: The Sponsor asked for clarification regarding the Agency's recommendation to pool Cohorts A and B for efficacy.

The Agency stated that while the two patient populations differ in specific aspects of prior therapies a pooled analysis may be used to support the efficacy in a refractory patient population.

Question 6: Does the agency agree with the proposed safety pooling strategy and the proposed analyses for CRS, ICANS, and PN as Adverse Events of Special Interest?

FDA Response to Question 6: *Refer to the preamble.*

We have the following comments:

- *In general, the pooling strategy for general safety appears reasonable.*
- *Include a flag for the different priming doses in Pool 2.*
- *The pooling strategy for CRS and ICANS should be consistent with the pooling strategy proposed for general safety.*

DISCUSSION: No Further discussion.

Question 7: Does the agency agree with the proposed plans for participant safety narratives and inclusion of eCRFs?

FDA Response to Question 7: *Refer to the preamble.*

- *You should include narratives for AEs of special interest (CRS, ICANS, and PN) for all grades, not just Grade 3 or higher. It may be acceptable to include just Grade 2 CRS events or higher. However, you should submit narratives and CRFs for patients who had Grade 1 or 2 CRS who received tocilizumab*
- *Deaths due to disease progression should be submitted in a hybrid format like the rest of the death narratives. We recommend including a free text narrative summary.*
- *Additional narratives may be requested during the review process.*

DISCUSSION: No Further discussion.

Question 8: Does the Agency agree with Pfizer's proposal for the presentation of safety information in the SCS and ISS?

FDA Response to Question 8: *No, we do not agree with your proposal to include the contents of the ISS in the SCS. You 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 located in Module 5.3.5.3 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: No Further discussion.

Question 9: Does the Agency agree with the plans for inclusion of data in and the timing for the safety update?

FDA Response to Question 9: *Refer to preamble.*

We do not agree with the plan to update efficacy data after BLA submission. Efficacy data should be complete at the time of the initial BLA submission.

In general, a 90-day safety update is appropriate for priority review. However, the determination of review designation and the timeline for safety update will be made at the time of submission.

DISCUSSION: No Further discussion.

Question 10: Does the Agency agree that the elranatamab BLA may be accepted into the RTOR program in accordance with the proposed schedule and the ORBIS pilot?

FDA Response to Question 10: *Refer to preamble.*

In general, submissions that may be considered for RTOR should

- *Demonstrate substantial improvements over available therapy which may include drugs previously granted breakthrough therapy designation for the same or other indications.*
- *Have a straightforward study design as determined by the review Division and the OCE.*
- *Have endpoints that can be easily interpreted.*

If interested in participating in the RTOR or Project Orbis program, at the time of top-line results of a pivotal trial, a written justification on why elranatamab should be considered should be submitted via an email to the appropriate application RPM.

Additionally, we recommend the use of an Assessment Aid (AAid). See Section 3.0 Additional Important information on Oncology Pilot Projects.

DISCUSSION: **The Sponsor requested further comment regarding their plans to initiate a rolling BLA in light of their Fast-Track Designation granted Jan 22nd, 2021 (See attached document).**

The Agency stated that the determination to grant rolling review will be made following receipt of a formal request. The Agency recommended that the Sponsor submit a formal request for rolling review with a planned timeline for submission and available data for the Agency to review.

Question 11: Does Agency agree that the BICR charter adequately assures independent response assessment in study C1071003?

FDA Response to Question 11: *Yes, the proposed revisions to the BICR charter appear reasonable.*

DISCUSSION: **No Further discussion.**

Additional Clinical Comments:

1. For assessment of neurologic adverse events, group preferred terms using, but not necessarily limited to the group terms below:
   a. Aphasia: aphasia, dysphasia
   b. Delirium: agitation, delirium, delusion, disorientation, hallucination, restlessness
   c. Encephalopathy: cognitive disorder, confusional state, depressed level of consciousness, disturbances in attention, encephalopathy, hypersomnia, leukoencephalopathy, memory impairment, mental status changes, paranoia, somnolence, stupor
   d. Tremor: head titubation, tremor

2. 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.

3. Submit separate datasets for CRS and neurotoxicity, if applicable. The dataset(s) should incorporate the following:

   CRS Dataset:
   - Each row assigned to a unique subject with CRS diagnosis per investigator's assessment.
   - 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.

NT 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 NT based on ICANS (immune effector cell-associated neurotoxicity syndrome) 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

4. 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.

To enhance retrieval of narratives, your submission should include a hyperlinked table tracking subject narratives by category, similar to the example below:

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

5. Include a dataset that includes the following information for all responders:

Subject ID	Disease assessment at screening*	Disease assessment at baseline (prior to treatment)*	Adjudicated best response to elranatamab	Disease assessment at progression *	Study day of progression
0001					
0002					
….					
…..					

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

Discussion: The Sponsor outlined the challenges with providing CRS data based on Lee 2014 criteria (See attached document). The Agency stated that it may be acceptable to provide CRS data based on ASTCT criteria alone if the requested variables including information on organ toxicity in patients who experience CRS are also included.

The Agency stated the CRS and NT dataset may be combined if it includes the requested variables. Additionally, the dataset should be sufficiently detailed to capture tocilizumab use including any AEs from tocilizumab, and duration of tocilizumab use. Additional information will be as a post meeting comment.

Additional Clinical Pharmacology Comments:

1. Address the following questions in the Summary of Clinical Pharmacology:
   a. What is the basis for selecting the doses and dosing regimen used in the registration trials to support your marketing application? Identify individuals who required dose modifications, and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.
   b. What are the exposure-response relationships for efficacy, safety and biomarkers in the target patient population?

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

2. Apply the following advice in preparing the clinical pharmacology sections of the original submission:
   a. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
   b. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate.
   c. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
      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 subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
      ii. Identify individual subjects with dosage modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dosage modifications in the datasets.

3. Submit a study report describing the population pharmacokinetic analyses and exposure-response analyses. Refer to Guidance for Industry for population PK, exposure-response relationships, and pharmacometric data and models submission guidelines.

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

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

6. 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.7. When you submit your QT evaluation report, please include a completed version of the most recent "QT Evaluation Report Submission Checklist" located at the IRT website (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/interdisciplinary-review-team-cardiac-safety-studies-formerly-qt-irt).

Post meeting Comments:

To inform the use of tocilizumab for the mitigation of CRS, provide data from multiple trials evaluating elranatamab.

i. To facilitate analysis of the use of tocilizumab (TCZ) in the treatment of CRS in patients treated with elranatamab, include a detailed summary of the reason(s) tocilizumab was indicated and administered (i.e., persistent hypotension, etc.) for the corresponding CRS grade.
ii. 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.
iii. Include in the BLA a document summarizing the initial CRS management instructions and each modification over the life of Study C1071003, and serial changes in CRS grading and management instructions in the elranatmab Investigator's Brochure. This can be a free-standing document or an appendix to the SCS/ISS.
iv. Include in the BLA, a document summarizing the initial ICANS management instructions and each modification over the life of Study C1071003, and serial changes in ICANS management instructions in the elranatamab Investigator's Brochure. This can be a free-standing document or an appendix to the SCS/ISS.
v. For the analyses of safety of use of tocilizumab, include in the SAP for SCS/ISS how you ascertained AEs for tocilizumab from the dataset submitted (e.g., state the data file and variable or a description of the algorithm that you used to identify AEs due to tocilizumab).
vi. For the analyses of efficacy of tocilizumab for treatment of CRS, include in the SAP for SCS/ISS the definition of response, and the data file and variable used to determine the date of the response. If you are using a derived variable to determine the data of response, ensure that the define file has an explanation of the derivation.

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

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

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

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

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

Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans.

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

FDARA REQUIREMENTS

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

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

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

[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

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

- RTOR[4]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- Assessment Aid[5]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No additional issues identified.

5.0 ACTION ITEMS

No action items identified.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor's response to preliminary comments.

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

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