CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761312Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 110489

MEETING MINUTES

Eisai Inc.
Attention: Berny Mullappally
Sr. Manager, Global Regulatory Affairs, Oncology Business Group
200 Metro Blvd.
Nutley, NJ 07110

Dear Mr. Mullappally:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for E7777,

We also refer to the teleconference between representatives of your firm and the FDA on June 28, 2022. The purpose of the meeting was to discuss the efficacy and safety data for E7777 intended for submission of a BLA. .

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

If you have any questions, contact me at (301) 796-4574 or by email denise.felluca@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
- Meeting Minutes

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

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: June 28, 2022; 11:00 AM-12:00 PM EST
Meeting Location: Teleconference

Application Number: IND 110489
Product Name: E7777
Indication: Treatment of patients with persistent or recurrent cutaneous T-cell lymphoma (CTCL) [redacted] (b) (4)
Sponsor Name: Eisai Inc.
Regulatory Pathway: 351(a) of the Public Health Service Act

Meeting Chair: Nicholas Richardson, DO, MPH
Meeting Recorder: Denise Felluca, PharmD, MBA

FDA ATTENDEES

Office of Oncologic Diseases/Division of Hematologic Malignancies II (DHMII)
Nicole Gormley, MD, Director
Nicholas Richardson, DO, MPH, Clinical Team Leader
Yvette Kasamon, MD, Clinical Team Leader
Candis Morrison, PhD, CRNP, Senior Clinical Analyst

OOD/Division of Hematology Oncology Toxicology
Brenda Gehrke, PhD – Pharmacology/Toxicology Team Leader
Moran Choe, PhD – Pharmacologist

Office of Biostatistics/Division of Biometrics IX
Lisa Rodriguez, PhD, Deputy Director
Jing Zhang, PhD, Statistical Reviewer

Office of Pharmaceutical Quality (OPQ)/Office of Biotechnology Products (OBP)
Chana Fuchs, PhD – CMC Team Leader

Office of Clinical Pharmacology/Division of Cancer Pharmacology I
Nan Zheng, PhD, Clinical Pharmacology Team Leader (Acting)
Ankit Shah, PhD, Clinical Pharmacology Reviewer

Office of Regulatory Operations for Oncologic Diseases/Division of Regulatory Operations
Theresa Carioti, MPH, Chief, Project Management Staff
Denise Felluca, PharmD, MBA, Regulatory Health Project Manager

SPONSOR ATTENDEES

Eisai Inc.
Berny Mullappally, Associate Director
Matthew Biondi, Senior Director
Maria Garrigan, Vice President, Global Regulatory Strategy, Oncology
Meijuan Li, Vice President, Biostatistics and Programming
Ric Woodman, Chief Clinical Officer, Oncology Business Group
Yasunobu Kai, Chief Strategy Officer, Oncology
Chean Eng Ooi, Senior Director, International Project Team Lead, E7777
Corina Dutcus, Vice President, Clinical Research
Nicholas Sauter, Director, E7777 Study Director
Donguyan Xing, Senior Director, Biostatistics
Sanae Yasuda, Head of Clinical Pharmacology Science
Theingi Thway, Director, Clinical Pharmacology
Thomas Visalli, Executive Director, Global Nonclinical Regulatory Affairs

Citius Pharmaceuticals, Inc. Development and Marketing Partner
Catherine Kessler, Executive Vice President Regulatory Affairs
Myron Czuczman, Chief Medical Officer
Kevin Carey, Vice President, Program Management
Preeti Singh, Vice President, Clinical Development and Medical Affairs
Gary F. Talarico, Executive Vice President, Operations
Emileigh Greuber, Regulatory Lead
Kelly Creigton, CMC Regulatory Lead

1.0 BACKGROUND

E7777 (denileukin diftitox) is being codeveloped by Eisai and Citius Pharmaceuticals, Inc. Citius will sponsor the BLA (761312) with Eisai acting as the US agent, and subsequently IND 110489 sponsorship will be transferred from Eisai to Citius.

E7777 is a recombinant fusion protein composed of the catalytic and membrane translocation of diphtheria toxin linked to full amino acid sequence for interleukin-2 (IL-2). E7777 has 2 mechanisms of action, a direct cytocidal action on tumor cells, and targeting regulatory helper T-cells. E7777 has the same active component (denileukin diftitox) as Ontak (BLA 103767), but has an improved purification process, as a result of higher active monomer content, relative to Ontak.

The purpose of this meeting is to discuss the totality of the efficacy and safety data for E7777 intended for submission in the Biologics License Application (BLA). The BLA will

be based on a pivotal single arm, phase 3 clinical trial of E7777 in subjects with persistent or recurrent CTCL (Study 302).

The Agency sent the Preliminary Meeting Comments to the Sponsor on June 22, 2022.

2.0 DISCUSSION

Question 1: *Does the Agency agree that the totality of data from E7777 Study 302, Study 205 and Study 101,* (b) (4) *could serve as the basis of marketing approval for E7777 should the overall response rate, magnitude of response, duration of response and safety observed with E7777 represent an acceptable benefit/risk profile?*

FDA Response to Question 1:
No. The data for E7777 based on studies 302, 205, and 101 will be the primary data supporting the assessment of efficacy and safety in the intended population. (b) (4) The acceptability of the data to support a regulatory action will be determined during the BLA review and will be a review issue.

We have the following additional comments.

a. Indication: (b) (4)

b. Diagnostic: We reiterate the potential need of a companion diagnostic with E7777 given the use of CD25 expression to select patients in the studies evaluating the safety and efficacy of E7777. As part of the BLA, you need to provide data to support whether CD25 expression is associated with the safe and effective use of E7777 (refer to meeting minutes from 10/02/2019, 01/26/2021, and 12/21/2021). We acknowledge the meeting request on May 13, 2022, to further discuss the data and approach regarding a CD25 diagnostic.

c. Primary endpoint: The statistical analysis plan (SAP) (Final Version 1.0) of Study E7777-G000-302 states that "The treatment will be considered efficacious and demonstrating the clinical benefit of E7777 if the lower limit of the 2-sided 95% exact CI of the observed ORR exceeds 25%". However, the E7777 pre-BLA briefing document reported that primary endpoint, ORR per IRC, was 36.2%

(95% CI: 24.99, 48.69) with a lower limit at the border line of the clinical critical value, possibly indicating a lack of robustness in the result. Ultimately, the interpretation of the efficacy analysis would be a review issue, which will be based on the totality of the evidence of efficacy and safety with internal consistency.

d. Efficacy population: (b) (4)

Discussion:

(b) (4)

The Agency reiterated that since E7777 and ONTAK are different products, ONTAK data would not be considered in the assessment of safety and efficacy for E7777 and no ONTAK data or datasets should be submitted with the E7777 BLA in this regard.

(b) (4) **, the Agency stated that the Sponsor should report the key efficacy data separately for patients in the lead-in, main portion, and for the total population.** (b) (4) **the efficacy data will be a review issue and determined during the BLA review.**

Question 2: *Does the Agency agree that a REMS is not warranted for E7777?*

FDA Response to Question 2:
The determination of whether a REMS is required to ensure that E7777 is safe and effective for its intended use will occur during the BLA review.

Discussion: No discussion occurred.

Question 3: *Does the Agency agree that persistent or recurrent CTCL and the totality of clinical data for E7777 presented from Study 302, Study 205, and Study 101 meet the qualifying criteria for Priority Review Designation for the BLA?*

FDA Response to Question 3:
The determination of a priority versus standard review occurs during the filing review of the BLA.

Discussion: **No discussion occurred.**

Question 4: *Does the Agency agree the completed nonclinical evaluation is sufficient to support the review of a BLA?*

FDA Response to Question 4:
As mentioned previously in the written responses to the Type C meeting dated (December 2021), we agree with your approach to submit all E7777 data (studies listed in Table 20) along with risk assessments of the potential for embryofetal toxicity and phototoxicity of E7777 in the BLA for E7777, and to cross-reference the existing nonclinical data for denileukin diftitox (manufactured as ONTAK) previously submitted in BLA 103767.

Your weight-of-evidence (WOE) assessment for the reproductive risk assessment may not rely on product-specific literature for which you do not have right-to-reference, including product labeling or FDA's Summary Basis of Approval, for products submitted under the 351(a) pathway. See the guidance for industry titled *Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations* for factors that could be included in a WOE approach https://www.fda.gov/media/124829/download. The adequacy of the WOE-based embryofetal risk assessment and the nonclinical data for E7777 and denileukin diftitox to support the marketing of E7777 will be determined during the review of the BLA.

Discussion: **No discussion occurred.**

Question 5: *Does the Agency agree with the proposed content of the Day 120 safety update report?*

FDA Response to Question 5:
Yes. The proposed content of the 120-day safety update report appears reasonable.

Discussion: **No discussion occurred.**

Question 6: *Does the Agency agree with this proposed immunogenicity assessment strategy?*

FDA Response to Question 6:
Pending review of the available information in BLA application, your plan for immunogenicity assessment appears reasonable. For your immunogenicity assessment, we recommend evaluating the effect of pre-existing ADA (either by status or by titer) and treatment-induced/boosted ADA on PK, efficacy, and safety, given the prevalence of ADA at baseline.

Refer to the following FDA Guidance for Industry for additional details regarding immunogenicity assessment:

a. *Assay Development for Immunogenicity Testing of Therapeutic Proteins*
b. *Immunogenicity Assessment for Therapeutic Protein Products*

In addition, we also recommend that brief summaries of the immunogenicity results are provided in relevant places in eCTD section 2.7. Clinical Summary and the full report in section 5.3.5.3 Reports of Analysis of Data from More than One Study. To facilitate the review of immunogenicity data, we recommend providing an Integrated Summary of Immunogenicity that includes (1) Immunogenicity Risk Assessment, (2) Tiered Bioanalytical Strategy and Assay Validation Summaries, (3) Clinical Study Design and Detailed Immunogenicity Sampling Plans, (4) Clinical Immunogenicity Data Analysis.

The need for additional analyses will be determined at the time of BLA review.

Additional general statistical comments for pre-NDA/BLA submission:

The submission should include following:

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

Discussion: No discussion occurred.

Additional general CMC comments for BLA submission:

a. To facilitate the Agency's review of the DS and DP manufacturing processes for E7777, provide the information for process parameters and in-process controls, as applicable, in the following tabular format. Please provide a separate table for each unit operation. The tables should summarize information from module 3 and may be submitted either to module 3.2.R or module 1.

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

[1]As applicable.
[2]For example, critical process parameter, key process parameter, non-critical process parameter, as described in module 3.
[3]This could be a brief verbal description and/or links to the appropriate section of the eCTD.
[4]Optional.
Please note that the requested summary information will not substitute requirements for detailed information and adequate data from process characterization and process validation studies in sections 3.2.S.2.5, 3.2.S.2.6, 3.2.P.2 and 3.2.P.3.5 to support the commercial manufacturing process.

b. To facilitate the Agency's review of the control strategy for E7777, provide information for quality attributes and process- and product-related impurities for the DS and DP in the following tabular format. The tables should summarize information from module 3 and may be submitted either to module 3.2.R or module 1.

Quality Attributes and Process and Product Related Impurities for DS and DP	Criticality Classification[1]	Impact[2]	Source[3]	Analytical Method(s)[4]	Proposed Control Strategy[5]	Justification of the Proposed Control Strategy[6]	Comment[7]

[1]For example, critical quality attribute or non-critical quality attribute.
[2]What is the impact of the attribute, e.g. contributes to potency, immunogenicity, safety, efficacy.
[3]What is the source of the attribute or impurity, e.g. intrinsic to the molecule, fermentation, protein A column.
[4]List all the methods used to test an attribute in-process, at release, and on stability. For example, if two methods are used to test identity then list both methods for that attribute.
[5]List all the ways the attribute is controlled, for example, in-process testing, validated removal, release testing, stability testing.
[6]This could be a brief verbal description and/or links to the appropriate section of the eCTD.
[7]Optional.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our May 13, 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 VI. 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. 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.

- 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.

- 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.

Discussion: The Sponsor acknowledged the content of a complete application and there were no agreements for any late submission components.

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

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.[3]

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.

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

[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

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

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.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[7]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[8]

MANUFACTURING FACILITIES

[7] http://www.fda.gov/ectd
[8] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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

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

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

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

Corresponding names and titles of onsite contact:

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

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[9] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[10]. Submit all related

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

manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[11]

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

[11] https://www.fda.gov/media/85061/download
[12] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program

facilitate efficient review.
- Assessment Aid[13]

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

[13] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

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

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were not action items.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor's response to the FDA Preliminary Comments is appended.

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

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

/s/

NICHOLAS C RICHARDSON
06/30/2022 01:39:34 PM

IND 110489

MEETING REQUEST-
WRITTEN RESPONSES

Eisai Inc.
Attention: Berny Mullappally, MS
Senior Manager, Global Regulatory Affairs, Oncology Business Group
155 Tice Blvd.
Woodcliff Lake, NJ 07677

Dear Mr. Mullappally:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for E7777.

We also refer to your submission dated October 25, 2021, containing a meeting request. The purpose of the requested meeting was to discuss format and content of upcoming Biologics License Application (BLA).

Further reference is made to our Meeting Granted letter dated November 2, 2021, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your November 22, 2021, background package.

If you have any questions, please contact me via email at denise.felluca@fda.hhs.gov or at 301-796-4574.

Sincerely,

{See appended electronic signature page}

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

Enclosure:

- Written Responses

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

U.S. FOOD & DRUG ADMINISTRATION

WRITTEN RESPONSES

Meeting Type: C
Meeting Category: Guidance

Application Number: IND 110489

Product Name: E7777
Indication: Treatment of patients with persistent or recurrent cutaneous T-cell lymphoma (CTCL) (b) (4)

Sponsor Name: Eisai Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

1.0 BACKGROUND

E7777 (denileukin diftitox) is intended to replace ONTAK (denileukin diftitox), which was marketed in the US from 1999 to 2014 for the treatment of persistent or recurrent, CD25 expressing CTCL. ONTAK (denileukin diftitox) is a CD25-directed cytotoxin that was granted accelerated approval on 05 February 1999 for the treatment of adult patients with persistent or recurrent CTCL whose malignant cells express the CD25 component of the IL-2 receptor. On 15 Oct 2008, the BLA approval for ONTAK was converted from an accelerated approval to full approval for CTCL. E7777 has the same active component (denileukin diftitox) as ONTAK but has an improved purity biologic drug product. Development of E7777 was embarked on due to a commitment from the original FDA approval (1999 letter) to improve the purification process to increase product purity. The Sponsor, Eisai Inc, is currently expecting to submit a BLA for E7777 in mid-2022 based one main, single-arm study (E7777-G000-302) and 2 supportive studies (E7777-J081-101 and E7777-J081-205), (b) (4) (b) (4).

2.0 QUESTIONS AND RESPONSES

Question 1: Eisai proposes the below planned presentation of efficacy data in Module 2.7.3, Summary of Clinical Efficacy (SCE). The text of the SCE will serve as Integrated Summary of Efficacy (ISE). In the ISE, there will be no integration of data from other E7777/ONTAK studies, and the in-text tables, listings and graphs will be based on the individual clinical study reports (CSR). Does FDA agree?

FDA Response to Question 1: In general, the proposed content for the Summary of Clinical Efficacy (SCE) is acceptable if supported by the submission of complete study-

specific datasets and complete CSRs for Studies E7777-G000-302 (Study 302), E7777-J081-101 (Study 101) and E7777-J081-205 (Study 205).

Refer to the additional clinical and statistical comments regarding the efficacy analysis of E7777.

Refer to "Additional Clinical Pharmacology Comments" regarding clinical pharmacology recommendations for dose- and exposure-response analyses on efficacy. FDA recommended efficacy endpoints in the dose- and exposure-response analyses include, but not limited to, ORR, DOR, TTR, PFS, and skin response. The exposure matrices in the proposed dose- and exposure-response analyses on efficacy should include C_{max} and AUC_{0-t} derived from population PK model. The adequacy of the dose- and exposure-response analyses on efficacy will be determined during BLA review.

Question 2: Eisai proposes the below plan for the presentation of safety data in Module 2.7.4, Summary of Clinical Safety (SCS). The text of the SCS will serve as Integrated Summary of Safety (ISS) and any additional tables, listings and graphs as necessary will be placed in Module 5.

FDA Response to Question 2: The proposed content for the SCS appears acceptable. We have the following recommendations regarding your pooled safety analysis.

- Ensure that all 3 studies of E7777 (E7777-G000-302, E7777-J081-101 and E7777-J081-205) are included in the ISS datasets, and that the ISS includes all the information needed to inform the safety analysis, including integrated datasets for: subject level data and demographics, disposition, adverse events, exposure, and laboratory analysis. Refer to the Additional Comments regarding an integrated analysis dataset of deaths.
- For the ISS ADAE.xpt dataset, ensure the same MedDRA version is utilized for all studies to permit pooling.
- The datasets should include flags to identify the various analysis populations.
- Clarify how AEs that occur after new anti-lymphoma therapy (NALT) will be assessed (i.e., whether the safety analysis is censored for NALT) and include a flag for these AEs in the ISS and study-specific AE datasets.

Refer also to the "Additional Clinical Comments" regarding dataset content and structure.

Refer to "Additional Clinical Pharmacology Comments" regarding clinical pharmacology recommendations for dose- and exposure-response analyses on safety. FDA recommended safety endpoints in the dose- and exposure-response analyses include, but not limited to, capillary leak syndrome, visual loss, infusion reactions, hematologic and non-hematologic adverse events and TEAEs resulting in dosage modifications (i.e., dose delay, dose reduction, dose discontinuation). The exposure matrices in the proposed dose- and exposure-response analyses on safety should include C_{max} and

AUC_{0-t} derived from population PK model. The adequacy of the dose- and exposure-response analyses on safety will be determined during BLA review.

Question 3: Does FDA agree with the cross-referencing between ONTAK application information previously submitted by the Sponsor to facilitate review and BLA life-cycle throughout the product review?

FDA Response to Question 3: Your proposal is acceptable provided you have a right of reference to the ONTAK BLA.

Question 4: Does FDA agree that a Day 120 safety update report is not necessary?

FDA Response to Question 4: No. We do not agree with omitting the Day 120 safety update, which remains a required component of the submission. In general, a safety update report that provides at least 4 months of additional data compared to the original data cutoff is recommended. Ensure to include narratives for any additional deaths, serious AEs, AEs of special interest, and AEs leading to dose discontinuation.

Question 5: Does FDA agree with the Sponsors' proposal for submission of datasets, hyperlinking strategy supporting the SCE and SCS?

FDA Response to Question 5: The proposed plan seems reasonable. Ensure that the supportive graphs and tables are well-organized in the navigation pane and have informatively named hyperlinks. The navigability of the submission will be a filing review issue.

Question 6: Does FDA agree with the planned Study Data Tabulation Model (SDTM) datasets and Analysis Data Model (ADaM) datasets proposed for this submission?

FDA Response to Question 6: Ensure that all study-specific and integrated datasets are in standard CDISC format. The submission should also include following:

- All raw as well as derived variables in .xpt format for Study 302.

(b) (4)

The BLA should include complete study-specific datasets to inform the safety, efficacy, and clinical pharmacology review for Studies 302, 101, and 205, in addition to the integrated datasets and CSRs, with all submissions provided in English.

Also refer to the "Additional Comments" regarding dataset content and structure.

Question 7: Does FDA agree with the submission of Define.xml with ARM (Analysis Result Metadata) and the submission of Define.xml without define.pdf for these applications?

FDA Response to Question 7: Submission of define files in pdf format is not mandatory, but please consider providing define.pdf files for Study 302 and the ISS.

The submission should include a mock-up define file to show the variables which will be included in the derived datasets for the primary and key secondary efficacy analyses including, but not limited to, the variables for reasons of censoring, dates of IRC determined events or censoring and variables for subgroup analyses, etc. Variables used for sensitivity analysis of the SAP should also be included.

Question 8: Does FDA agree with the submission of .txt format programs for key analyses only?

FDA Response to Question 8:
The following should be included:

- SAS programs used to create the derived datasets for the efficacy endpoints and the SAS programs used for efficacy data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs.
- SAS programs for derived datasets and the analyses which are associated with the results presented in the proposed package insert as well as any interim analysis if performed.

Question 9: Does FDA agree with the Sponsor's proposal to submit all E7777 data along with risk assessments of the potential for embryofetal toxicity and phototoxicity of E7777 in the E7777 BLA, and to cross-reference the existing nonclinical data for denileukin diftitox (manufactured as ONTAK) previously submitted in BLA 103767?

FDA Response to *Question 9:* We agree with your approach to submit all E7777 data along with risk assessments of the potential for embryofetal toxicity and phototoxicity of E7777 in the BLA for E7777, and to cross-reference the existing nonclinical data for denileukin diftitox (manufactured as ONTAK) previously submitted in BLA 103767.

Your weight-of-evidence (WOE) assessment for the reproductive risk assessment may not rely on product-specific literature for which you do not have right-to-reference, including product labeling or FDA's Summary Basis of Approval, for products submitted under the 351(a) pathway. See the guidance for industry titled Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations for factors that could be included in a WOE approach https://www.fda.gov/media/124829/download. The adequacy of the WOE-based embryofetal risk assessment and the nonclinical data for E7777 and denileukin diftitox to support the marketing of E7777 will be determined during the review of the BLA.

ADDITIONAL COMMENTS

Additional Clinical Comments:

1. **Companion diagnostic:** As discussed at the Type C meeting on January 26, 2021, the expectation is that a companion diagnostic will likely be needed, that you should plan to submit the application for a companion diagnostic at the time of the BLA submission. In preparation for that, the Agency had recommended a presubmission to CDRH.

2. **Assessment aid:** We recommend that this submission include an assessment aid. See information below regarding details of submitting an assessment aid as part of the Oncology Center of Excellence's pilot program.

3. **Efficacy data:** To facilitate assessment of efficacy and response adjudication, the BLA should include the following details regarding efficacy assessments:

    a. Response confirmation: Ensure to consistently report confirmed ORR rather than ORR assessed at one timepoint. Per Global Response Score (GRS) criteria, all changes in tumor measurements should be confirmed by repeat assessment no less than 4 weeks after criteria for response is first met. Define the minimum window used to confirm response.

    In addition to the GRS that considers the totality of responses in each disease compartment, report confirmed responses individually in the skin, lymph nodes, viscera and blood. Include a flag or variable in the datasets to indicate that the responses have been confirmed.

    b. Integrated efficacy dataset: For Study 302, include an integrated efficacy dataset that includes all the patients treated on the study, with 1 patient per row. At minimum, include the list of variables below to permit adjudication of response:
        - USUBJID
        - Study
        - Treatment received
        - Date of first objective response (GRS) per IRC
        - Date of confirmed objective response (GRS) per IRC
        - Confirmed best overall response (GRS) per IRC
        - Confirmed best overall response (GRS) per investigator
        - Involved compartments at baseline
        - Response in skin (IRC)
        - Response in lymph nodes
        - Response in blood
        - Response in viscera

        DOR data: Corresponding columns for DOR per investigator and IRC including reference start date (date of first objective response), date of Censor for DOR or DOR event, and detailed reason for censor.

c. Timing of efficacy analysis: In general, all responding patients should have a minimum of 12 months of follow up for DOR, measured from the date of first objective response to the date of last objective disease assessment. Sufficient follow-up for durability of response is necessary in order to inform the treatment effect, longer-term safety, and overall benefit/risk.

4. **Safety data**

a. Narratives: Include narratives for serious and fatal AEs as well as AEs leading to treatment discontinuation and AEs of special interest (AESIs). In addition include:

- Narratives for all deaths occurring within 90 days of the last dose of E7777 irrespective of cause. For patients with progressive disease as the reported cause of death, include sufficient information to discern whether there is a potential contribution of study treatment to the outcome.

- Narratives for capillary leak syndrome and visual loss of any grade. The narratives should provide sufficient information to inform the suspected etiology, such as infection.

- For participants that discontinued E7777 for reasons other than AEs or inefficacy (such as patient decision or physician decision), we recommend to provide a table that briefly explains the reason for that decision, in order to inform the tolerability of the regimen.

To enhance navigability of narratives, within the navigation pane, provide a table of contents that organizes narratives by topic (deaths, SAE, AESIs, etc.) with hyperlinks to each case. Include a tabular summary of the subject numbers
with narratives by category and hyperlinks to those narratives, for example as presented in following table:

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

b. Laboratory analysis datasets

- Assign a unique number to each row.

- Include a baseline grade for each row, in addition to the toxicity grade for post-treatment measures.
- Include a baseline flag, and a flag for post-baseline labs obtained within the primary safety analysis window (e.g., within 30 days of last study treatment but before NALT).
- Include laboratory toxicity grading that indicates the directionality of the abnormality at baseline and post-treatment, for example for potassium, "-3" for grade 3 hypokalemia, "3" or "+3" for grade 3 hyperkalemia.
- Provide a shift column that describes the change from baseline grade to posttreatment grade. For example, for change from grade 1 hyperkalemia to grade 1 hypokalemia post-treatment, the shift column for potassium would specify "+1 to -1", indicating treatment-emergent hypokalemia.
- Include a treatment-emergent flag, with treatment-emergent defined as a new abnormality or worsening of grade from baseline. In cases having an abnormal post-baseline grade but missing baseline grade, please designate the treatment-emergent status as "unknown" rather than "no".
- An example of a corresponding table of treatment-emergent lab abnormalities is provided below. In this table, a shift from grade 3 to grade 4 would be included in the "Grade ≥ 3" column, as would a shift from grade < 3 to grade ≥3.

Treatment-emergent laboratory abnormality	Number evaluable *	All grade		Grade ≥ 3		Grade 4	
		n	%	n	%	n	%
Hematology							
Hemoglobin decrease							
Platelet decrease							
Neutrophil decrease							
Chemistry							
Potassium increase							
AST increased							
* Generally defined as the number of patients with a baseline and at least one post-baseline grade for the particular lab.							

c. ADAE datasets
   - Assign a unique number to each row
   - Ensure the full MedDRA hierarchy is provided.
   - Grouped terms: Provide a list or .xpt file of grouped preferred terms.
   - Include flags in the ISS and indication-specific AE datasets for
     - AESIs
     - treatment-emergent AEs that occur during the primary safety analysis window
     - treatment-emergent AEs that occur during the primary safety

analysis window but prior to initiation of NALT, if different from above
- AEs that occur after NALT

d. Exposure: To facilitate exposure analysis for efficacy and safety, provide a summary exposure analysis dataset for Study 302 having one patient per row that includes: flags for various populations, regimen, starting dose, duration of exposure, relative dose intensity, date of permanent study treatment discontinuation with reason, # of dose delays, date of first dose delay, # of dose reductions, date of first dose reduction, # of dose interruptions, date of first dose interruption.

e. Death summary dataset: Include an analysis dataset summarizing all reported deaths and the reasons for Study 302. Include columns time since last study treatment, whether death occurred after disease progression / relapse, whether death occurred after NALT, and the date of NALT.

Additional Statistical Comment:
For Pivotal study 302, it is unclear if the ORR "benchmarked" against a historical placebo arm is intended to employ a formal comparison against an external control. FDA would not agree with a plan to compare with the historical placebo arm in ONTAK study 11. The populations from the two studies may not be comparable due to differences in the evaluation of the study endpoints, contemporality of the data, length of follow-up, number and location of sites, and concomitant treatments allowed. In a single arm trial, FDA does not consider any inferential procedures to evaluate the trial results. FDA's efficacy evaluation will be based on the lower limit of a 95% confidence interval to exceed a clinically relevant response rate, which may be supported by information obtained from ONTAK study 11. In a single arm trial, convincing ORR will need to be supported by adequate magnitude and duration and an acceptable risk/benefit ratio.

Additional Clinical Pharmacology Comments:
The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application should be consistent with FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format". 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.

Address the following questions in the Summary of Clinical Pharmacology:
1. 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.
2. What are the dose- and exposure-response relationships for efficacy, safety and biomarkers?

3. 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?
4. What is the impact of immunogenicity on exposure, efficacy and safety?

Apply the following advice in preparing the clinical pharmacology sections of the original submission:

1. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.

2. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate.

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

4. Submit the following for the population pharmacokinetic analysis reports:
    - Standard model diagnostic plots
    - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
    - Model parameter names and units in tables.
    - Summary of the report describing the clinical application of modeling results.

Refer to the pharmacometric data and models submission guidelines.

5. Submit the following information and data to support the population pharmacokinetic analysis:
    - SAS transport files (*.xpt) for all datasets used for model development and validation
    - A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
    - Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)

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

7. 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.

8. 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.

9. 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).

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

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

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020,

contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is 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.

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

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]

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

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

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.

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[4]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid[5]

ADVANCING ONCOLOGY DECENTRALIZED TRIALS

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

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

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

/s/

YVETTE L KASAMON
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