CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215039Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 143387

MEETING PRELIMINARY COMMENTS

Novartis Pharmaceuticals Corporation
Attention: Nupur Mittal, PharmD
Senior Global Program Regulatory Manager, Regulatory Affairs, Oncology
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Mittal:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BYL719 (alpelisib).

We also refer to your correspondence, received June 1, 2021, requesting a meeting to provide the FDA the currently available top line efficacy and safety results from EPIK-P1, to obtain agreement that these data are sufficient to support filing for the proposed indication and on the slightly revised content of the NDA submission, as well as the strategy for submission under the RTOR Program.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated 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.

If you have any questions, call me at (240) 402-9558.

Sincerely,

{See appended electronic signature page}

Jacqueline Glen, MS
Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments
NDA OPQ Review and Evaluation

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: July 9, 2021, 8:00 AM – 9:00 AM, ET
Meeting Location: Teleconference

Application Number: 143387
Product Name: BYL719 (alpelisib)
Indication: PIK3CA-related overgrowth spectrum (PROS)
Sponsort Name: Novartis Pharmaceuticals Corporation
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetics Act

FDA ATTENDEES (tentative)

Harpreet Singh, Director, Division of Oncology 2 (DO2)
Amy Barone, Clinical Team Leader, DO2
Sonia Singh, Clinical Reviewer, DO2
Emily Wearne, Acting Nonclinical Team Leader, Division of Hematology/Oncology Toxicology (DHOT) Products
Sachia Khasar, Nonclinical Reviewer, DHOT
Pallavi Mishra-Kalyani, Biometrics Team Leader, Division of Biometrics V (DBV)
Arup Sinha, Biometrics Reviewer, DBV
Jeanne Fourie Zirkelbach, Clinical Pharmacology Team Leader, Division of Cancer Pharmacology II (DCP II)
Wentao Fu, Clinical Pharmacology Reviewer, DCP II
Anamitro Banerjee, Branch Chief, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)
Xing Wang, Quality Assessment Lead, ONDP, OPQ
Olen Stephens, Drug Product Reviewer, ONDP, OPQ
Donna Rivera, Associate Director for Pharmacoepidemiology, OCE
Angelica Dorantes, Branch Chief, Biopharmaceutics Branch 1 (BB1), ONDP, OPQ
Banu S. Zolnik, Biopharmaceutics Team Leader Reviewer, BB1, ONDP, OPQ
Mei Ou, Biopharmaceutics Reviewer, BB1, ONDP, OPQ
Jacqueline Glen, Regulatory Health Product Manager, Division of Regulatory Operations (DRO)

SPONSOR ATTENDEES

Oliver Jung, PhD, Global Program Head
Fabrice Branle, MD, Global Program Clinical Head
Athanasia Papadimitriou, MD, Clinical Development Medical Director
Nii Ankrah, MD, Global Medical Director
Mary Paul Lisha, MD, US Medical Director

Kevin Tianxiang Han, PhD, Sr Principle Scientist, Pharmacokinetic Sciences
Stuart Turner BPharm, MPH, Executive Director RWE & Data Science
Nathalie Fretault, MSc, Sr Director, Global Biostatistics
Antonia Ridolfi, MSc, Associate Director, Biostatistics
Paul OConnell, MSc, Associate Director Biostatistics
Sabino Vesce, MD, Global Program Safety Lead
Sheryl LeRoy, BS, Regulatory Affairs CMC Oncology Head
David Yao, PharmD, Regulatory Affairs CMC Senior Manager
Rachael Steiner-Swiat, MSc, MBA, Regulatory Affairs, Global Head, Oncology
Nina Katz, PharmD, Sr Global Program Regulatory Director
Nupur Mittal, PharmD, Sr Global Program Regulatory Manager

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for July 9, 2021 at 8:00 AM – 9:00 AM, ET between Novartis Pharmaceuticals Corporation and the Division of Oncology 2. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

BACKGROUND

On June 1, 2021, Novartis Pharmaceuticals Corporation (Novartis) submitted a Type B meeting request to discuss the planned Type 10 New Drug Application (NDA) submission for alpelisib for the treatment of adult and pediatric patients aged 2 years and older with PIK3CA-related overgrowth spectrum (PROS). Novartis seeks to submit this application based on data derived from a retrospective chart review. The purpose and primary objectives of this pre-NDA meeting are to discuss top line efficacy and safety results from EPIK-P1 and obtain agreement on revised content of the NDA submission and timeline for submission under the Real Time Oncology Review (RTOR) Program. On June 18, 2021, Novartis submitted meeting materials.

Regulatory History

Alpelisib was approved on May 24, 2019 (NDA 212526, Piqray), in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor positive (HR-positive), human epidermal growth factor receptor-2 negative (HER2-negative), PIK3CA-mutated, advanced or metastatic breast cancer, as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

On May 17, 2019, IND 143387 was submitted for the development of alpelisib in PROS. A pre-IND meeting was held on July 25, 2019, to discuss Novartis's planned NDA based on data from a retrospective study of patients with severe or life-threatening PROS who received alpelisib through compassionate use protocols. FDA stated that their decision on a marketing application and the appropriate regulatory pathway will be based on an analysis of the totality of the evidence, including an assessment of the magnitude of benefit on different endpoints, photographic or video evidence if available, the durability of the benefit, and the safety profile of the drug, given that the clinical significance of the 20% tumor volume reduction would be unclear in the absence of other supporting data.

On November 14, 2019, a teleconference was held between FDA and Novartis to discuss the status of the ongoing development program of alpelisib in PROS. FDA agreed that the NDA could be submitted through the Real-Time Oncology Review (RTOR) program.

On February 6, 2020, Novartis submitted a protocol for Study CBYL719F12002 entitled, "Retrospective chart review study of patients with PIK3CA-Related Overgrowth Spectrum (PROS) who have received alpelisib as part of an expanded access program (EPIK-P1)."

On March 4, 2020, FDA issued an Inadequate Proposed Pediatric Study Request (PPSR) letter in response to a PPSR submitted by Novartis, detailing the issues as to why FDA was unable to issue a Written Request and recommended Novartis resubmit a PPSR addressing those issues.

On April 2, 2020, a Type B pre-NDA meeting was held to discuss the content and format of the planned application for the treatment of patients age two years and older with PROS. FDA agreed to the overall proposed content of the Type 10 NDA and Novartis's plan to cross-reference Piqray (alpelisib) NDA 212526. Additionally, FDA informed Novartis that they would need to conduct fertility studies in male and female rodents and carcinogenicity studies (may be completed as postmarketing requirements), as well as submit any available pharmacology data supporting mechanism and rationale for the use of alpelisib in the proposed patient population.

Novartis has also submitted the following additional studies:

- EPIK-P2, entitled "A Phase II double-blind study with an upfront, 16-week randomized, placebo-controlled period, to assess the efficacy, safety and pharmacokinetics of alpelisib in pediatric and adult patients with PROS" (submitted May 27, 2020).
- EPIK-P3, entitled "A Phase II study to evaluate the long-term safety and efficacy of alpelisib in patients with PROS who previously participated in Study EPIK-P1" (submitted June 23, 2021).

Apelisib for the treatment of PROS has been granted:

- Breakthrough Therapy Designation (November 13, 2019)
- Orphan Drug Designation (November 18, 2019)

Nonclinical

Alpelisib is an inhibitor of phosphatidylinositol-3-kinase (PI3K) with inhibitory activity predominantly against PI3Kα. Gain-of-function mutations in the gene encoding the catalytic α-subunit of PI3K (PIK3CA) lead to activation of PI3Kα and Akt-signaling, cellular transformation, and the generation of tumors in in vitro and in vivo models. Alpelisib (Piqray) is an approved drug. Novartis plans to cross-reference the nonclinical data submitted to NDA 212526 for the PROS NDA. Consistent with the FDA advice given during the initial pre-NDA meeting on April 02, 2020, Novartis has included in the Table of Contents (Module 4), literature references and reproductive and developmental toxicity (fertility) studies to support the proposed PROS indication. In addition, FDA advised Novartis that given the unmet medical need, they could submit the results of carcinogenicity studies as post-marketing requirements. Novartis has since submitted a special protocol assessment for a rat carcinogenicity study.

Clinical

Disease Background
PIK3CA encodes the catalytic subunit, p110α, of the protein PI3K. Somatic gain-of-function mutations in the PIK3CA gene underlie the rare, mosaic disorders comprising PROS. PROS is an umbrella term encompassing the heterogenous genotypes and phenotypes observed in affected
patients and includes fibroadipose hyperplasia or overgrowth (FAO); hemihyperplasia multiple lipomatosis (HHML); and congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal (CLOVES) syndrome.

There are no curative medical therapies and no FDA-approved agents available for PROS. Current management of these disorders consists of surgical procedures such as debulking or amputation (although regrowth often occurs after resection), sclerotherapy, endovascular occlusive procedures, and pain management. Off-label use of sirolimus has also been investigated in patients with PROS; however, findings from

clinical studies have been notable for limited efficacy and frequent adverse events.

Study Supporting Planned NDA
The application is based on the results of EPIK-P1, the completed retrospective chart review study of patients with PROS who have received alpelisib as part of a compassionate use program. Fifty-seven patients (39 pediatric and 18 adult) treated in the compassionate use program at seven sites in five countries participated in EPIK-P1. Adult patients received alpelisib at a starting dose of 250 mg once daily on a continuous basis with adjustments made for toxicity (dose level -1: 200 mg/day, dose level -2: 150 mg/day). Pediatric patients (children younger than age 18) received alpelisib at a starting dose of 50 mg orally once daily with interruptions as needed for toxicity but no dose reductions permitted.

The efficacy population consists of 37 patients (26 pediatric and 11 adult) who have at least one target lesion and an imaging scan performed on the index date (date of initiation of alpelisib) or up to 24 weeks prior to the index date for at least one target lesion. The primary endpoint was defined as the proportion of patients with at least 20% reduction in the sum measurable target lesion volume (sum of 1 to 3 lesions), as assessed by a central review of imaging scans, and measured by the change between the index date and 24 weeks. Key secondary endpoints include percent change in the sum of all measurable lesion volume, duration of response, safety and tolerability of alpelisib, and assessment of changes in several variables to support clinical benefit including use of concomitant PROS-related medications, surgeries, as well as PROS clinical outcomes (e.g., functional status, PROS symptoms and complications).

EPIK-P1: Efficacy Results
Novartis reports that there were 12 responders in a subset of 32 patients from the efficacy population who had available response assessment at Week 24, yielding an overall response rate (ORR) of 37.5% (95% CI: 21.1, 56.3); considering the efficacy population of 37 patients the ORR is 32.4% (95% CI: 18.0, 49.8). Novartis states that median duration of response is not estimable; there were no progressions or deaths observed in the 12 responders at the data cut-off of March 9, 2020. Median time to censoring was 14.6 months (min: 0.03, max: 42.94). The mean percentage change in the sum of target lesion volume at Week 24 was -13.66% (min: -57.1, max: 15%) in 31 patients with imaging assessments at the index date and Week 24. Median duration of follow-up was 18.1 months (range: 4.4, 49.9). At the time of the data cut-off, 52 patients (36 pediatric and 16 adult) were still receiving alpelisib.

A summary of results for analyses of other secondary endpoints, including clinician-reported clinical outcomes are described in detail in the document “EPIK-P1 First Interpretable Results (FIR)” and summarized in Table 1 below (copied from page 3 of the same document).

Table 1: Summary of the results

Key parameter	Definition	Outcome
Proportion of patients with surgery	Number and % of patients with surgeries due to PROS progression (rescue surgeries) during the study period	Proportion (n/N): **2/57 (3.5%)**
Change in functional status	Proportion of patients with improvement in functional assessment (ECOG, Karnofsky, Lansky)	Proportion (n/N) at Week 24: **18/47 (38.3%)**
	Proportion of patients with pain reduction	Proportion (n/N) at Week 24: **31/42 (73.8%)**
Change in PROS symptoms and complications	Proportion of patients with improvement of the four most frequently reported signs and symptoms	Proportion (%) at Week 24: **Fatigue 76.2%** **Vascular malformation 78.9%** **Disseminated intravascular coagulation 55.2%** **Limb asymmetry 69.0%**
Safety	Incidence of AEs in the Full study population	(pediatric; adults; overall) **Any AEs: 79.5%; 88.9%; 82.5%** **Grade ≥ 3 AEs: 10.3%; 50.0%; 22.8%** **Serious AEs: 25.6%; 61.1%; 36.8%** **AEs leading to discontinuation: None** **Deaths: None**

EPIK-P1: Safety Results
The most common adverse events (AEs) in the full study population (n=57) were diarrhea (~16%), hyperglycemia (~12%) and aphthous ulcer (~10%). The most frequent Grade 3 or 4 AE in the full study population was cellulitis. Adverse events of special interest (AESIs) included GI toxicity, stomatitis and hyperglycemia. There were no adverse events leading to treatment discontinuation or deaths.

DISCUSSION

Clinical

1. Does the Agency agree that the results from EPIK-P1 are adequate to substantiate the efficacy and safety of alpelisib in patients with PROS, and that the results of this study support filing for regular/full approval?

   FDA Response: The results of EPIK-P1 may be adequate to support the approval of alpelisib for the treatment of patients with PROS; see Additional Comment #9 regarding the need for additional information about duration of response. Our decision on a marketing application and the appropriate regulatory pathway will be based on an analysis of the totality of the evidence, including an assessment of the magnitude of benefit on different endpoints, photographic or video evidence, the durability of the benefit, and the safety profile of the product (given that the clinical significance of the 20% lesion volume reduction would be unclear in the absence of other supporting data).

As previously stated, FDA also notes that there are several aspects of drug development (e.g., pharmacokinetic and pharmacodynamic assessment to determine appropriate dosing in pediatric and adult patients; effectiveness in patients with a broad spectrum of disease, etc.) that will not have been sufficiently addressed at the time of NDA submission and may require post-marketing requirements or commitments.

Also, FDA does not agree to proposed primary complete case analysis which excludes patients without a response assessment in the pre-specified timeframe from the primary analysis population. All 37 patients should be included in the denominator for the calculation of response rate, and those without a response assessment in the pre-specified window of assessment should be considered non-responders.

Regulatory

2. Does the Agency agree that the slightly revised content of the Type 10 NDA as outlined in the proposed electronic Common Technical Document (eCTD) table of contents (TOC) constitutes a complete application?

FDA Response: FDA agrees that, in general, the proposed revised content of the Type 10 NDA as outlined in the meeting materials is acceptable; however, we have the following comments:

a. Include an Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) in the eCTD. In accordance with the regulations for NDA submissions (21 CFR 314.50(d)(5)(v) and 21 CFR 314.50(d)(5)(vi)), the ISE and ISS are required in applications submitted to the FDA; however, the ISE and ISS may refer to the Clinical Overview. You may also refer to "Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document" located at https://www.fda.gov/downloads/drugs/guidances/ucm136174.pdf

b. In reference to Appendix 1 to the Clinical Overview (Module 5.3.5.3), in addition to serious adverse events and deaths, include treatment discontinuations and any AESIs (if identified) in the line-listing narratives and a tabular summary. Please clarify the data cut-off for safety data for the NDA, as the listing of Module 5 content suggests this information will be provided up to February 28, 2021, but the data cut-off is elsewhere listed as March 9, 2020.

c. Regarding Module 5.3.5.4:

i. Provide a listing of the specific datasets and the data elements that will be included in the complete ADaM dataset package.

ii. Confirm that photographs and videos provided will be clearly labeled with the patient identifier, timepoint in treatment course, and collated in a series for each patient to permit easy access and identification.

iii. For responders (n=12), please provide a summary in tabular form including the extent of disease at baseline and throughout treatment (labeled with respective timepoints), reference to any associated photographs or videos (file names), and a list of relevant clinical outcomes with reference to the source documentation.

3. Does the Agency agree with the slightly revised content and timeline of the batches to be submitted under the RTOR Program?

FDA Response: Regarding the revised content, please refer to our response to Question 2. FDA does not object to the proposed timeline of the batches to be submitted under the RTOR Program; however, use of the Product Quality Assessment Aid, and earlier submission of Module 3 components (see Additional Comment #8) and the draft labeling will facilitate review.

4. Does the Agency agree with the following justification to be submitted within the Type 10 NDA in support of a request for Priority Review?

FDA Response: We acknowledge that PROS is a serious condition with significant unmet need, as well as the justification you have provided in support of a request for Priority Review; however, a determination regarding Priority Review will be made by the review team within 60 days of the receipt of the application.

5. Does the Agency agree that the safety of alpelisib in PROS can be appropriately managed via product labeling and routine pharmacovigilance activities and that a Risk Evaluation and Mitigation Strategies (REMS) is not necessary?

FDA Response: It is premature for us to comment on whether the safety of alpelisib in PROS can be managed via product labeling and routine pharmacovigilance activities. A decision regarding whether Risk Evaluation and Mitigation Strategies (REMS) will be required will be made during the review of the application.

6. Does the FDA agree that convening an Oncologic Drug Advisory Committee (ODAC) to discuss the forthcoming Type 10 NDA is not warranted given the structured and robust manner in which the data were abstracted in EPIK-P1, the

totality of evidence supporting clinical benefit, as well as the well-established and manageable safety profile of alpelisib?

FDA Response: Based on the currently available data provided, at this time we do not foresee the need for an Oncologic Drug Advisory Committee (ODAC) to discuss the forthcoming Type 10 NDA; however, we reserve the right to involve an advisory committee to review and evaluate any data concerning the safety and effectiveness of marketed and investigational human drug products for use in the treatment of cancer at any stage of a medical product review process as well as after a product has been approved and marketed.

Quality

7. In EPIK-P1, 22.2% (4/18) of adult patients had at least one dose reduction and 25.6% (10/39) of pediatric patients had at least one dose increase from their respective starting doses. Therefore, Novartis plans to seek approval of a 125 mg film-coated tablet to facilitate dose modifications.

   Based on the above, does the Agency agree with the following:

   a. The approach to submit a bio-waiver request for the proposed commercial alpelisib 125 mg film-coated tablet in the Type 10 NDA?

   FDA Response: We agree with your proposal of requesting a biowaiver for the proposed 125 mg strength of alpelisib tablets. Please note that our decision on granting the biowaiver for this strength will be made during the NDA's review.

   b. That the drug product registration stability bracketing proposal for the 125 mg strength is acceptable to support the Type 10 NDA submission and the shelf-life?

   FDA Response: The bracketing proposal for the 125 mg strength appears acceptable. Determination of shelf life for all product strengths will be determined during NDA review in the context of all batch, stability, and bridging data available at that time.

Additional Comments:

CMC

8. The CMC modules will be submitted in the last wave of submissions. To facilitate a faster review, FDA requests the use of the Product Quality Assessment Aid attached to this communication. If possible, components of Module 3 that are complete (for example, most of m3 except for 3.2.S.7 and 3.2.P.8) could be

submitted ahead of the intended schedule. You may submit a submission plan for CMC sections to the Agency for an agreement.


NDA OPQ
Assessment Aid (RTC

Clinical

9. Submit a summary of duration of response for responding patients in EPIK-P1, including the median, percentage of patients with response duration of 6 months or greater, 12 months or greater, and provide the corresponding cut-off date. You may provide a per-patient listing of duration of response and indicate which patients have ongoing responses.

10. In your application, provide sensitivity analyses of the primary endpoint of response rate using the previously defined scan windows for the baseline scan (up to 12 weeks prior to index date) and the 24-week response assessment (between 20 and 28 weeks).

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our June 24, 2021 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 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]

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

FDARA REQUIREMENTS

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

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

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

PRESCRIBING INFORMATION

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

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

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and

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

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.[6]

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 *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[7]

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*

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

Specifications.[8]

ONCOLOGY PILOT PROJECTS

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

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

- Assessment Aid[10]

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

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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/

JACQUELINE J GLEN
07/06/2021 04:20:03 PM

IND 143387

MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Nupur Mittal, Pharm.D.
Senior Global Program Regulatory Manager, Regulatory Affairs, Oncology
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Mittal:[1]

Please refer to your investigational new drug application (IND) file for alpelisib.

We also refer to the teleconference between representatives of your firm and the FDA on April 2, 2020. The purpose of the meeting was to obtain agreement from the Agency on the strategy of the planned NDA submission, including the content and format of the dossier.

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, please call me at (240) 402-6397.

Sincerely,

{See appended electronic signature page}

Kelie Reece, Ph.D.
Regulatory Health Project Manager
Division of Oncology 2
Division of Regulatory Operations for Oncologic Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- "Response to preliminary feedback from FDA Final.pdf"

[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-NDA
Meeting Date and Time:	April 2, 2020, 3:00 PM – 4:00 PM
Meeting Location:	Teleconference
Application Number:	IND 143387
Product Name:	Alpelisib
Proposed Indication:	PIK3CA-related overgrowth spectrum
Sponsor Name:	Novartis Pharmaceuticals Corporation
Meeting Chair:	Suzanne Demko, P.A.-C.
Meeting Recorder:	Kelie Reece, Ph.D.

FDA ATTENDEES

Gregory Reaman, M.D.	Acting Associate Director, Pediatric Oncology, OCE
Harpreet Singh, M.D.	Acting Division Director, DO2/OOD
Suzanne Demko, P.A.-C.	Clinical Team Leader, DO2/OOD
Sonia Singh, M.D.	Clinical Reviewer, DO2/OOD
Amy Barone, M.D.	Clinical Reviewer, DO2/OOD
Denise Casey, M.D.	Clinical Reviewer, DO2/OOD
Sujay Shan, M.D.	Clinical Fellow, OND/OOD
Whitney Helms, Ph.D.	Nonclinical Team Leader, DHOT/OOD
Sachia Khasar, Ph.D.	Nonclinical Reviewer, DHOT/OOD
Pallavi Mishra-Kalyani, Ph.D.	Statistical Team Leader, DBV/OB
Arup Sinha, Ph.D.	Statistical Reviewer, DBV/OB
Wentao Fu, Ph.D.	Clinical Pharmacology Reviewer, DCPV/OCP
Ramesh Raghavachari, Ph.D.	Chief, Branch I, DPMAI/OLDP
Xing Wang, Ph.D.	Product Quality Team Leader, DNDPI/ONDP
Kelie Reece, Ph.D.	Regulatory Health Project Manager, DRO-OD/ORO

SPONSOR ATTENDEES

Oliver Jung, Ph.D.	Global Program Head
Mary Lisha Paul, M.D.	Associate Medical Director
Fabrice Branle, M.D.	Sr. Clinical Development Medical Director
Nathalie Fretault, M.Sc.	Sr. Director, Global Biostatistics
John Robinson, Ph.D.	Global Therapeutic Area Lead-Oncology Reg Affairs
Nina Katz, Pharm.D.	Global Program Regulatory Director
Nupur Mittal, Pharm.D.	Sr. Global Program Regulatory Manager

BACKGROUND

On January 30, 2020, Novartis Pharmaceuticals Corporation (Novartis) submitted a Type B meeting request to discuss the strategy of the planned New Drug Application (NDA) submission for alpelisib for the treatment of PIK3CA-related overgrowth spectrum (PROS). Novartis seeks to submit this NDA based on data derived from a retrospective chart review that will serve as the basis for regular approval. The primary objective of the meeting is to obtain agreement on the content and format of the application for the proposed treatment of patients age two years and older with PROS.

Regulatory History

Alpelisib was initially developed under IND 107078, submitted on May 21, 2010, for the treatment of advanced solid tumors. This IND includes two ongoing studies (CBYL719X2101 and CBYL719Z2102).

On December 18, 2018, Novartis submitted NDA 212526 to the Division of Oncology Products 1 (DOP1). NDA 212526 was granted priority review through FDA's Real Time Oncology Review (RTOR) pilot program.

Alpelisib was approved under the proprietary name of Piqray on May 24, 2019, in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor positive (HR-positive), human epidermal growth factor receptor-2 negative (HER2-negative), PIK3CA-mutated, advanced or metastatic breast cancer, as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

On May 17, 2019, IND 143387 was submitted for the development of alpelisib in PROS. A pre-IND meeting was held on July 25, 2019, to discuss Novartis's planned NDA based on data from a retrospective study of patients with severe or life-threatening PROS who received alpelisib through compassionate use protocols. Regarding the chart review, FDA encouraged Novartis to collect all data to support their position that alpelisib may provide benefit to patients including direct or indirect (e.g., imaging) effects. FDA stated that their decision on a marketing application and the appropriate regulatory pathway will be based on an analysis of the totality of the evidence, including an assessment of the magnitude of benefit on different endpoints, photographic or video evidence if available, the durability of the benefit, and the safety profile of the drug, given that the clinical significant of the 20% tumor volume reduction would be unclear in the absence of other supporting data.

On November 13, 2019, alpelisib was granted Breakthrough Therapy Designation (BTD) for the treatment of patients with PROS.

On November 14, 2019, a teleconference was held between FDA and Novartis to discuss the status of the ongoing development program of alpelisib in PROS and to assess whether FDA can help facilitate Novartis's planned NDA submission given the

unmet need of the selected patient population. Novartis briefed FDA on their timeline of planned activities. Novartis noted that all prospective sites had agreed to participate in the retrospective chart review, and that they were seeking IRB approval from study sites and obtaining consent from patients eligible to participate in the study. Data collection was scheduled to begin in March 2020. FDA offered to review any submitted protocols, electronic case report forms (eCRF) and statistical analysis plans (SAP) as expeditiously as possible. FDA was also receptive to real-time data entry validation and cleaning such that Novartis could send study data to FDA in batches and agreed that this NDA could be submitted through the Real-Time Oncology Review (RTOR) program.

On November 18, 2019, alpelisib was granted Orphan Drug Designation for the treatment of PROS.

On November 27, 2019, Novartis submitted a request for proprietary name review for the proposed primary name VIJOICE.

On November 27, 2019, Novartis submitted a draft protocol for Study CBYL719F12002 entitled, “Retrospective chart review study of patients with PIK3CA-Related Overgrowth Spectrum (PROS) who have received alpelisib as part of an expanded access program (EPIK-P1).”

On February 20, 2020, the alpelisib in PROS development program was discussed in a monthly pediatric TCON held amongst health regulatory agencies including FDA (b) (4) (b) (4). Potential issues relating to the NDA submission (e.g., lack of pharmacokinetic data in children) and the design of the planned prospective study protocol were addressed. A common commentary capturing the salient points of this TCON and recommendations was subsequently sent to Novartis on March 17, 2020.

Chemistry, Manufacturing and Controls (CMC)

The PROS proposed commercial 50 mg and 200 mg FCT formulations have been slightly modified from the FDA approved Piqray (alpelisib) 50 mg and 200 mg film-coated tablet formulations for product differentiation purposes while retaining the same overall chemical composition (no change on Table core). Novartis is transferring the bulk manufacture of Piqray (alpelisib) to a new facility within the registered manufacturing site of Novartis Pharma Stein AG, Switzerland. The new equipment is of the same SUPAC class and sub-class. However, considering the higher automation grade and slightly different capacity of the equipment, process improvements and adaptations are to be submitted to NDA 212526 as a Prior Approval Supplement (PAS) and subsequently will be implemented for both Piqray (alpelisib) and the PROS proposed commercial FCTs.

Nonclinical

Alpelisib is an inhibitor of phosphatidylinositol-3-kinase (PI3K) with inhibitory activity predominantly against PI3Kα. Gain-of-function mutations in the gene encoding the

catalytic α-subunit of PI3K (PIK3CA) lead to activation of PI3Kα and Akt-signaling, cellular transformation and the generation of tumors in in vitro and in vivo models. Alpelisib (PIQRAY) is an approved drug. Novartis does not plan to conduct any new nonclinical studies to support the proposed indication and will cross-reference the nonclinical data submitted to NDA 212526.

Clinical

Disease Background

PI3K/Akt and the mammalian target of rapamycin (mTOR) signaling pathways are crucial to cell growth and survival. Aberrant activation of the PI3K/Akt/mTOR pathway leads to downstream effects including competitive growth advantage and angiogenesis, thereby promoting tumor development and resistance to treatment.

PIK3CA encodes the catalytic subunit, p110α, of the protein PI3K. Somatic gain-of-function mutations in the PIK3CA gene underlie the mosaic disorders comprising PI3KCA-related overgrowth spectrum (PROS). PROS is an umbrella term encompassing the heterogenous genotypes and phenotypes observed in affected patients and includes fibroadipose hyperplasia or overgrowth (FAO); hemihyperplasia multiple lipomatosis (HHML); and congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal (CLOVES) syndrome.

The incidence of PROS is estimated to be approximately 1 in 70,000 people. Clinical diagnostic criteria consist of segmental overgrowth (e.g., adipose, muscle, skeletal or nerve tissue), vascular malformations (e.g., capillary, venous, arteriovenous malformation, lymphatic), and epidermal nevi. PROS is often associated with congenital or early childhood-onset overgrowth, thus making it a predominantly pediatric disease, but in some patients may continue as progressive overgrowth into adulthood.

The known and emerging clinical entities associated with somatic PIK3CA mutations can range from localized overgrowth, such as macrodactyly, to large and potentially life-threatening overgrowth that may impact major vessels and critical organs. PROS can cause renal or cardiac dysfunction, pain, functional impairment (e.g., walking or swallowing) or other complications, including recurrent superficial infections, thromboembolism, pulmonary hypertension and hemorrhage, that may be debilitating and cause early mortality.

There are no curative medical therapies and no FDA-approved agents available for PROS. Current management of these disorders consists of surgical procedures such as debulking or amputation (although regrowth often occurs after resection), sclerotherapy, endovascular occlusive procedures, and pain management. Off-label use of sirolimus has also been investigated in patients with PROS; however, findings from clinical studies have been notable for limited efficacy and frequent adverse events.

Initial Clinical Experience: Alpelisib in PROS

As described by Venot et al. (2018) in Nature, alpelisib has been studied in a postnatal mouse model of PROS/CLOVES syndrome that partially recapitulates the human disease. The study drug was reported as being effective in preventing and improving disease-related organ dysfunction observed in these animals. Subsequently, nineteen patients (15 children and 4 adults) with severe or life-threatening PROS received alpelisib via an expanded access program in France. In the same publication, these patients were reported to have improvement in disease symptoms and minimal side effects while receiving the study drug.

The investigators first administered alpelisib to two patients (one adult at a dose of 250 mg daily, and a 9-year-old girl at a dose of 50 mg daily), who were suffering from severe clinical manifestations of PROS/CLOVES syndrome and had life-threatening complications, under compassionate care protocols. These patients had progressed after prior debulking surgeries and medical therapies including rapamycin. Both experienced progressive reduction in tumor size that was associated with a variety of clinical benefits (e.g., improved heart and renal function, and reversal of scoliosis).

Thereafter, 17 additional patients (14 children and 3 adults) with gain-of-function mutations in the PIK3CA gene, who had life-threatening complications and/or were scheduled for debulking surgery, received alpelisib. As assessed by MRI, 64.7% of patients (11/17; 95% confidence interval [CI]: 38.3, 85.8) experienced ≥ 20% reduction in volume of the target lesion at 3 months; and 88.2% of patients (15/17; 95% CI: 63.6, 98.5) had ≥ 20% reduction in volume at 6 months. In terms of pediatric patients, 85.7% (12/14; 95% CI: 57.2, 98.2) experienced ≥ 20% reduction in a target lesion by 6 months. Overall, radiological response was observed in all patients with mean volume of target lesions decreased by 27.2 ± 14.6% and 37.8 ± 16.3% after 90 days and 180 days, respectively.

In terms of safety findings, the investigators acknowledged a short follow-up period and reported discrete mouth ulcerations (grade 1) which regressed spontaneously in three patients, and transient hyperglycemia in two patients. There was no reported organ toxicity associated with alpelisib as assed by heart, liver, kidney function, and blood testing.

Managed Access Program (MAP)

Novartis issued a global MAP to allow patients with PROS to receive alpelisib. A clinical protocol that serves as a guidance document for the treatment and monitoring of patients under this MAP was submitted to IND 107078 in January 2019. As of January 2020, 103 patients have been approved to receive alpelisib for PROS and 76 have received such treatment for this investigational indication.

Retrospective Chart Review Study

Novartis is conducting a medical chart review (Study CBYL719F12002 [EPIK-P1]) of patients 2 years of age and older who have received alpelisib through expanded access

programs worldwide. Approximately 65 patients of the 103 patients who have received approval under the MAP meet the inclusion criteria of EPIK-P1.
The primary objective of this study is to describe the effectiveness of alpelisib as measured by the percentage of patients who have at least 20% reduction in measurable target lesion volume (sum of 1 to 3 lesions) at a scheduled time point of approximately 24 weeks (+/- 4 weeks). Imaging will be reviewed by a central panel of radiologists. The secondary objectives of this retrospective study are to evaluate safety and tolerability of alpelisib, and to assess changes in the following: the sum of measurable target lesion volume, the sum of all measurable (target and non-target) lesion volume, type of medications used and non-drug interventions (e.g., concomitant PROS-related medications, PROS-related surgeries) implemented and to document duration of treatment/response, PROS symptoms and complications (e.g., chronic bleeding, pain), functional status (e.g., work/school/pre-school attendance, mobility), health resource use (e.g., emergency room visits, hospitalizations), and clinical assessments (e.g., laboratory tests, vital signs).

The selected patient population will consist of pediatric and adult patients who have a confirmed diagnosis of PROS, a documented mutation in the PIK3CA gene, and were described by the treating physician as having severe or life-threatening disease manifestations that necessitated treatment. Patients will have consented to participate in the study (pediatric patients will have a parent/guardian provide consent) as required by local regulations, been treated with at least one dose of alpelisib at a MAP site and have an available medical chart history for review.

Pediatric Strategy
Novartis submitted a PPSR for alpelisib on November 27, 2019, in order to obtain a Written Request. Within the PPSR, Novartis proposes to conduct and submit data from the retrospective chart review study (EPIK-P1) and well as a prospective phase II study (CBYL719F12201, EPIK-P2) in patients with PRO (b) (4) The studies outlined in the PPSR are also included in a Pediatric Investigational Plan (PIP) application that was submitted to EMA on November 29, 2019.

FDA sent Preliminary Comments to Novartis on February 13, 2020.

DISCUSSION

Regulatory

1. *Does the Agency agree with the content of the Type 10 NDA as outlined in the draft eCTD table of contents (TOC)?*

   FDA Response: The overall content of the Type 10 NDA as outlined in the draft eCTD TOC (Table 2-1 on page 9 of the briefing package) appears acceptable; however, Module 4 (Nonclinical) may not be absent from the application. Please cross-reference the original NDA as needed. Please refer to FDA's response to

Question 8 for more information. FDA requests that the case report forms provided in module 5.3.5.4 be submitted in PDF format and include relevant photography and videography for review by the clinical team, and that other patient experience data such as natural history studies in PROS be submitted in this section as well.

Further, FDA acknowledges your plan to seek regular approval for alpelisib for the proposed indication of adult and pediatric patients aged 2 years and older for the treatment of PROS; however, there are several aspects of drug development (e.g., pharmacokinetic and pharmacodynamic assessment to determine appropriate dosing in pediatric and adult patients; effectiveness in patients with a broad spectrum of disease, etc.) that will not have been sufficiently addressed at the time of NDA submission. FDA reiterates that the decision on a marketing application, the appropriate regulatory pathway, and the final indication will depend on an analysis of the totality of the evidence (i.e., safety and efficacy data), including an assessment of the magnitude of clinical benefit, the durability of the benefit and the safety profile of the product.

Novartis' Response received via email 03/31/20: Novartis confirms that Module 4 will be cross-referenced to NDA 212526 as applicable. In addition, Novartis will include the Venot et al 2018 publication in Module 4.3 (Literature References) to support the mechanism of alpelisib in PROS as well as the rationale for its use (as per FDA's preliminary comments in response to Question 8).

Novartis confirms that the CRFs provided in Module 5.3.5.4 will be submitted in PDF format and will be accompanied by available photographs and videos.

Novartis wishes to seek clarification from the Agency on the preliminary comment above regarding the inclusion of "other patient experience data such as natural history studies in PROS" in Module 5.3.5.4.

As previously communicated to the Agency, the best supportive care (BSC) cohort (which was originally included to assist with ascertaining the natural history of PROS) was excluded from Study BYL719F12002 (EPIK-P1) after further investigation of feasibility. The inclusion of a BSC cohort within the study would have prolonged the overall study timelines and would have delayed the submission to the FDA. Moreover, since the protocol for Study BYL719F12002 (EPIK-P1) was finalized (submitted to FDA on 06-Feb-2020; Serial # 0018) following FDA review (FDA comments received on 20-Dec-2019 and 21-Jan-2020), it was Novartis' understanding that the exclusion of the BSC cohort was accepted by the FDA.

Nonetheless, it is worth noting that information on the natural history of the disease will still be captured in Study BYL719F12002 (EPIK-P1) via collection of the following:

- Six (6)-month history of a patient's disease captured during the pre-index period
- Information on prior surgeries and PROS medications captured from the time of each patient's diagnosis

This information will be summarized within the Clinical Study Report and the Clinical Overview.

In addition, Novartis is exploring opportunities to further characterize the natural history of PROS (e.g., via a non-interventional study and/or via a registry). However, no additional information on the natural history of PROS will be available in time for the original Type 10 NDA submission.

Lastly, information on the natural course of the disease will also be collected in the prospective phase II study (EPIK-P2) in the context of the randomized, placebo-controlled period.

Discussion during the Meeting: FDA clarified that patient experience data available, such as natural history study in PROS separate from the retrospective study, could be submitted to Module 5, but this is not a requirement.

FDA acknowledged Novartis' plan to submit a Type 10 NDA. FDA finds this acceptable as alpelisib is an approved drug, and Novartis will be seeking a new indication as well as proprietary name that are distinct from the original NDA.

2. *Does the Agency agree with Novartis' proposal for submission of the NDA components?*

FDA Response: Yes, FDA agrees with your proposal to submit a CDISC-compliant NDA under the RTOR program. Regarding the non-CDISC datasets and patient profiles proposed for submission after database lock and prior to submission of batch 1 under RTOR, FDA will accept this data for early familiarization with study patients and acknowledges that Novartis does not intend to perform any analyses on the non-CDISC datasets.

Novartis' Response received via email 03/31/20: Novartis is actively working to meet the submission timelines outlined in the Type B briefing package. However, we are aware that sites may experience delays in data collection due to the COVID-19 pandemic. As such, Novartis will apprise the Agency of updated timelines once they are available.

Novartis appreciates that FDA will accept the non-CDISC datasets and patient profiles after the EPIK-P1 database lock and prior to submission of batch 1 of the NDA under the RTOR pilot program to familiarize themselves with the study patients. Please note that Novartis plans to submit these components to IND 143387. No further discussion is needed.

Discussion during the Meeting: There was no discussion of this item during the meeting.

3. *Does the Agency agree with Novartis' proposal to cross-reference Piqray (alpelisib) NDA 212526?*

FDA Response: Yes, FDA agrees with the proposal to cross-reference Piqray (alpelisib) NDA 212526. For all sections of this application that will refer to the original NDA, provide appropriate cross references with live links for ease of access.

Novartis' Response received via email 03/31/20: Novartis acknowledges the Agency's feedback. Since Novartis is planning to submit a Type 10 NDA, our understanding is that direct linkage to NDA 212526 will not be possible. However, Novartis intends to add live links where possible that will navigate the Reviewers to a detailed cross reference document in Module 1.4.4 (Cross-reference to previously submitted information). This detailed cross reference document will contain all relevant information to facilitate Reviewer access to relevant documents previously submitted. No further discussion is needed.

Discussion during the Meeting: There was no discussion of this item during the meeting.

4. *Does the Agency agree to an exemption for pediatric studies?*

FDA Response: Yes, FDA agrees with the plan to request a waiver of pediatric studies as part of the planned NDA, as long as the complete submission is before August 18, 2020.

Novartis' Response received via email 03/31/20: Novartis wishes to seek clarification from the Agency on the preliminary comment above. As agreed upon with the FDA during the 25-July-2019 Type B meeting, Novartis' understanding is that the Type 10 NDA being proposed will not be considered to be an "original" application and, therefore, would not be subject to FDARA PREA despite our plans to submit the complete NDA after it goes into effect on 18-Aug-2020. As such, Novartis kindly requests that the Agency confirms that our Type 10 NDA, which is covered by an orphan drug designation (designation request # DRU-2019-7108), will be considered under 21 CFR 314.55 which indicates that drugs for which orphan drug designation has been granted are exempt from the required assessment of safety and effectiveness of the drug product in the corresponding pediatric subpopulation.

Furthermore, given the significant unmet medical need in patients with PROS and the potential for alpelisib to address this need, Novartis would like to move forward with submitting the proposed NDA for Agency review as soon as possible and while the PPSR/draft Written Request is under Agency review.

Novartis is seeking FDA's confirmation that initiation of our submission under the RTOR pilot program will not preclude Novartis from qualifying for pediatric exclusivity. Specifically, Novartis is seeking FDA guidance as to the exact timeframe by which the Written Request must be issued in order for Novartis to be eligible for qualifying for pediatric exclusivity. For example:

- Is it acceptable for Novartis to initiate the proposed NDA submission while the PPSR/draft Written request is under review?
- Can the Agency confirm that Novartis would be eligible for qualifying for pediatric exclusivity as long as the Written Request is issued prior to NDA approval?

Discussion during the Meeting: FDA stated that the waiver request should be made at the time of the application submission and cannot be agreed to in advance; however, FDA acknowledges that alpelisib has Orphan Drug Designation for the treatment of PROS and that a Type 10 NDA would be exempt from PREA requirements and not subject to the amended FDARA regulations.

Regarding initiation of the proposed NDA submission, while the PPSR is under review, FDA stated that any data that are submitted to FDA prior to issuance of the Written Request will not be able to be included in the Written Request. FDA advised Novartis that a Written Request that has been issued by FDA prior to submission of an application, if any data in that application will also be required data in the Written Request. Novartis proposed a teleconference prior to submission of a revised PPSR to expedite review, and FDA acknowledged the unmet need of patients with PROS and indicated that a TCON is reasonable and can be arranged.

Regarding exclusivity, FDA stated it is premature to discuss pediatric exclusivity at this time; the decision on exclusivity will be made at the time of final submission of complete study reports as outlined in the Written Request and only if all the terms of the Written Request have been met.

5. *Does the Agency agree that a user fee waiver is acceptable?*

FDA Response: Yes, FDA agrees that a user fee waiver is acceptable.

Novartis' Response received via email 03/31/20: Novartis acknowledges the Agency's agreement. No further discussion is needed.

Discussion during the Meeting: There was no discussion of this item during the meeting.

6. *Given the fact that the NDA is based on a retrospective chart review study (EPIK-P1) and there will be no prospective follow-up of the patients as part of that study, does the Agency agree that a Safety Update for the alpelisib PROS NDA*

is not required and can be waived?

FDA Response: Yes, FDA agrees that because the data for this NDA will be from abstracted medical records and not a traditional clinical trial, a Safety Update for this NDA can be waived.

Novartis' Response received via email 03/31/20: Novartis acknowledges the Agency's feedback. No further discussion is needed.

Discussion during the Meeting: There was no discussion of this item during the meeting.

CMC

7. *Does the Agency agree that the drug product registration stability data proposal is acceptable for the NDA submission and to support the shelf-life?*

FDA Response: The drug product registration stability data proposal for the NDA submission appears reasonable according to the meeting briefing book. However, shelf-life of the PROS drug product will be determined during the NDA review, based on the overall assessment of drug product release and stability data submitted, facility changes and manufacturing process modifications.

Novartis' Response received via email 03/31/20: Novartis acknowledges the Agency's feedback. No further discussion is needed.

Discussion during the Meeting: There was no discussion of this item during the meeting.

Nonclinical

8. *Novartis believes that the nonclinical package previously submitted to Piqray (alpelisib) NDA 212526 is complete and supports the registration of alpelisib in patients with PROS. Does the Agency agree?*

FDA Response: No, we do not agree that the nonclinical package previously submitted to NDA 212526 for Piqray (alpelisib) is complete and supports the registration of alpelisib in patients with PROS. In addition to the data in the cross-referenced NDA you will need to conduct a fertility studies in male and female rodents to support (b) (4) (b) (4). Also, you will need to conduct carcinogenicity studies to support (b) (4); however, you can complete these studies as post-marketing requirements. requirements. Finally, submit any available pharmacology data (or references such as Venot et al 2018) that help support the mechanism and rationale for the use of alpelisib in the proposed patient

population.

Novartis' Response received via email 03/31/20: Novartis agrees to conduct the requested fertility and carcinogenicity studies as post-marketing requirements. Novartis will include the Venot et al 2018 publication in Module 4.3 (Literature References) to support the mechanism of alpelisib in PROS as well as the rationale for its use in the proposed patient population. No further discussion is needed.

Discussion during the Meeting: FDA clarified that the fertility studies were expected as a part of the original NDA submission but that given the timing and unmet medical need, FDA would accept these studies as postmarketing requirements, as proposed by Novartis. FDA requested clarification on timelines for when fertility studies could be initiated.

Clinical Pharmacology

9. *Novartis believes that the clinical pharmacology package previously submitted to Piqray (alpelisib) NDA 212526 is complete and supports the registration of alpelisib in patients with PROS. Does the Agency agree?*

FDA Response: Additional data or clinical pharmacology studies may be needed based on review of the proposed initial NDA for the PROS indication.

Novartis' Response received via email 03/31/20: Novartis acknowledges the Agency's feedback. No further discussion is needed.

Discussion during the Meeting: There was no discussion of this item during the meeting.

Clinical

10. *Does the Agency agree with Novartis' proposal to limit clinical summary documents to a Clinical Overview only?*

FDA Response: FDA acknowledges that this NDA is based on data from a single retrospective study. The proposal to limit clinical summary documents to a Clinical Overview only is acceptable since it will include information typically found in a Summary of Clinical Safety and a Summary of Clinical Efficacy. Further, FDA agrees that an ISS and ISE is not required for this application.

Novartis' Response received via email 03/31/20: Novartis acknowledges the Agency's feedback. No further discussion is needed.
Discussion during the Meeting: There was no discussion of this item during the meeting.

11. *Does the Agency agree with Novartis' proposal for submission of narratives and CRFs?*

FDA Response: FDA agrees with the proposal for submission of narratives and CRFs and requests that Novartis also provide safety narratives for patients who experienced death within 30 days of the last dose of alpelisib.

Novartis' Response received via email 03/31/20: Novartis acknowledges the Agency's feedback and plans to provide safety narratives for patients who experienced death within 30 days of the last dose of alpelisib (if any). No further discussion is needed.

Discussion during the Meeting: There was no discussion of this item during the meeting.

12. *Does the Agency agree with Novartis' proposal for the submission of electronic datasets and analysis programs?*

FDA Response: Please include in your submission (a) SAS programs that produced all efficacy results, (b) all raw as well as derived variables in .xpt format, (c) SAS programs by which the derived variables were produced from the raw variables, for example, the SAS program(s) for deriving response status (such as CR, PR SD, PD) from original individual tumor measurements.

Novartis' Response received via email 03/31/20: Novartis acknowledges the Agency's feedback and will include the following in our submission as requested:

a. SAS programs that produced all efficacy results
b. all raw as well as derived variables in .xpt format
c. SAS programs by which the derived variables were produced from the raw variables, for example, the SAS program(s) for deriving response status (such as CR, PR SD, PD) from original individual tumor measurements.

No further discussion is needed.

Discussion during the Meeting: There was no discussion of this item during the meeting.

ADDITIONAL COMMENTS

Statistics

13. In reference to the Statistical Analysis Plan (SAP) submitted to IND 143387 on February 20, 2020 for EPIK-P1, FDA has the following comments:

a. Please clarify the calculation of duration of response (DOR) in the event of a death. Page 14 of the SAP states that the end date for DOR is "the date of the first documented disease progression or death due to underlying disease." Any death, regardless of cause, should be considered as an event in the calculation of DOR.

Novartis' Response received via email 03/31/20: Novartis confirms that any death, regardless of cause, will be considered as an event in the calculation of DOR. The statistical analysis plan will be amended accordingly.

Discussion during the Meeting: There was no discussion of this item during the meeting.

b. FDA considers the analysis using imputed data for those assessments that are missing at 24 weeks post index date to be sensitivity analyses, as the missing at random assumption cannot be verified. The primary analysis should be a complete case analysis.

Novartis' Response received via email 03/31/20: Novartis wishes to seek clarification from the Agency on the preliminary comment above.

Reference is made to:

- The draft Study BYL719F12002 Statistical Analysis Plan (SAP) submitted to the FDA on 09-Dec-2019 (Serial No. 0012) for review and comment.
- FDA's email dated 02-Jan-2020 containing a comment on the SAP regarding the planned primary analysis that includes imputation of missing data by a missing at random assumption.
- Novartis' response to above FDA comment submitted on 23-Jan-2020 (Serial No. 0016)
- FDA's email dated 04-Feb-2020 acknowledging the receipt of the response submitted on 23-Jan-2020 regarding the missing data and advising that Novartis include procedures to minimize missing data and assessments.

The primary objective of EPIK-P1 is to describe the efficacy of alpelisib as measured by the proportion of patients with response at week 24. The aim is to quantify the effect of alpelisib and to provide evidence of efficacy. In order to ensure an unbiased estimation of the treatment effect, the primary analysis is based on the efficacy set (e.g., all patients with an imaging scan performed on the index date for at least one target lesion).

A preliminary estimation based on feasibility assessment showed that the percentage of patients with missing data for the primary endpoint is

expected to be low and linked to medical practice at some participating sites. The assumption of missing at random (MAR) therefore appears appropriate. The partially observed data for these patients, i.e., the MRI scans at baseline and at week 48 as well as covariates such as age, are planned to be used to inform the unmeasured week 24 outcome while accounting for the added uncertainty due to missing data.

The complete case analysis will be performed as a sensitivity analysis to investigate the robustness of the primary analysis.

Novartis believes that the proposed approach to imputing missing information for the primary analysis is appropriate, and that the pre-planned sensitivities analyses (including the complete case analysis) will ensure a robust interpretation of the primary efficacy measure in Study CBYL719F12002 (EPIK-P1).

Discussion during the Meeting: Novartis clarified reasons for potential existing data for patients considered non-responders and those missing due to age. Novartis anticipates the percentage of patients with missing data for the primary endpoint to be low and likely limited to a few participating sites.

Due to the small size of the proposed retrospective study, FDA stated that the plan for using multiple imputations would not be acceptable for the primary analysis. FDA reiterated that the complete case analysis should be the primary analysis for the proposed study. The analysis using multiple imputations could be a sensitivity analysis, and FDA would consider these results in the review process.

FDA recognizes the impact of COVID-19 on the proceedings of this study and acknowledges Novartis' plan to amend the study protocol due to delays. Novartis noted that data collection for approximately 65 patients may be delayed. FDA acknowledges Novartis' proposal to apply a cutoff date in late February and Novartis will submit a protocol amendment for FDA review.

Regulatory

14. FDA acknowledges your plan to submit an Assessment Aid. The Assessment Aid is based on the FDA Multidisciplinary Review template with most sections divided into two parts, clearly delineated to emphasize ownership of each position as either the Applicant's position or the FDA's position. The applicant fills in their positions in the relevant sections; these should be concise and only include critical information. Please note, the descriptive analyses of changes in clinical outcome and associated changes in tumor size are an important component of the overall benefit-risk assessment of alpelisib in the intended population;

therefore, FDA expects that these patient-level data (e.g., summary table or individual patient narratives) be included in the Assessment Aid (for example, in section 8.1.5 “Integrated Assessment of Effectiveness”).

Please refer to the following FDA website which describes this program.

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

Novartis’ Response received via email 03/31/20: Novartis acknowledges the Agency’s feedback. No further discussion is needed.

Discussion during the Meeting: There was no discussion of this item during the meeting.

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).

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 FDA's Guidance on Formal Meetings Between the FDA and Sponsors or Applicants[3] to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[4]

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[2] https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm544641.htm

[3] See the guidance for industry *"Formal Meetings Between the FDA and Sponsors or Applicants."*

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

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 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:*

[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

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.

MANUFACTURING FACILITIES

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

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)				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the

draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[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.
- AssessmentAid[9]

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

[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

ACTION ITEMS

There are no action items.

ATTACHMENTS AND HANDOUTS

(b) (4)

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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/

KELIE M REECE
04/02/2020 10:17:58 PM