# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 218466Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 143387

**MEETING PRELIMINARY COMMENTS**

Novartis Pharmaceuticals Corporation
Attention: Nina Katz, PharmD
Senior Global Program Regulatory Director, Oncology
One Health Plaza
East Hanover, New Jersey 07936-1080

Dear Dr. Katz:[1]

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

We also refer to your correspondence, received February 27, 2023, requesting a meeting to discuss the acceptability of data from Study F12101 to support a Type 3 NDA for the 50 mg granules dosage form for patients with difficulties swallowing tablets and to discuss the content of the Type 3 NDA submission.

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 FDA policy, you should not make audio or visual recordings of the discussion at this meeting. Consistent with 21 CFR 10.65(e), the official record of this meeting will be the FDA-generated minutes.

If you have any questions, contact me at Jacqueline.Glen@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

Jacqueline Glen, MS
Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO2

[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.

Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

# PRELIMINARY MEETING COMMENTS

| | |
|---|---|
| **Meeting Type:** | Type B |
| **Meeting Category:** | Pre-NDA |
| **Meeting Date and Time:** | April 25, 2023 at 4:00 PM – 5:00 PM, Eastern Time (ET) |
| **Meeting Location:** | Face to face virtual meeting |
| **Application Number:** | 143387 |
| **Product Name:** | Alpelisib |
| **Indication:** | Treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PIK3CA-Related Overgrowth Spectrum (PROS) who require systemic therapy |
| **Sponsor Name:** | Novartis Pharmaceuticals Corporation |
| **Regulatory Pathway:** | 505(b)(1) of the Federal Food, Drug, and Cosmetic Act |

**FDA ATTENDEES (tentative)**

Nicole Drezner, Acting Deputy Director, DO2
Diana Bradford, Cross Disciplinary Team Leader, DO2
Sonia Singh, Clinical Reviewer, DO2
Claudia Miller, Acting Nonclinical Team Leader, Division of Hematology/Oncology Toxicology (DHOT) Products
Sachia Khasar, Nonclinical Reviewer, DHOT
Hong Zhao, Clinical Pharmacology Team Leader, Division of Cancer Pharmacology II (DCP II)
Wentao Fu, Clinical Pharmacology Reviewer, DCP I
Xing Wang, Quality Assessment Lead, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)
Olen Stephens, Drug Product Reviewer, ONDP, OPQ
Anitha Govada, Biopharmaceutics Team Lead/SPQA, Biopharm Branch 1, ONDP, OPQ
Payal Agarwal, Biopharmaceutics Reviewer, BB1, ONDP, OPQ
Jacqueline Glen, Regulatory Health Product Manager, Division of Regulatory Operations (DRO)

**SPONSOR ATTENDEES**

Oliver Jung, PhD, Global Program Head
Monika Wroclawska, MD, Global Program Clinical Head
Athanasia Papadimitriou, MD, Sr Clinical Development Medical Director
Elise Burmeister Getz, PhD, Director, PK Sciences
Keroles Nakhla, PharmD, Principal Scientist, PK Sciences
Sabino Vesce, PhD, Sr Global Program Safety Lead
Mary Lisha Paul, MD, US Medical Director

Nathalie Fretault, MSc, Executive Director, Global Biostatistics
Suman Sen, PhD, Senior Director, Global Biostatistics
Daniel Niederer, PhD, Director, Technical Research and Development
Anil Kumar Reddy Kasireddy, MSc, Director, Regulatory Affairs CMC
Elisa Cerruti, PhD, Global Labeling Manager, Regulatory Affairs
John Robinson, PhD, Global Therapeutic Area Lead, Regulatory Affairs
Oliver O'Connell, PhD, Sr Global Program Regulatory Manager
Kelly Ohlinger, PharmD, Post-Doctoral Fellow, Regulatory Affairs
Nina Katz, PharmD, Sr Global Program Regulatory Director

**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 April 25, 2023 at 4:00 PM – 5:00 PM, Eastern Time (ET) via April 25, 2023 at 4:00 p.m. to 5:00 p.m., Eastern Time (ET) via virtual meeting 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

Regulatory History
On May 24, 2019, alpelisib (NDA 212526, Piqray) was approved 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 April 5, 2022, alpelisib (NDA 215039, Vijoice) was approved for adult and pediatric patients two years of of age and older with severe manifestations of PIK3CA-related overgrowth spectrum (PROS) who require systemic therapy. The approved dosage form is film coated tablets (FCTs) in strengths of 50, 125 and 200 mg.

Meeting Purpose
Novartis plans to submit a Type 3 NDA in support of a new dosage form, 50 mg granules in a packet, for use in patients who have difficulty swallowing whole tablets.

Novartis seeks FDA feedback on the acceptability of data from Study F12101 to support the planned application and to obtain agreement on the contents of the Type 3 NDA submission.

Planned NDA Contents

The Type 3 NDA will be supported primarily by data from Study F12101 with cross-references to prior alpelisib NDAs (Vijoice and Piqray), as noted on pages 21-22 of the briefing package. The application will include safety data from Study F12101, conducted in healthy subjects, in the Clinical Overview; however, no new clinical data from clinical trials in patients will be provided. The proposed contents of the NDA are described in Table 2-4 of the briefing package and will include the following in Module 5:

- Narratives and case report forms for adverse events (AEs) leading to treatment discontinuation and AEs of special interest
- Bioresearch Monitoring (BIMO) Part I documentation

Novartis proposes to omit the Summary of Clinical Safety (SCS), the Summary of Clinical Efficacy (SCE), the Integrated Summary of Safety (ISS) and the Integrated Summary of Efficacy. Additionally, a safety update will not be provided.

## DISCUSSION

### Clinical

1. Does the Agency agree that the data from Study F12101, which demonstrate bioequivalence between the 50 mg granule and the 50 mg FCT dosage forms in the fed state, support registration of the 50 mg granule dosage form for use in patients prescribed Vijoice 50 mg who have difficulties swallowing tablets whole (i.e., pediatric patients 2 to less than 18 years of age and adult patients who require dose reduction to 50 mg)?

   **FDA Response**: The data from Study F12101 appears acceptable to support your proposed NDA submission. However, the bioequivalence between the 50 mg granule and the 50 mg FCT dosage forms will be determined during FDA review of your NDA submission.

### Regulatory

2. Does the Agency agree with the proposed content of the Type 3 NDA as outlined in the draft electronic common technical document (eCTD) table of contents (TOC)?

**FDA Response**: Yes, the proposed contents appear acceptable. A final determination will be made at the time of submission of the original NDA.

3. Does the Agency agree that a User-fee waiver is acceptable given that the new dosage form will only be used in patients with PROS, a disease in which alpelisib has been designated an orphan drug?

**FDA Response**: Yes, we agree.

4. Does the Agency agree with Novartis' proposal to cross-reference Piqray (alpelisib) NDA 212526 and Vijoice (alpelisib) NDA 215039?

**FDA Response**: Yes, your plan to cross-reference Piqray (alpelisib) NDA 212526 and Vijoice (alpelisib) NDA 215039 is acceptable.

5. Does the Agency agree that an exemption for pediatric studies can be requested at the time of the forthcoming Type 3 NDA submission in support of a new dosage form of alpelisib?

**FDA Response**: Yes, you may request an exemption for pediatric studies at the time of the planned Type 3 NDA submission in support of a new dosage form of alpelisib. A determination regarding the request will be made during review of the NDA.

6. Does the Agency agree that a categorical exclusion from the environmental risk assessment (ERA) can be requested in the forthcoming Type 3 NDA given the establishment of bioequivalence between the alpelisib 50 mg granules and the 50 mg FCTs and the fact that registration of the granule dosage form will not result in an increase in the use of alpelisib?

**FDA Response**: Yes, a request for a categorical exclusion from the environmental risk assessment would be appropriate for your proposed NDA. In the request for an exclusion from the risk assessment, reiterate the justification explained in your meeting package.

7. Does the Agency agree that the proposed Vijoice USPI to be included in the forthcoming Type 3 NDA can include applicable revisions recently approved within the Piqray USPI?

**FDA Response**: Yes, the proposal appears acceptable.

**Programming**

8. Does the Agency agree with Novartis' proposal for the submission of electronic datasets and codes for the primary analysis?

**FDA Response**: Yes, the proposal appears acceptable. A final determination will be made at the time of submission of the original NDA.

## PREA REQUIREMENTS

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

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

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

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

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

## FDARA REQUIREMENTS

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

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

## PRESCRIBING INFORMATION

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

---

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

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

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

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

---

[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

## SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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

- Assessment Aid[7]

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

---

**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
04/20/2023 12:44:56 PM

# CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

| | |
|---|---|
| **IND/NDA/BLA #** | IND 143387 |
| **Request Receipt Date** | September 18, 2019 |
| **Product** | Alpelisib (BYL719) |
| **Indication** | PIK3CA-Related Overgrowth Spectrum (PROS) |
| **Drug Class/Mechanism of Action** | Phosphatidylinositol-3-kinase (PI3K) inhibitor |
| **Sponsor** | Novartis Pharmaceuticals Corporation |
| **ODE/Division** | OHOP/Division of Oncology Products 2 |
| **Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)** | November 15, 2019<br>(Technical 60 day date: November 17, 2019) |

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

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

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

   Alpelisib is intended for the treatment of patients with PIK3CA-related overgrowth spectrum (PROS).

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

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

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

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

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

***If 4a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:***

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

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

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

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

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

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

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

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

Deny Breakthrough Therapy Designation ☐

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

---

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

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

- *Information regarding the disease and intended population for the proposed indication.*
- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

*Alpelisib: Mechanism of Action and Clinical Development Program*

Alpelisib (BYL719) is an oral, alpha-specific class I phosphatidylinositol-3-kinase (PI3K) inhibitor.[1] The PI3K/Akt and the mammalian target of rapamycin (mTOR) signaling pathways are important in cell growth and survival and have been shown to govern normal vascular development.[2] Aberrant activation of these pathways occurs in human

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

cancer and results in perturbed cellular processes that lead to downstream effects including competitive growth advantage and angiogenesis, thereby promoting tumor development and resistance to treatment.[3,4] The *PIK3CA* gene encodes the alpha catalytic subunit of the enzyme PI3K, a lipid kinase that is involved in cell proliferation, motility, apoptosis, and glucose metabolism.[5] Alpelisib is reported to selectively inhibit this catalytic subunit of PI3K.

Alpelisib has been approved 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.

Alpelisib has been investigated as a single agent and as combination therapy with targeted agents, endocrine therapy or chemotherapy in cancer patients (breast cancer and other advanced malignancies), patients with hepatic impairment, and in healthy volunteers in a total of 24 clinical studies. As of May 2018, approximately 1,977 patients have been cumulatively exposed to alpelisib. The most commonly observed adverse reactions to alpelisib include hyperglycemia, elevated creatinine, diarrhea, rash, reduced lymphocyte count, elevated gamma-glutamyl transferase and alanine aminotransferase (ALT), nausea, vomiting, and stomatitis.

Alpelisib has also been provided to patients with PIK3CA-Related Overgrowth Spectrum (PROS) through compassionate use protocols. Novartis designed a global managed access program, also referred to as Study BYL719F12001M, which commenced in May 2018, and as of May 2019, has provided access to alpelisib for 59 patients in 10 countries. The clinical data supporting this breakthrough therapy designation request (BTDR) are derived from a published case series[6] describing the outcomes of 19 patients (15 children and 4 adults), who had severe or life-threatening PROS or were scheduled for debulking surgery and received alpelisib at a single center in France through an ATU (Temporary Authorisation for Use). Novartis contends that the volumetric reduction of target lesions and the associated clinical benefits observed in these patients provides direct evidence of the effectiveness of alpelisib as a treatment for patients with PROS.

*Disease Background: PIK3CA-related Overgrowth Spectrum (PROS)*
PROS is an umbrella term encompassing a group of rare disorders characterized by asymmetric and sporadic lesions with uncontrolled growth that result in progressive disability. Heterogeneous genotypes and phenotypes resulting from mosaic gain-of-function mutations in the *PIK3CA* gene are observed in affected patients.[7] In addition to confirmation of the genetic mutation and congenital or early childhood-onset, clinical diagnostic criteria consist of segmental overgrowth (e.g., adipose muscle, skeletal or nerve tissue), vascular malformations (e.g., capillary, venous, arteriovenous malformation, lymphatic), epidermal nevi, and isolated features (e.g., overgrown limbs, macrodactyly).[8] PROS includes clinical entities such as fibroadipose hyperplasia or overgrowth (FAO); hemihyperplasia multiple lipomatosis (HHML); and congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal (CLOVES) syndrome.[9]

The incidence of PROS is estimated to be approximately 1 in 70,000; however, prevalence is difficult to determine due to the rarity of the condition, recent characterization, and varying presentations, some of which may result in misdiagnosis. Although PROS is predominantly a pediatric disease, growth trajectories of lesions vary, and the disease may manifest as progressive overgrowth in adulthood. Severity of the PROS phenotype can range from localized overgrowth to large and potentially life-threatening lesions that may impact major vessels and critical organs. PROS has been associated with organ dysfunction (e.g., cardiac, renal, endocrine), functional impairment (e.g., walking due to limb overgrowth or due to spinal cord involvement, swallowing), severe pain, and other complications such as bleeding, chronic lung disease, pulmonary hypertension, thromboembolism, and recurrent infections.[10] These morbidities can be debilitating and cause early mortality.

*Current Treatment Options in PROS*

There are no curative interventions and no agents approved for the treatment of PROS. Current management consists of multidisciplinary care with surgical procedures such as debulking or amputation (although regrowth often occurs after resection), sclerotherapy, occlusive endovascular procedures, and pain management.[11] 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.[12,13] Medical therapy with sirolimus may be considered on a case-by-case basis after taking into account the drug's safety profile.

*Regulatory History*

**IND 107078**

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 (CYBL719X2101 and CBYL719Z2102).

**NDA 212526**

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 HR-positive, HER2-negative, PIK3CA-mutated advanced or metastatic breast cancer following progression on or after an endocrine-based regimen.

**IND 143387**

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 supplemental NDA based on data from a retrospective chart review of patients with severe or life-threatening PROS who received alpelisib through compassionate use protocols. Novartis plans to seek accelerated approval with these results and intends to conduct a single arm, multicenter study in patients with broad spectrum of disease to confirm clinical benefit.

On August 29, 2019, the managed access protocol to provide alpelisib for patients with PROS (Study BYL719F12001M) that was originally filed to IND 107078 in January 2019 was transferred to IND 143387.

On September 18, 2019, Novartis submitted a BTDR for the proposed treatment of patients with PROS.

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

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

Novartis considers a response rate based on a ≥20% volumetric reduction of PROS target lesions to be a clinically meaningful endpoint to support this BTDR. Novartis contends that this level of lesion shrinkage is associated with an improvement in tumor-related symptoms and functional impairment and as such, is preliminary evidence of clinical benefit.

There are no standard response criteria that have been established for PROS. As stated in a prior briefing document submitted for a pre-IND meeting, Novartis's rationale for selection of volumetric reduction as the primary endpoint in this disease is based upon the observation that volumetric measurements have been shown to detect changes in lesion size earlier and more precisely than one- or two-dimensional measurements in a

progressive disease with irregularly shaped lesions (e.g., benign nerve sheath tumors in neurofibromatosis). Further, Novartis notes that the 20% threshold for volumetric reduction is widely used in oncology for the objective assessment of changes of tumor/lesion size based on intra-/inter-observer agreement.

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

- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
- *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

DOP2 agrees that volumetric reduction of target lesions in PROS in conjunction with observed improvement in tumor-related symptoms, quality of life, disfiguring lesions, functional organ improvement, or physical function may serve as preliminary evidence of clinical benefit to support a BTDR.

Response Evaluation Criteria in Solid Tumors (RECIST) has been commonly been used to define measurability and to assess treatment response in oncology. Although RECIST offers advantages of being standardized, reproducible, and associated with a low risk of inter-reader variability, 2-dimensional linear assessments may not be optimal for tumors characterized by atypical growth patterns.

Volumetric measurements based on magnetic resonance imaging (MRI) represent an alternative method for determining tumor size, and MRI tumor volume reduction has been incorporated into disease-specific response guidelines used in clinical trials. For example, the Response Evaluation in Neurofibromatosis (NF) and Schwannomatosis (REiNS) criteria are standardly used to assess response in plexiform neurofibromas and schwannomas, both benign, slowly-growing lesions that can cause significant morbidity.[14] The Tumor Measurement Working Group of the REiNS reports that volumetric analysis detected tumor progression (lesion volume increase ≥20%) much earlier than linear measurements and was associated with less variation in inter- and intraobserver assessment. Additionally, volumetric measurements based on MRI are thought to more accurately reflect the actual size of a lesion with less sensitivity to differences in body position and can reproducibly detect small changes over time. The REiNS criteria consider a partial response to be a decrease in the volume of the target lesion by at least 20% compared to baseline, and a complete response is defined as disappearance of the target lesion. Of note, the MAP/ERK kinase (MEK) inhibitor selumetinib received breakthrough therapy designation for the treatment of NF-related plexiform neurofibroma on the basis of response rate as determined by volumetric analysis according to the REiNS criteria. Similarly, Novartis proposes that a ≥20% tumor volume reduction is clinically meaningful in PROS, which is also characterized by sporadic growth and large, irregularly shaped lesions. Novartis plans to use this threshold of volumetric reduction to define treatment response in the planned retrospective chart review and the prospective trial.

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

None.

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

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*

- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

There are no approved therapies for PROS; however, the mTOR inhibitor sirolimus has been used off-label in this patient population. According to published literature, radiographic response rates have been modest and drug-related adverse events (AEs) common. Parker et al. evaluated the safety and efficacy of low-dose sirolimus in 39 patients (22 children and 17 adults) with PROS and progressive overgrowth in an open-label, multicenter, investigator-initiated study.[12] The primary outcome was percentage change in the tissue volumes of affected and unaffected sites as measured by dual energy X-ray absorptiometry (DXA) during 26 weeks of untreated run-in followed by 26 weeks of sirolimus administration. Twenty-three patients were evaluable for the primary outcome. A reduction of 7.2% (standard deviation [SD] 16.0; p=0.04) was observed in the volume of affected tissues during sirolimus treatment. Study findings were also notable for frequent AEs with 28 of 39 participants having at least one AE possibly related to sirolimus, and 7 patients experiencing AEs leading to sirolimus discontinuation. Further, no differences were detected in QOL scores before and after treatment.

Another study by Adams et al. assessed a higher dose of sirolimus in a heterogenous cohort of patients with primarily vascular malformations.[13] Although genetic characterization was not reported, some patients were likely to have PROS based on clinical phenotypes. Sirolimus was administered in 28 day courses. Sixty-one patients were enrolled with 57 patients evaluable for efficacy at the end of 6 courses, and 53 evaluable at the end of 12 courses. Disease response was determined by radiologic assessment, a functional impairment score and health-related QOL. No patient exhibited a complete response, and 87% of participants had a partial response, and in some cases only due to changes in QOL measures. Grade 3 and higher toxicities attributed to sirolimus included blood/bone marrow-related AEs in 27% of patients. Two patients were unable to complete treatment due to drug-related toxicity.

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

No other agents being studied for this indication, or a very similar indication, have requested breakthrough therapy designation.

**11. Information related to the preliminary clinical evidence:**

**a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.**

Supportive evidence for the BTDR consists of Novartis's summary of the published case series (Venot et al. 2018) describing outcomes in 19 patients with PROS who received alpelisib through a compassionate use protocol. Based upon reported effectiveness of alpelisib in a postnatal mouse model of PROS/CLOVES that partially recapitulates

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

the human disease, alpelisib was initially administered to two patients with CLOVES syndrome who were suffering from severe clinical manifestations of the disease and life-threatening complications.

Patient 1 was a 29-year old man who presented with left leg hypertrophy, scoliosis, multiple nevi, and severe vascular malformations that were refractory to multiple debulking surgeries and prior sirolimus treatment. The patient's medical condition was significant for severe systolic heart failure, renal dysfunction, and saddle anesthesia due to spinal cord compression. He was receiving palliative care when he started daily alpelisib at a dose of 250 mg. He experienced global vascular tumor shrinkage with a 72% volume decrease at 18 months. He was also reported to have normalization of his cardiac output (reduced from 18 L/min/$m^2$ to 3 L/min/$m^2$), improved renal function (estimated glomerular filtration rate [eGFR] increased from 33 to 52 ml/min/1.73 $m^2$) and partially regained bladder function with improved saddle anesthesia. Patient 2 was a nine year old girl with scoliosis, left leg hypertrophy, vascular malformations and hypertrophic back muscles. She was treated with daily alpelisib at a dose of 50 mg and experienced 24% reduction in her left leg volume and 71% reduction in intra-abdominal tumor volume after 12 months. Further, hypertrophic muscles in her back were reported to shrink rapidly and her scoliosis was reversed after 6 months without any other intervention.

Subsequent to this, 17 additional patients with varying diagnoses (e.g., CLOVES syndrome, megalencephaly-capillary malformation [MCAP], localized overgrowth syndrome) were treated with alpelisib at the same daily pediatric (50 mg) or adult (250 mg) dose under compassionate use. Patients were followed at regular intervals (weekly for eight weeks, every two weeks for one month and then monthly). Glycemia was evaluated daily for the first month and then progressively less frequently. Patients underwent a physicial examination and performance status measurement at all time points. The investigators report monitoring growth of children at all clinical appointments, and laboratory testing (complete blood count, kidney and liver functions, glycosylated hemoglobin measurements) was performed at each time point. Glycemia was monitored after all meals for two months and then the monitoring became progressively less frequent. MRI studies were performed prior to alpelisib initiation and then after three and six months of treatment.

In addition to volumetric tumor reduction, which is supported by photographic evidence of lesion shrinkage in all 19 patients in the publication, these patients are reported to have experienced improved mobility, pain control, organ function, cessation of chronic gastrointestinal bleeding or hematuria, or resolution of dyspnea. The most striking examples include two patients who were described as being opioid dependent and confined to bed prior to alpelisib administration, and after 6 months of treatment, were not requiring any pain medications and able to walk again.

**Table 1: Clinical Benefit Observed in Patients Receiving Alpelisib in the Venot et al. (2018) Case Series**

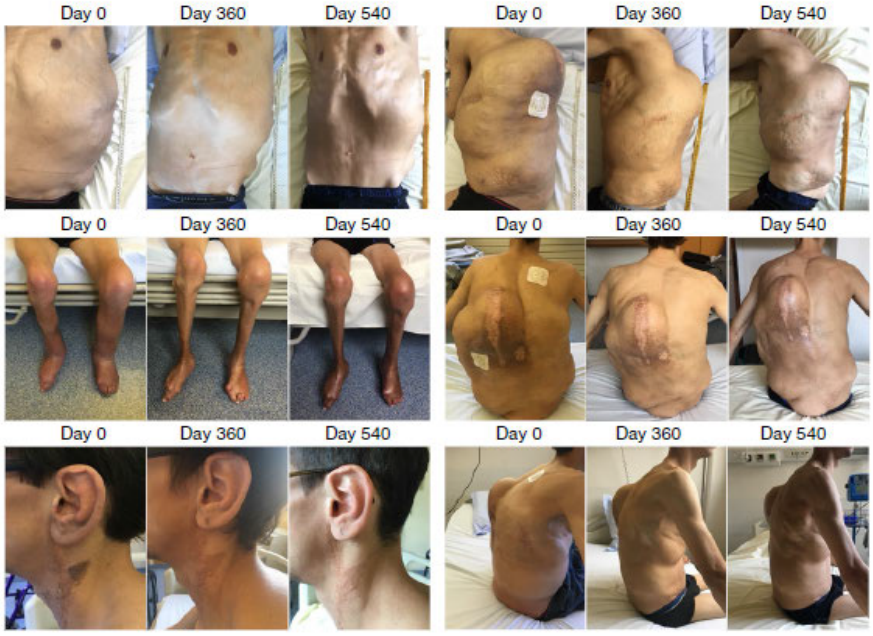
| | # of Patients |
|---|---|
| Capable of walking | 2 |
| Stopped opioid treatment | 2 |
| Improved cardiac and renal function | 1 |
| Correction of scoliosis | 1 |
| Improved saddle anesthesia and partially regaining bladder function | 1 |

The BTDR submission includes summary tables from the original publication that list relevant diagnoses and disease manifestations of patients, indications for alpelisib administration, percentage change in target lesion

volume after 3 and 6 months of alpelisib treatment, as well as improvement in disease manifestations (e.g., cardiac and renal function, scoliosis, disfiguring lesions, ability to walk, etc.) and clinical benefit in the form of symptom management (e.g., cessation of opioid treatment). The authors report that the mean volume of target lesions decreased by 27.2% (SD 14.6) and 37.8% (SD: 16.3) after 3 and 6 months of alpelisib treatment, respectively. Using a threshold of 20% volumetric reduction in target lesions, 11 out of 17 or 64.7% (95% confidence interval [CI]: 38.8, 85.8) of patients showed treatment response after 3 months, and 15 out of 17 or 88.2% (95% CI: 63.6, 98.5) of patients showed treatment response after 6 months.

The following images are copied from the Venot publication and reflect the tumor reduction observed in Patient 1. Lesion shrinkage correlated with improvement in cardiac, renal, neurosensory and bladder function.

Figure 1. Treatment Response in Patient 1




**b. Include any additional relevant information. Consider the following in your response**:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*
- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*
- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

The data submitted by Novartis in support of the BTDR are derived from a single published report of a case series of 19 patients who received alpelisib under compassionate use regulations at a medical center in France. DOP2 considers the submitted data based on this publication to be preliminary clinical evidence of substantial clinical benefit as nearly 90% of these patients exhibited a ≥20% volumetric reduction in target lesions after 6 months of treatment, and most importantly, lesion shrinkage was associated with clear benefit such as improved cardiac output in a patient with heart failure and the ability to walk independently after having been previously opioid-dependent and bedridden. In terms of safety, three patients were reported to have self-resolving grade 1 stomatitis,

and two patients experienced hyperglycemia, including an obese patient who achieved glycemic control through a modified diet, and another patient with a history of diabetes who required optimization of his medication regimen. These adverse events did not result in discontinuation of alpelisib.

Taking into consideration that there are no available therapies for PROS, the current management of this disease is largely symptom-based, patients with severe or life-threatening overgrowths are at increased risk of undergoing morbid and potentially futile surgical procedures in cases of regrowth, and the safety profile of the agent appears tolerable, alpelisib represents a substantial improvement over alternative treatment options for patients with PROS.

Regarding the original publication, the authors report receiving funding from the European Research Council and declare that there are no competing interests. Of note, Novartis does not yet have access to the source data and has not conducted its own verification of the reported results. The sponsor is seeking to collect this information as part of its retrospective chart review (of all patients who received alpelesib as part of its managed/compassionate use program).

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

☒ GRANT:

Provide brief summary of rationale for granting:

*Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.*

☐ DENY:

Provide brief summary of rationale for denial:

*Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:*

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

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

   At a pre-IND meeting to discuss the development of alpelisib for the proposed treatment of PROS, DOP2 provided guidance to the sponsor on the planned retrospective study of patients two years of age and older with severe or life-threatening PROS who received alpelisib through expanded access programs (i.e., ATU and the global managed access program). This chart review of approximately 60 patients with a primary endpoint of percentage of patients with 20% volumetric reduction in the sum of 1 to 3 target lesions at three months would serve as the basis for a for a supplemental NDA seeking accelerated approval. DOP2 also provided advice to the sponsor regarding the design of an open-label, uncontrolled, multicenter study of up to 80 patients with PROS who have a broad spectrum of disease, which would be conducted post-marketing. The planned primary endpoint of this study is percentage of patients with 20% volumetric reduction in the sum of 1 to 3 target lesions at six months.

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

**14. List references, if any:**


1. Juric D, Rodon J, Tabernero J, et al. Phosphatidylinositol 3-Kinase α-Selective Inhibition With Alpelisib (BYL719) in *PIK3CA*-Altered Solid Tumors: Results from the First-in-Human Study. *Journal of Clinical Oncology* 2018; 36: 1291-1299.
2. Graupera M, Potente M. Regulation of angiogenesis by PI3K signaling networks. *Elsevier* 2013; 319: 1348-1355.
3. Madsen RR, Vanhaesebroeck B, Semple RK. Cancer-Associated *PIK3CA* Mutations in Overgrowth Disorders. *Trends in Molecular Medicine* 2018; 24: 856-870.
4. Fruman DA, Honyin C, Hopkins BD, et al. The PI3K Pathway in Human Disease. *Cell* 2017; 170: 605-635.
5. Kuentz P, St-Onge J, Duffourd Y, et al. Molecular diagnosis of *PIK3CA*-related overgrowth spectrum in 162 patients and recommendations for genetic testing. *Genetics in Medicine* 2017; 19: 989-997.
6. Venot Q, Blanc T, Rabia SH, et al. Targeted therapy in patients with PIK3CA-related overgrowth syndrome. *Nature* 2018; 558: 540-546.
7. Mirzaa G, Conway R, Graham JM, et al. *PIK3CA*-Related Segemental Overgrowth. *Gene Reviews* 1992-2019; http://www.ncbi.nlm.nih.gov/books/NBK1116/
8. Keppler-Noreuil KM, Rios JJ, Parker VE, et al. *PIK3CA*-Related Overgrowth Spectrum (PROS): Diagnostic and Testing Eligibility Criteria, Differential Diagnosis, and Evaluation. *American Journal of Medical Genetics* 2015; 167: 287-295.
9. Keppler-Noreuil KM, Sapp JC, Lindhurst MJ, et al. Clinical delineation and natural history of the *PIK3CA*-related overgrowth spectrum. *American Journal of Medical Genetics* 2014; 164: 1713-1733.
10. Luks VL, Kamitaki N, Vivero MP, et al. Lymphatic and Other Vascular Malformative/Overgrowth Disorders Are Caused by Somatic Mutations in *PIK3CA*. *Journal of Pediatrics* 2015; 166: 1048-1054.
11. Keppler-Noreuil KM, Parker VE, Darling TN, et al. Somatic Overgrowth Disorders of the PI3K/AKT/mTOR Pathway & Therapeutic Strategies. *American Journal of Medical Genetics* 2016; 172: 402-421.
12. Parker VE, Keppler-Noreuil KM, Faivre L, et al. Safety and efficacy of low-dose sirolimus in the PIK3CA-related overgrowth spectrum. *Genetics in Medicine.* 2019; 21: 1189-1198.
13. Adams DM, Trenor CC, Hammill A, et al. Efficacy and Safety of Sirolimus in the Treatment of Complication Vascular Anomalies. *Pediatrics* 2016; 137: 1-10.
14. Dombi E, Ardern-Holmes SL, Babovic-Vuksanovic D, et al. Recommendations for imaging tumor response in neurofibromatosis clinical trials. *American Academy of Neurology* 2013; 81: S33-S40.


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

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

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

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

**Revised 3/18/19/M. Raggio**

---

**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/

---

SONIA SINGH
11/12/2019 10:54:22 AM

SUZANNE G DEMKO
11/12/2019 11:02:49 AM

STEVEN J LEMERY
11/12/2019 02:05:05 PM