CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215039Orig1s000

OTHER REVIEW(S)

Addendum to Clinical Inspection Summary Dated February 8, 2022

Date	April 1st, 2022
From	Lee Pai-Scherf, MD Karen Bleich, MD Kassa Ayalew, MD, MPH Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Sonia Singh, MD Diana Bradford, MD Harpreet Singh, MD, Division Director Division of Oncology 2 Office of Oncologic Products
NDA #	215039
Applicant	Novartis Pharmaceuticals Corp.
Drug	Alpelisib (BYL719)
NME (Yes/No)	No
Therapeutic Classification	Kinase inhibitor
Proposed Indication(s)	Treatment of adult and pediatric patients aged 2 years and older with PIK3CA-Related Overgrowth Spectrum (PROS)
Consultation Request Date	November 8, 2021
Summary Goal Date	February 15, 2022
Action Goal Date	April 6, 2022
PDUFA Date	April 6, 2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

This Clinical Inspection Summary (CIS) Addendum provides a summary of the clinical investigator inspection of Dr. Guillaume Canaud with regards to study EPIK-PI. At the time of the initial CIS, inspection of Dr. Canaud was ongoing.

On-site inspection of Dr. Canaud revealed no significant findings. Based on the results of the inspection, the Study EPIK-P1 overall appears to have been conducted adequately and the data generated by Dr. Canaud's site appear to be acceptable in support of the proposed indication in the NDA.

I. BACKGROUND

Refer to CIS entered into DARRTS on 2/9/2022.

II. RESULT

Dr. Guillaume Canaud (Site # 3000)
Necker Hospital
149 rue de Sevres
Paris cedex 15, NA 75015
France

Inspection dates: 02/07 – 02/17/2022

Dr. Canaud was inspected as a surveillance inspection for the retrospective chart review study EPIK-PI. This is the first inspection for Dr. Canaud.

Data from 44 subjects enrolled at the site were included in study EPIK-PI. Source documents of all 44 subjects were reviewed and compared to the line listings submitted to the NDA. Records reviewed included inclusion and exclusion criteria, adverse events reporting, laboratory assessment, test article dosing, concomitant medications, and study related procedures.

Two discrepancies were observed between the source records and the data submitted to the NDA:

- Two subjects had MRI scans performed at the site that were not assessed by the BICR. Both scans were submitted to (b) (4) for BICR assessment by the site, per source records.
  - Subject (b) (6) had an MRI of the abdomen performed on (b) (6) approximately 16 weeks from initiation of study drug. Based on the site report, the subject had stable disease. The subject achieved a response based on BICR assessment of the CT scan at Week 24 on (b) (6)
  - Subject (b) (6) had an MRI of the abdomen on (b) (6), 10 weeks from initiation of study drug. Based on the site report, the status of the disease was comparable to previous scans. The subject was a non-responder and had stable disease assessed by BICR based on the CT scans at Week 12 and Week 24 .

Reviewer's comment: Based on source records, the MRIs were submitted to the imaging CRO for BICR assessment. It is unclear why these scans were not read by BICR, however, based on the available information, this observation is unlikely to have impacted on the overall efficacy findings of the study.

- Underreporting of laboratory assessment was observed in 2 instances: Subject (b) (6)

had HbA1c performed on (b) (6) valued 5.6% and Subject (b) (6) had Hb A1c assessed on (b) (6) valued 5.6% that were not entered in the eCRF and reported to the NDA.

Reviewer's comment: These discrepancies appear to be isolated events and did not result in harm to the subjects given that in both instances, the HbA1c values were within institutional normal ranges (4.5 %- 6%).

Other documents reviewed during the inspection include financial disclosure forms, delegation log, training records, investigational drug accountability, and sponsor's monitoring reports and other source documents. Because EPIK-PI is a retrospective chart review study, no ethic committee oversight was required. Similarly, subjects were not consented for the retrospective study, but were presented with a letter allowing them to object to their information being included in the study. Source records indicated that no subjects objected having their data included in the study.

The inspection found no regulatory violations at the site. No Form FDA 483 was issued to Dr. Canaud at the conclusion of the inspection.

{See appended electronic signature page}

Lee Pai-Scherf, MD
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Karen Bleich, M.D.
Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

DARRTS: NDA 215039
Review Division /Project Manager: Maritsa Stephenson
OSI/Database PM/Dana Walters
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

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/s/

LEE HONG PAI SCHERF
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KAREN B BLEICH
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KASSA AYALEW
04/06/2022 12:34:40 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 4, 2022
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 215039
Product Name and Strength:	Vijoice (alpelisib) Tablets, 50 mg, 125 mg, and 200 mg
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corp.
OSE RCM #:	2021-1509-1
DMEPA 2 Team Leader (Acting):	Janine Stewart, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on March 21, 2022 for Vijoice. Division of Oncology 2 (DO2) requested that we review the revised container labels and carton labeling for Vijoice (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Stewart, J. Label and Labeling Review for Vijoice (NDA 215039). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 MAR 04. RCM No.: 2021-1509.

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/s/

JANINE A STEWART
04/04/2022 02:33:13 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 03/14/22

To: Maritsa Stephenson, Regulatory Project Manager, DO2

From: Rachael Conklin, Team Leader
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Deputy Division Director, OPDP

Subject: OPDP Labeling Comments for Vijoice (alpelisib) tablets, for oral use

NDA: 215039

In response to DO2's consult request dated October 6, 2021, OPDP has reviewed the proposed package insert (PI), patient package insert (PPI), and carton and container labeling for the original NDA/BLA submission for Vijoice (alpelisib) tablets, for oral use (Vijoice).

Labeling: OPDP's review of the proposed PI are based on the draft labeling emailed to OPDP on March 7, 2022, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the proposed carton and container labeling and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Rachael Conklin at Rachael.Conklin@fda.hhs.gov.

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/s/

RACHAEL E CONKLIN
03/14/2022 03:21:43 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	March 10, 2022
To:	Maritsa Stephenson, PharmD, BCPS Regulatory Project Manager **Division of Oncology II (DO2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rachael Conklin, MS, RN Team Leader **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	VIJOICE (alpelisib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 215039
Applicant:	Novartis Pharmaceuticals Corporation

1 INTRODUCTION

On October 6, 2021, Novartis Pharmaceuticals Corporation submitted for the Agency's review an original New Drug Application (NDA) 215039 for VIJOICE (alpelisib) tablets with a proposed indication for the treatment of adult and pediatric patients aged 2 years and older with PIK3CA-Related Overgrowth Spectrum.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology II (DO2) on October 7, 2021, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for VIJOICE (alpelisib) tablets.

2 MATERIAL REVIEWED

- Draft VIJOICE **(**alpelisib**)** tablets PPI received on October 6, 2021, and received by DMPP and OPDP on March 4, 2022.
- Draft VIJOICE **(**alpelisib**)** tablets Prescribing Information (PI) received on October 6, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 4, 2022.
- Approved PIQRAY **(**alpelisib**)** tablets**,** NDA 212526 labeling dated July 20, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
03/10/2022 03:19:22 PM

RACHAEL E CONKLIN
03/10/2022 03:25:22 PM

BARBARA A FULLER
03/10/2022 03:33:55 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 4, 2022
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 215039
Product Name, Dosage Form, and Strength:	Vijoice (alpelisib) Tablets, 50 mg, 125 mg, and 200 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corp.
FDA Received Date:	July 12, 2021 and September 29, 2021
OSE RCM #:	2021-1509
DMEPA 2 Team Leader (Acting):	Janine Stewart, PharmD

1 REASON FOR REVIEW

As part of the approval process for Vijoice (alpelisib) Tablets, the Division of Oncology 2 (DO2) requested that we review the proposed Vijoice prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F-– N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed Prescribing Information (PI), container label, and carton labeling for Vijoice to identify deficiencies that may lead to medication errors and other areas of improvement.

Our review of the PI, container label and carton labeling identified areas of vulnerability that can be modified to improve the clarity of the information presented. We note the packaging configurations and the dosing information presented on the container labels and carton labeling and the information provided in Section 16 How Supplied of the PI maybe optimized to mitigate the risk of dispensing and administration errors and to support patient adherence to the proposed dosing regimen.

4 CONCLUSION & RECOMMENDATIONS

The proposed Vijoice PI, container labels and carton labeling may be optimized to support users understanding of the proposed packaging configurations. Further, the container labels and

carton labeling may be improved to support compliance with the proposed dosing regimen to mitigate the risk of medication errors that may be associated with confusion regarding the strength and number of tablets in each carton and the dosing regimen. We provide specific recommendations in Section 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 2 (DO2)

A. Prescribing Information

1. How Supplied/Storage and Handling Section

a. Consider revising the presentation of information in Section 16: How Supplied/Storage and Handling to clarify the description of each of the proposed packaging configurations; for example, as follows:

Daily Dose	**Each child-resistant carton contains**	**Each blister pack contains**	**NDC**
50 mg daily dose	One 28-day supply blister pack	28 tablets; 50 mg alpelisib per tablet	NDC 0078-1021-84
125 mg daily dose	One 28-day supply blister pack	28 tablets; 125 mg alpelisib per tablet	NDC 0078-1028-84
250 mg daily dose	**Two** 14-day supply blister packs (56 tablets total)	14 tablets: 200 mg alpelisib per tablet, and 14 tablets: 50 mg alpelisib per tablet	NDC 0078-1035-02

4.2 RECOMMENDATIONS FOR NOVARTIS PHARMACEUTICALS CORP.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. As currently presented, the expiration date format is defined as "MMM YYYY". This is inconsistent with FDA draft guidance. FDA recommends that the expiration date be expressed as YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date. *See Draft Guidance: Product Identifiers Under the Drug Supply Chain Security Act-Questions and Answers*. Available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf.

B. Container Labels- Pull Out Blister cards

1. The 250 mg blister card statement “250 mg = 200 mg tablet + 50 mg tablet” in pale green lacks contrast and may be difficult to for some to read. Revise the statement to appear with increased contrast to improve readability.

2. The statement [redacted (b) (4)]” can be improved to facilitate patient comprehension regarding the daily dosage. To minimize the risk of wrong dose errors, revise this statement to read “250 mg daily dose: Take one 200 mg tablet and one 500 mg tablet once daily with food” and enhance the visibility and prominence of the statement by using bold type.

    a. Make similar revisions for the 125 mg and 50 mg strengths.

3. We are concerned that users will have difficulty keeping track of their schedule if treatment is interrupted. To the bottom of the blister card, add the statement “Fill in date of your first dose: _/__/__” to prompt the user to use this date as a marker to optimize compliance with the treatment schedule.

4. As proposed the 50 mg and the 125 mg professional sample blister cells are not labeled Day 1 through Day 14 (professional sample) or Day 1 through Day 28 (commercial). To facilitate patient adherence to the daily dosing schedule and for consistency with the blister cards of the 250 mg packaging configurations, label the blister cells with the Day number.

C. Carton Labeling- Blister Card Sleeve & Outer Carton

1. Revise and relocate the statement on the back panel that reads [redacted (b) (4)]” to appear on the PDP and to read: “Recommended Dosage: Take one 200 mg tablet and one 50 mg tablet once daily with food. Swallow tablets whole. DO NOT chew, crush, or split tablets. See prescribing information for complete dosage information and instruction for patients who are unable to swallow whole tablets.

2. Revise the strength and dosage statements to facilitate patient comprehension regarding the daily dose and the number of tablets or tablet combinations required to achieve the stated dosage.

    a. Example (not true to layout, size, spacing, color, etc.):

250 mg daily dose
Take one 200 mg tablet and one 50 mg tablet once daily.

b. Repeat the recommended revision above for the 125mg daily dose and 50mg daily dose blister card and outer carton labeling.

3. The net quantity statement may be improved to clarify what the carton contains. Add the statement "28-Day Supply" to appear above the "Contains: Two 14-day blister packs each containing 28 tablets:" (250 mg daily dose outer carton)

   a. Repeat the recommended revision above for the 125mg daily dose and 50mg daily dose blister card sleeve and outer carton labeling. For example:

      "28-Day Supply" to appear above the "Contains: One blister pack containing 28 tablets:"

   b. For the 250 mg blister card sleeves, revise as follows:

      "14-Day Supply" to appear above the "Contains: One blister pack containing 28 tablets:"

      200 mg | 50 mg

      14 tablets 14tablets

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Vijoice received on September 29, 2021 from Novartis Pharmaceuticals Corp., and the listed drug (LD).

Table 2. Relevant Product Information for Vijoice and the Listed Drug		
Product Name	Vijoice	Piqray [a]
Initial Approval Date	N/A	May 24, 2019
Active Ingredient	alpelisib	alpelisib
Indication	Indicated in adult and pediatric patients aged 2 year and older for the treatment of PIK3CA-related overgrowth spectrum (PROS).	Indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (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.
Route of Administration	Oral	Oral
Dosage Form	Tablets	Tablets
Strength	50 mg, 125 mg, and 200 mg	Tablets: 50 mg, 150 mg, 200 mg
Dose and Frequency	Maximum daily dose in adult patients: 250 mg once daily. • First dose reduction: (b) (4) mg once daily • Second dose reduction: (b) (4) mg once daily • (b) (4)	Maximum daily dose: 300 mg (two 150 mg tablets) once daily. Dose modifications for adverse reactions: • First dose reduction: 250 mg (one 200 mg tablet and one 50 mg tablet) once daily. • Second-dose reduction: 200 mg (one 200 mg tablet) once daily.

[a] Piqray [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2021 JUL 07. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212526Orig1s004lbl.pdf

	Maximum daily dose pediatric patients: 50 mg once daily	
How Supplied	250 mg daily dose: Each carton contains 2 blister packs (56 tablets total). Each blister pack contains a 14-day supply of 28 tablets (14 tablets, 200 mg alpelisib per tablet and 14 tablets, 50 mg alpelisib per tablet) 125 mg daily dose: Each carton contains 1 blister pack . Each blister pack contains a 28-day supply of 28 tablets (28 tablets, 125 mg alpelisib per tablet) 50 mg daily dose: Each carton contains 1 blister pack. Each blister pack contains a 28-day supply of 28 tablets (28 tablets, 50 mg alpelisib per tablet)	300 mg daily dose: Each carton contains 2 blister packs. Each blister pack contains a 14-day supply of 28 tablets (28 tablets, 150 mg alpelisib per tablet). 250 mg daily dose: Each carton contains 2 blister packs. Each blister pack contains a 14-day supply of 28 tablets (14 tablets, 200 mg alpelisib per tablet and 14 tablets, 50 mg alpelisib per tablet). 200 mg daily dose: Each carton contains 1 blister pack. Each blister pack contains a 28-day supply of 28 tablets (28 tablets, 200 mg alpelisib per tablet).
Storage	Store at 20°C to 25°C (68°F to 77°F)	Store at 20°C to 25°C (68°F to 77°F)
Container Closure	Blister pack	Blister pack

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APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Vijoice labels and labeling submitted by Novartis Pharmaceuticals Corp..

- Container label received on July 12, 2021
- Carton labeling received on July 12, 2021
- Professional Sample Blister cards received on July 12, 2021
- Professional Sample Carton Labeling received on July 12, 2021
- Prescribing Information (Image not shown) received on September 29, 2021, available from \\CDSESUB1\evsprod\nda215039\0004\m1\us\proposed-vijoice-uspi.pdf

G.2 Label and Labeling Images

Professional Sample

Container label – pull out blister card (50 mg daily dose, 125 mg daily dose, and 200 mg daily dose)

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[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JANINE A STEWART
03/04/2022 02:55:52 PM

Clinical Inspection Summary

Date	February 8, 2022
From	Lee Pai-Scherf, MD Karen Bleich, MD Kassa Ayalew, MD, MPH Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Sonia Singh, MD Diana Bradford, MD Harpreet Singh, MD, Division Director Division of Oncology 2 Office of Oncologic Products
NDA #	215039
Applicant	Novartis Pharmaceuticals Corp.
Drug	Alpelisib (BYL719)
NME (Yes/No)	No
Therapeutic Classification	Kinase inhibitor
Proposed Indication(s)	Treatment of adult and pediatric patients aged 2 years and older with PIK3CA-Related Overgrowth Spectrum (PROS)
Consultation Request Date	November 8, 2021
Summary Goal Date	February 15, 2022
Action Goal Date	April 6, 2022
PDUFA Date	April 6, 2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study EPIK-P1 were submitted to the Agency in support of NDA 215039 for alpelisib for the above proposed indication. Two clinical investigators (Drs. Marilyn Liang and Guilaume Canaud) were selected for clinical inspection.

On-site inspection of Dr. Liang revealed no significant findings. Based on the results of the inspection, the Study EPIK-P1 overall appears to have been conducted adequately at Dr. Liang's site and the data generated by Dr. Liang's site appear to be acceptable in support of the proposed indication in the NDA.

Investigation of Dr. Guilaume Canaud's site is ongoing at the time of this inspection summary. On-site inspection initiation was delayed due to travel restrictions related to the COVID-19

pandemic. An amendment to this inspection summary will be introduced once the Establishment Inspection Report (EIR) for Dr. Guilaume is available for GCP assessment and compliance by OSI.

II. BACKGROUND

Novartis submitted NDA 215039 seeking approval for alpelisib for the treatment of adult and pediatric patients age 2 years and older with PIK3CA-Related Overgrowth Spectrum (PROS).

Clinical data from study EPIK-P1 (CBYL719F12002), a retrospective medical chart review of patients with severe or life-threatening PROS who have received alpelisib as part of a compassionate use program (named Temporary Authorization for Use [ATU] in France or the Managed Access Program [MAP] by Novartis outside of France), were submitted to support this NDA.

The study abstract data from all eligible patients at all participating sites that had been previously recorded in the medical charts to assess the efficacy and safety of alpelisib for the treatment of the heterogeneous manifestations of PROS.

The study period is defined as the period from the index date up to the cut-off date (09-Mar-2020). The index date (baseline) was defined as the date of alpelisib initiation. The pre-index date period was defined as the period from up to 24 weeks prior to the index date through to the day prior to the index date. During the study period, all available data were collected from the index date up to the cut-off date.
Eligible subjects may only be included in the study after providing IRB/IEC approved informed consent (assent for pediatric patients).

The application includes safety data from 57 subjects aged 2 years and older with severe or life-threatening PROS and had documented evidence of mutation in the PIK3Ca gene as determined by a local laboratory. Subjects must have been treated with at least one dose of alpelisib. The efficacy population consists of 32 patients who had a scan at baseline with a measurable lesion as determined by the ICRR and had scan available to evaluate response at week 24.

The primary efficacy endpoint is the proportion of patients with response at Week 24 as assessed by an independent central radiology review (ICRR) of imaging scans.

The data cutoff date of the study is 03/09/2020. Seven clinical sites from 5 countries France (3 sites), Spain (1 site), Australia (1 site), Ireland (1 site) and U.S. (1 site) participated in the study.

Two clinical investigators were identified for inspection by DO2 and OSI: Dr. Guillaume Canaud (Site # 3000), enrolled 77% (44 of 57) subjects included in the retrospective chart

review study. Site # 5000 (Dr. M. Liang) was the only domestic site that enrolled subjects in study EPIK-PI.

III. RESULT

1. **Dr. Marilyn Liang** (site # 5000)
300 Longwood Ave
Boston Children's Hospital
Boston, MA 2215

Inspection dates: 12/8/2021 – 12/14/2021

Dr. Liang was inspected as a surveillance inspection for Study EPIK-PI. This is the first inspection for Dr. Lian.

The initial CI for the study was Dr. Denise Adams, who is no longer at the clinical site. Dr. Liang assume the CI responsibilities for the trial, chiefly oversee study close-out activities.

Data from two subjects ((b) (6)) were part of Study EPIK-PI: at the time of the inspection, one subject ((b) (6)) continues to be treated with alpelisib under the compassionate use program and 1 subject had discontinued from treatment due to an adverse event.

Source documents for the 2 subjects enrolled at the site were reviewed in depth. Both subjects met protocol specified inclusion and exclusion criteria. Study subject (b) (6) and parents of subject (b) (6) signed the informed consent form as per regulation requirements.

There was no underreporting of AEs or SAEs or significant protocol deviations.

There were no discrepancies or issues with the imaging process when compared to the information submitted to the NDA. All scans during the study period were submitted to central imaging review.

Other documents reviewed during the inspection include From FDA 1572, delegation of authority log, IRB approvals and associated documents, financial disclosure forms, training records, investigational drug accountability, and other source documents. No discrepancies or regulatory violations were observed.

The inspection found no regulatory violations at the site. No Form FDA 483 was issued to Dr. Liang at the conclusion of the inspection.

2. Dr. Canaud, Guillaume (site # 3000)
149 rue de Sevres
Paris cedex 15, NA 75015
FRA

Investigation of Dr. Guilaume Canaud's site is ongoing at the time of this inspection summary. An amendment to this inspection summary will be introduced once the Establishment Inspection Report (EIR) for Dr. Guilaume is available for GCP assessment and compliance by OSI.

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Lee Pai-Scherf, MD
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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