CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215039Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA OPQ Review and Evaluation

NDA 215039
Review # 01

OPQ RECOMMENDATION: APPROVAL

Drug Substance Retest Period: A cross reference is made to Alpelisib drug substance sections of approved NDA #212526, registered as Piqray®
FDA Assessment: Retest date of (b) (4) months may be granted when stored at the proposed storage conditions

Drug Product Expiration Dating Period: Proposed shelf life is 36 months and storage condition is (b) (4).
FDA Assessment: An expiration dating period of 36 months may be granted when stored at the proposed storage conditions.

Drug Name/Dosage Form	Alpelisib Film-Coated Tablets
Strength	50 mg, 125 mg, 200 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Indication	PIK3CA-related overgrowth spectrum (PROS)
Applicant	Novartis Pharmaceutical Corporation
US agent, if applicable	N/A

[FDA will complete these sections.]

Submit Date(s)	October 6, 2021
Received Date(s)	October 6, 2021
PDUFA Goal Date	April 6, 2022
Division/Office	Division of Oncology 2/Office of Oncologic Diseases
Review Completion Date	February 25, 2022
Established Name	**Alpelisib**
(Proposed) Trade Name	Vijoice
Pharmacologic Class	Kinase inhibitor
Recommendation on Regulatory Action	Approval

All FDA assessment is indicated in colored fonts: Executive Summary, Drug Substance, Drug Product, Environmental Assessment, labeling, Process, Facility, Biopharmaceutics, and Microbiology.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Pre-submission	*07/12/2021*	*OPMA*
Pre-submission	*09/08/2021*	*All*
Pre-submission	*09/20/2021*	*Biopharm*
Original NDA submission	*10/06/2021*	*All*
Quality Amendment	*11/16/2021*	*OPMA*
Quality Amendment	*12/08/2021*	*DP*
Quality Amendment	*02/02/2022*	*OPMA*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
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Drug Product	Olen Stephens	Xing Wang
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Regulatory Business Process Manager	Rabiya Haider	-
Application Technical Lead	Xing Wang	-
ORA Lead	N/A	-
Environmental	Olen Stephens	Xing Wang

RELATED/SUPPORTING DOCUMENTS

DMFs:

[Applicant will complete]				[FDA will complete]	
DMF #	**Type**	**Holder**	**Item Referenced**	**Status**	**Comments**
(b) (4)	Type III	(b) (4)		Adequate	Same as NDA 212526
	Type III			Adequate	Same as NDA 212526

Other Documents: *IND, RLD, or sister applications*

[Applicant will complete this section.]

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	143387	PROS IND. Cross reference anchor IND is 107078
NDA	212526	Piqray® NDA approved for the treatment of patients with HR-positive/HER2-negative advanced or metastatic breast cancer in the US (approved on 24-May-2019). Dosage form and strengths: 50 mg, 150 mg and 200 mg film-coated tablets

CONSULTS

[FDA will complete this section.]

None

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Evaluation of the Quality Information

[Applicant to provide link to the data in m3 sections as appropriate]

1. EXECUTIVE SUMMARY

[FDA (b) (4) will complete this section.]

Alpelisib (BYL719) is an oral α-specific class I phosphatidylinositol-3-kinase (PI3K) inhibitor. Alpelisib in combination with fulvestrant was approved by the Agency on 24-May-2019 under the name of Piqray for HR-positive/HER2-negative advanced or metastatic breast cancer (NDA 212526: 50 mg, 150 mg, and 200 mg). Postzygotic somatic mutations in PIK3CA have also been identified in a spectrum of overgrowth disorders comprising a wide group of clinically recognizable mutation-driven malformations now commonly known as PROS. Novartis has submitted type 10 NDA 215039 for VIJOICE (alpelisib) 50 mg, 125 mg, and 200 mg film-coated tablets for the treatment of adult and pediatric patients aged 2 years and older with PROS.

Alpelisib drug substance refers to NDA 212526. No new drug substance related information is noted in the current NDA 215039 submission; no impurity issue related to (b) (4) is noted in DS section.

The drug product formulation is derived from the approved PIQRAY® (alpelisib) tablets, using the same (b) (4). The VIJOICE (alpelisib) tablets contain the same quantitatively proportional formulation as PIQRAY® for the tablet core. The only change in the qualitative composition is in the pigments used in the (b) (4) film-coating. NDA 215039 for alpelsib film coated tablets uses the same drug product specifications for PIQRAY® (alpelsib) film coated tablets with the exception for the visual appearance of the film coat and the debossing. The difference in pigments and debossing are not expected to affect the drug product dissolution, quality, and in vivo performance. The applicant is relying upon stability data for the cross referenced and approved NDA212526 for PIQRAY® with limited stability data for the proposed 50 mg, 125 mg, and 200 mg tablets in this NDA. An expiration dating period of 36 months may be granted when stored at the proposed storage conditions.

Per 21CFR320.22(d)(2), the biowaiver request for the proposed middle strength of Alpelisib Tablets (yellow shades), 125 mg, is granted due to the following reasons:
a) Pharmacokinetic information/data of alpelisib have been reviewed in the approved NDA 212526, showing the linear pharmacokinetics of alpelisib with respect to dose and time in the tested dosage range of 30 mg to 450 mg under fed conditions.
b) The proposed Alpelisib Tablets (yellow shades), 50 mg, 125 mg and 200 mg, are compositional proportional with respect to the active and inactive ingredients across strengths.
c) The proposed Alpelisib Tablets (yellow shades), 50 mg, 125 mg and 200 mg, are manufactured using the same manufacturing process, at the same manufacturing site, controlled via the same specifications, and packaged in the same container closure system.

d) The one time point dissolution data support that the proposed Alpelisib Tablets (yellow shades), 50 mg, 125 mg and 200 mg have consistent dissolution during the stability testing.

The manufacturing process for Alpelisib 50 mg, 125 mg, and 200 mg (yellow shades) is based on the approved automated manufacturing process used for Piqray® (NDA 212526) using the same equipment and manufacturing process. The only change between Piqray® and Vijoice® is the difference in the film-coating pigment for product differentiation and debossing. The microbiological risk related to manufacturing process (b) (4) were assessed in previous review for Piqray®. The waiver of microbiological testing for the proposed drug product is further supported by 12 batches of Alpelisib 50 mg, 125 mg, and 200 mg film-coated tablets (yellow shades) manufactured at the commercial site.

All facilities are recommended for approval based on acceptable compliancy history and relevant manufacturing experience. No pre-approval inspection is identified.

The claim for categorical exclusion from an environmental assessment in accordance with 21 CFR 25.31(b) is acceptable.

In conclusion, OPQ recommends APPROVAL of NDA 215039.

Life Cycle Considerations:
[FDA (b) (4) to include any life-cycle considerations here]
(b) (4) yields were observed for the new strength- 125 mg. Yields from validation/commercial batches should be evaluated during next inspection.

2. APPLICATION BACKGROUND

Alpelisib is being administered to an increasing number of patients with a confirmed diagnosis of PROS and severe or life threatening disease via compassionate use programs in several countries worldwide (under the Managed Access Program (MAP) outside France and ATU in France). A clinical protocol that serves as a guidance document for the treatment and monitoring of patients under Managed Access Program (MAP) (CBYL719F12001M) was submitted to IND 107078 on 31-Jan-2019 (Serial No. 0603) and used to open IND 143387 for PROS on 11-Sep-2019 under an administrative split process. Considering the meaningful number of patients that are being treated globally with alpelisib under the compassionate use programs in this rare condition with high unmet medical need, as well as the results generated by Venot et al 2018, Novartis initiated a development program for alpelisib in PROS under IND 143387 after consultation with the FDA consisting mainly of data from a retrospective chart review study (EPIK-P1) and a prospective Phase II study (EPIK-P2).

Alpelisib was granted orphan-drug designation for the treatment of PROS on 18-Nov-2019 (DRU-201-7108; [correspond-grant-orphan-designation-20191118]). Alpelisib was granted breakthrough therapy designation for the treatment of patients with PROS on 13-Nov-2019 [correspond-grant-breakthrough-designation-20191113].

3. SUMMARY OF CMC SPECIFIC PRESUBMISSION AGREEMENTS

The Applicant's Position:

Date	Description	Pre-NDA agreements
02-Apr-2020	Type B pre-NDA meeting with the FDA to obtain agreement on the strategy of the planned NDA submission, including the content and format of the dossier for the proposed treatment of patients 2 years and older with PROS. The following was the CMC question: • Does the Agency agree that the drug product registration stability data proposal is acceptable for the NDA submission and to support the shelf-life?	The FDA agreed to the proposed drug product registration stability data for the NDA submission.
09-Jul-2021	Type B pre-NDA meeting was scheduled to discuss the top-line efficacy and safety results from EPIK-P1 and obtain agreement on the revised content and timeline of 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 PROS. The following was the CMC question: 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:	• FDA agreed to the proposal of requesting a biowaiver for the proposed 125 mg strength of alpelisib tablets. • FDA agreed with the bracketing proposal for the 125 mg strength. • Novartis agreement with the FDA to submit a Product Quality Assessment Aid within this Type 10 NDA to facilitate a faster review. As communicated in the response document addressing

	• The approach to submit a bio-waiver request for the proposed commercial alpelisib 125 mg film-coated tablet in the Type 10 NDA? • 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? Meeting was cancelled after preliminary comments were received	preliminary comments that was submitted to the FDA, Novartis has cross-referenced Piqray (alpelisib) NDA 212526 where applicable for information previously submitted in Module 3 (drug substance and drug product). • Agreement with the FDA to submit the Module 3 components on 08-Sep-2021, earlier than the intended schedule.

The FDA's Assessment: ***Consistent with FDA's records***

[FDA will complete this section.]

4. ENVIRONMENTAL ASSESSMENT

The Applicant's Position:

As set forth in 21 CFR Part 25.31(b), action on a New Drug Application (NDA) is categorically excluded from the requirement to prepare an Environmental Assessment (EA) or an Environmental Impact Statement (EIS) if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be less than 1 part per billion (ppb). "Increased use", as defined in 21 CFR Part 25.5(a), will occur if the drug is "administered at higher dosage levels, for longer duration or for different indications than were previously in effect, or if the drug is a new molecular entity."

Novartis Pharmaceuticals Corporation is submitting a Type 10 New Drug Application (NDA 215039) for alpelisib (BYL719). Alpelisib is an oral α-specific class I phosphatidylinositol-3-kinase (PI3K) inhibitor belonging to the 2-aminothiazole class of compounds. Alpelisib potently inhibits p110α, in its wild-type form as well as when constitutively activated by somatic mutations, and inhibits less strongly the β, δ, and γ isoforms of PI3K.

Alpelisib in combination with fulvestrant was approved by the United States (US) Food and Drug Administration (FDA) on 24-May-2019 under the name of Piqray® 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.

The indication being proposed in this Type 10 NDA is for the treatment of adult and pediatric patients 2 years and older with PIK3CA-related overgrowth spectrum (PROS).

Novartis certifies that this Type 10 NDA submission for alpelisib qualifies for a categorical exclusion in accordance with 21 CFR Part 25.31(b) as the estimated environmental intake concentration of the active moieties, alpelisib, will be significantly less than 1 ppb, based on the peak production estimates within the next five years.

Further, Novartis states that, to the best of its knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment and would thus require the preparation of at least an Environmental Assessment.

The FDA's Assessment: ***Adequate***

The applicant gave estimated total production for all US relevant dosage forms and strengths of alpelisib over the next five years. The maximum estimated products is (b) (4) kg in 2026, which would yield an EIC of (b) (4) ppb, which is significantly lower than the 1 ppb limit that would require an environmental assessment. Novartis states that to the best of their knowledge there are no extraordinary circumstances to consider regarding the requirement for an environmental assessment. The applicant's request for a waiver from the environmental assessment is accepted.

5. FACILITIES

(b) (4)

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

Comparability Protocols for post-approval changes and comparability protocols for facilities or manufacturing (if any)
N/A
The FDA's Assessment: ***Adequate***

[FDA will complete this section.]

8. BIOPHARMACEUTICS

a. BCS CLASSIFICATION

Applicant to fill:	FDA assessment (FDA to fill):
BCS Classification: BCS II	Acceptable

Information to support the BCS Class II designation request, if applicable.
Link: Summary of biopharmaceutics is available in CTD section 2.7.1 of Piqray NDA #212526. Page#:

b. DISSOLUTION TEST

The dissolution test method and requirements applied for Alpelisib 50 mg, 125 mg and 200 mg film-coated tablets (yellow shades) are same as that used for the dissolution testing of Piqray® commercial batches.

USP Apparatus	Paddle Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criterion
II	75 ± 3 rpm	900 mL	37 ± 0.5 °C	0.6 % CTAB (cetyltrimethyl ammonium bromide) in pH 4.5 acetate buffer	Not less than (b) (4) % (Q value) of the declared content after 30 minutes.

The discriminatory power of the dissolution method has been established and is already justified and approved in Piqray® NDA (Please see Appendix 6, 3.2.P.2 (document 6003036_P2_M_840_1) of Piqray® NDA #212526).

Biopharmaceutics Figure 1: Dissolution Profiles as a function of:

a. Impact of medium pH on dissolution

Applicant to insert figure here:	Applicant's comments:
FDA Comment: *Please see the FDA's Assessment for section 8b below*	

b. Impact of paddle Speed on dissolution Applicant to insert figure here:	Applicant's comments:
FDA Comment: *Please see the FDA's Assessment for section 8b below*	
c. Impact of parameter X on dissolution (add as appropriate) Applicant to insert figure here:	Applicant's comments:
FDA Comment: *Please see the FDA's Assessment for section 8b below*	
d. Impact of parameter Y on dissolution (add as appropriate) Applicant to insert figure here:	Applicant's comments:
FDA Comment: *Please see the FDA's Assessment for section 8b below*	
e. Impact of parameter Z on dissolution (add as appropriate) Applicant to insert figure here:	Applicant's comments:
FDA Comment: *Please see the FDA's Assessment for section 8b below*	
f. Justification for selection of the acceptance criteria (or criterion) Applicant to indicate whether complete dissolution profile data are available for all stability timepoints. Applicant to insert multipoint dissolution profile in a graphical format from clinical/PK and primary registration batches figure(s) here:	Applicant's comments:
FDA Comment: *Please see the FDA's Assessment for section 8b below*	

	Applicant to fill:	FDA assessment: *Please see the FDA's Assessment for section 8b below*
The dissolution method is discriminating for:		
i) Particle size distribution (PSD) Link[1]:	Choose an item.	Not applicable Page#:
ii) Polymorph/solid state form Link[1]:	Choose an item.	Not applicable Page#:
iii) Formulation variations Link[1]:	Choose an item.	Not applicable Page#:
iv) Manufacturing process variations Link[1]:	Choose an item.	Not applicable Page#:
v) Other (specify): Link[1]:	Choose an item.	Not applicable Page#:

[1]The applicant to provide link to the appropriate section in the submission. FDA reviewer may update the link as needed.

The FDA's Assessment for Section 8b:

The proposed drug product, Alpelisib Film-Coated Tablets (*yellow shades*), 50 mg (*light yellow*), 125 mg (*dark yellow*) and 200 mg (*pale yellow*), is an immediate-release dosage form for oral administration for the treatment of patients with PIK3CA-related overgrowth spectrum (PROS). This Applicant had a drug product, Piqray® (*pink and red shades*), Alpelisib Film-Coated Tablets 50 mg (*light pink*), 150 mg (*pale red*) and 200 mg (*light red*) for the treatment of patients with HR-positive/HER2-negative advanced or metastatic breast cancer, approved under NDA 212526 on 05/24/2019.

Per the Applicant, the proposed and approved Alpelisib Tablets have the same qualitative and quantitative composition for core tablets but differ in pigments (*yellow shades vs. pink and red shades*) in the (b) (4) film-coating and debossing to allow for product differentiation. The manufacturing process of the proposed Alpelisib Film-Coated Tablets (*yellow shades*) is based on the approved manufacturing process used for Piqray®. The manufacturing site (Novartis Pharma Stein AG, Stein Switzerland) for the proposed Alpelisib Film-Coated Tablets (*yellow shades*) is the same site as Piqray®.

Since the biopharmaceutical properties of the drug substance, Alpelisib, including physicochemical properties, analytical methods and pharmacokinetics (PK), have been submitted in NDA 212526, no new PK samples/data are collected for patients with PROS receiving Alpelisib in the currently submitted retrospective chart review study (EPIK-P1) in this NDA 215039. To support the current NDA 215039, a 505(b)(1), the Applicant provided a report of clinical overview including the information with regards to serious adverse events (SAEs) and deaths in PROS patients, a report of population PK of alpelisib in patients with PROS, an addendum to nonclinical overview previously submitted to NDA 212526 (a brief overview of the transporter study DMPK R2000201 that was completed after Piqray® NDA submission), and the summaries of literature information specifically relevant to the PROS indication.

Biopharmaceutics Review for this NDA 215039 focuses on: (1) the in vitro dissolution method and acceptance criteria as a quality control (QC) test for the proposed drug product, (2) the need of bridging, (3) biowaiver request for the proposed middle strength of Alpelisib Tablets, 125 mg.

In Vitro Dissolution Testing of the Finished Drug Product:
The following dissolution method and acceptance criteria are acceptable as the QC test for the proposed Alpelisib Tablets, 50 mg, 125 mg and 200 mg.

USP Apparatus	II (Paddle)
Rotation Speed	75 rpm
Medium and Volume	900 mL of 0.6% cetyltrimethylammonium bromide (CTAB) in acetate buffer pH 4.5
Temperature	37 ± 0.5°C
Acceptance Criteria	Q = (b) (4)% in 30 minutes

The drug substance, Alpelisib, is considered a BCS II (low solubility, high permeability) compound[1]. The Applicant referred the drug substance information to the approved NDA 212526.

The composition of the proposed Alpelisib Tablets (*yellow shades*), 50 mg, 125 mg, and 200 mg is presented in Table 1 below. The three strengths of the proposed drug product are compositional proportional with respect to the tablet core.

Table 1: Composition of the proposed Alpelisib Film-Coated Tablets (*yellow shades*), 50 mg, 125 mg and 200 mg
(*from Table 1-2 of M.2.3 of NDA 215039*)

Ingredients	Amount per film-coated tablet (mg)			Function	Reference to standards
	50 mg	125 mg	200 mg		
Tablet core					
Alpelisib [1]	50.00	125.00	200.00	Active ingredient	Novartis monograph
(b) (4) Microcrystalline cellulose	(b) (4)				Ph. Eur., USP/NF, JP
Mannitol (b) (4)					Ph. Eur., USP/NF, JP
(b) (4)					Ph. Eur., USP/NF, JP
Sodium starch glycolate (b) (4)					Ph. Eur., USP/NF, JP
Hypromellose					Ph. Eur., USP/NF, JP
Magnesium stearate [2]					Ph. Eur., USP/NF, JP
(b) (4)					Ph. Eur., USP/NF, JP
Weight of tablet core:					
Film-coating					
(b) (4)	(b) (4)				Novartis monograph
Hypromellose					Ph. Eur., USP/NF, JP
Iron oxide, red (b) (4)					Regulation (EU) 231/2012 [5], USP/NF, JPE
Macrogol 4000, Polyethylene glycol (PEG) 4000					Ph. Eur., USP/NF
Talc					Ph. Eur., USP/NF, JP
(b) (4)					Novartis monograph
Titanium dioxide (b) (4)					Ph. Eur., USP/NF, JP
(b) (4)					Ph. Eur., USP/NF, JP
					Ph. Eur., USP/NF
					Ph. Eur., USP/NF, JP
					Novartis monograph
					Ph. Eur., USP/NF, JP
Iron oxide, yellow (b) (4)					Regulation (EU) 231/2012 [6], USP/NF, JPE
(b) (4)					Ph. Eur., USP/NF
					Ph. Eur., USP/NF, JP
					Ph. Eur., USP /NF, JP
Total weight of film-coated tablet:	127.00	314.3	500.00		

[1] Alpelisib (b) (4)

(b) (4)

[1] NDA 212526-ORIG-1, IQA Review, Biopharmaceutics Section, dated 03/20/2019: https://panorama.fda.gov/internal/document/preview?versionID=5c928f74013256762b1d980e3fcefb09&ID=5c927d4e001b64d15f50630f7fea2062

The comparison between the approved Piqray® and proposed Alpelisib Tablets are presented in the following Tables 2 to 4. Per the Applicant, the difference in pigment and debossing are within Level 1 change per the principles of FDA SUPAC-IR guidance.

Table 2: Description of the approved Piqray (*pink and red shades*) and the proposed Alpelisib Tablets (*yellow shades*), 50 mg, 125 mg, and 200 mg (*from Table 1-1 of M.2.7.1 of NDA 215039*)

Strength	Description of alpelisib film-coated tablets	
	Formulation E (Piqray®, approved NDA)	**Formulation F (Formulation in yellow shades)**
50 mg	**Light pink**, unscored, round and curved with beveled edges film-coated tablet, imprinted with "**L7**" on one side and "NVR" on the other side Approximate size: Diameter: 7.2 mm	**Light yellow**, unscored, round and curved film-coated tablet with beveled edges, debossed with "**C7**" on one side and "NVR" on the other side Approximate size: Diameter: 7.2 mm
125 mg	**Not applicable**	**Dark yellow, unscored, ovaloid and curved film-coated tablet with beveled edges, debossed with "Y7" on one side and "NVR" on the other side Approximate size: Length: 13.2 mm Width: 5.7 mm**
150 mg	**Pale red, unscored, ovaloid and curved with beveled edges film-coated tablet, imprinted with "UL7" on one side and "NVR" on the other side Approximate size: Length: 14.2 mm Width: 5.7 mm**	**Not applicable**
200 mg	**Light red**, unscored, ovaloid and curved with beveled edges film-coated tablet, imprinted with "**YL7**" on one side and "NVR" on the other side Approximate size: Length: 16.2 mm Width: 6.5 mm	**Pale yellow**, unscored, ovaloid and curved film-coated tablet with beveled edges, debossed with "**CL7**" on one side and "NVR" on the other side Approximate size: Length: 16.2 mm Width: 6.5 mm

Source [Module 3.2.P.2]

Table 3: Composition comparison between the approved Piqray (*pink and red shades*) 50 mg and 200 mg and the proposed Alpelisib Tablets (*yellow shades*) 50 mg and 200 mg (*from Table 1-2 of M.2.7.1 of NDA 215039*)

Ingredients	Piqray® film-coated tablets (approved NDA)		Alpelisib film-coated tablets, (yellow shades)	
	Amount per 50 mg tablet (mg)	Amount per 200 mg tablet (mg)	Amount per 50 mg tablet (mg)	Amount per 200 mg tablet (mg)
Tablet core				
Alpelisib [1]	50.00	200.00	50.00	200.00
(b) (4)				(b) (4)
Microcrystalline cellulose (b) (4)				
Mannitol, (b) (4)				
(b) (4)				
Sodium starch glycolate				
Hypromellose				
Magnesium stearate [2]				
(b) (4)				
Film-coating				
(b) (4)				
Hypromellose				
Iron oxide, black (b) (4)				
(b) (4)				
Macrogol 4000, Polyethylene glycol (PEG) 4000				
Talc				
(b) (4)				
Iron oxide, red (b) (4)				
(b) (4)				
(b) (4)				
Titanium dioxide (b) (4)				
(b) (4)				

(b) (4)	(b) (4)			(b) (4)
Iron oxide, yellow	(b) (4)			
	(b) (4)			
Total weight of film-coated tablet:		127.00	500.00	127.00	500.00

[1] Alpelisib (b) (4)

(b) (4)

Table 4: Description of SUPAC Level 1 changes between the approved Piqray (*pink and red shades*) 50 mg and 200 mg and the proposed Alpelisib Tablets (*yellow shades*) 50 mg and 200 mg (*from Table 1-3 of M.2.7.1 of NDA 215039*)

		50 mg film-coated tablets				200 mg film-coated tablets			
		Piqray® (Light pink, approved NDA)	Alpelisib (Light yellow)	% w/w difference out of the total target dosage form (A-B)		Piqray® (Light red, approved NDA)	Alpelisib (Pale yellow)	% w/w difference out of the total target dosage form (C-D)	
Ingredient	**Function**	**Amount per tablet in mg (A)**	**Amount per tablet in mg (B)**		**SUPAC Level classification**	**Amount per tablet in mg (C)**	**Amount per tablet in mg (D)**		**SUPAC Level classification**
Alpelisib [1]	Active ingredient	50.00	50.00	Nil	No change	200.00	200.00	Nil	No change
(b) (4)				(b) (4)	No change			(b) (4)	No change
Microcrystalline cellulose (b) (4)									
Mannitol, (b)					No change				No change
(b) (4)					No change				No change
					No change				No change
Sodium starch glycolate									
Magnesium stearate [2]					No change				No change
(b) (4)					No change				No change

Ingredient	Function	50 mg film-coated tablets: Piqray® (Light pink, approved NDA) Amount per tablet in mg (A)	50 mg film-coated tablets: Alpelisib (Light yellow) Amount per tablet in mg (B)	50 mg film-coated tablets: % w/w difference out of the total target dosage form (A-B)	50 mg film-coated tablets: SUPAC Level classification	200 mg film-coated tablets: Piqray® (Light red, approved NDA) Amount per tablet in mg (C)	200 mg film-coated tablets: Alpelisib (Pale yellow) Amount per tablet in mg (D)	200 mg film-coated tablets: % w/w difference out of the total target dosage form (C-D)	200 mg film-coated tablets: SUPAC Level classification
Hypromellose				(b) (4)	No change			(b) (4)	No change
Macrogol 4000, Polyethylene glycol (PEG) 4000					No change				No change
Talc					No change				No change
Iron oxide, black (b) (4) (b) (4)					SUPAC Level 1				SUPAC Level 1
Iron oxide, red (b) (4) (b) (4)					SUPAC Level 1				SUPAC Level 1
Titanium dioxide (b) (4)					SUPAC Level 1				SUPAC Level 1
Iron oxide, yellow (b) (4)					SUPAC Level 1 [12]				SUPAC Level 1 [12]
Total weight of film-coated tablet:		127.00	127.00			500.00	500.00		

Per the Applicant, the manufacturing process for the proposed Alpelisib Tablets is based on the approved automated manufacturing process used for the approved Piqray (NDA 212526/S-002, approved on 11/23/2020[2]). The same ranges (b) (4) are approved for Piqray and applied to the proposed Alpelisib Tablets (*yellow shades*) 50 mg, 125 mg and 200 mg.

The proposed Alpelisib Tablets (*yellow shades*) 50 mg, 125 mg and 200 mg are manufactured at same manufacturing site with the approved Piqray, which is Novartis Pharma Stein AG, Schaffhauserstrasse, 4332 Stein, Switzerland (FEI/DUNS: 3002653483/488152505).

Therefore, the Applicant adapted the same approved dissolution method and acceptance criterion from the approved drug product, Piqray® 50 mg, 150 mg and 200 mg, as a quality control (QC) dissolution test for the proposed drug product, Alpelisib Tablets (*yellow shades*) 50 mg, 125 mg and 200 mg. The dissolution method and acceptance criterion are listed as below:

USP Apparatus	II (Paddle)
Rotation Speed	75 rpm
Medium and Volume	900 mL of 0.6% cetyltrimethylammonium bromide (CTAB) in acetate buffer pH 4.5
Temperature	37 ± 0.5°C
Acceptance Criteria	Q = (b) (4)% in 30 minutes

2 https://panorama.fda.gov/internal/document/preview?versionID=5fbc36b60115db8ea3f7d018e7547baa&ID=5fbbdc270104684085489662f038c590

The one time point of dissolution data at 30 minutes of the pre-validation batches, the validation batches and the registration stability batches of the proposed Alpelisib Tablets (*yellow shades*) 50 mg, 125 mg and 200 mg are summarized by this Reviewer and presented in Table 5 below. Per the Applicant, the three development batches ("pre-validation") were manufactured at the commercial scale, using the commercial equipment to demonstrate the robustness of the manufacturing process within the proposed process parameter ranges prior to formal process validation. The pre-validation and validation batches were manufactured using the same process. The registration batches are reported for six months under the long-term and accelerated stability conditions in the current submission.

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Table 5: Dissolution data at 30 minutes of the pre-validation batches, the validation batches and the registration batches of the proposed Alpelisib Tablets (*yellow shades*) 50 mg, 125 mg and 200 mg (*from M.3.2.P.5.4 and M.3.2.P.8.3 of NDA 215039*)

Alpelisib Tablets	Batch Numbers	Dissolution at 30 minutes (b) (4)
50 mg	Pre-validation batch 1010026051	
	Pre-validation batch 1010026241	
	Pre-validation batch 1010026053	
50 mg	Validation batch SXU26	
	Validation batch SXU27	
	Validation batch SXU28	
50 mg (*25°C/60% RH, 0-6 months*)	Stability batch 32063410	
	Stability batch 32063409	
	Stability batch 32064499	
125 mg	Pre-validation batch 1010026054	

		(b) (4)
	Pre-validation batch 1010026243	
	Pre-validation batch 1010026057	
125 mg	Validation batch SXU42	
	Validation batch SXU46	
	Validation batch SXU47	
125 mg (*25°C/60% RH, 0-3 months*)	Stability batch 32083906	
	Stability batch 32083909	
	Stability batch 32084104	
200 mg	Pre-validation batch 1010026058	
	Pre-validation batch 1010026242	
	Pre-validation batch 1010026060	
200 mg	Validation batch SXU38	
	Validation batch SXU39	
	Validation batch SXU40	
200 mg (*25°C/60% RH, 0-6 months*)	Stability batch 32063431	
	Stability batch 32063432	
	Stability batch 32063433	

Overall, the minor changes in pigments (*yellow shade vs. pink and red shades*) and debossing are not expected to affect the drug product dissolution. The one time point dissolution data are supportive for the proposed dissolution acceptance criterion. Therefore, the proposed dissolution method and acceptance criterion are acceptable for the proposed drug product, Alpelisib Tablets (*yellow shades*) 50 mg, 125 mg and 200 mg.

c. BRIDGING THROUGHOUT DRUG PRODUCT DEVELOPMENT (FORMULATION, PROCESS, OR SITE CHANGE)

Novartis has developed a slightly modified formulation, Alpelisib 50 mg, 125 mg and 200 mg film-coated tablets (yellow shades) which is based on the Piqray® (approved NDA) formulation, Alpelisib 50 mg, 150 mg and 200 mg film-coated tablets (pink and red shades). The colors have been adapted from the Piqray® film-coated tablets (approved NDA) for product differentiation purposes while retaining the same tablet core composition to maintain the consistent and reproducible manufacture of a high quality drug product. All three proposed Alpelisib 50 mg, 125 mg and 200 mg film-coated tablets (yellow shades) have core tablets of the same composition (i.e., qualitatively the same and quantitatively dose proportional with respect to the active and inactive components) and use different pigments in the (b) (4) film-coating compositions to allow for product differentiation. A comparison of the descriptions of Piqray® (approved NDA) and Alpelisib 50 mg, 125 mg and 200 mg film-coated tablets (yellow shades) is provided in Table 2-1, 3.2.P.2 (document 6004997_SM_A_P2_840); differences are highlighted in **bold** text.

In addition, the 50 mg and 200 mg strengths of Alpelisib film-coated tablets (yellow shades) have core tablets of the same composition as Piqray® (approved NDA) with minor modifications in the pigments used in the (b) (4) film-coating compositions and debossing to allow for product differentiation.

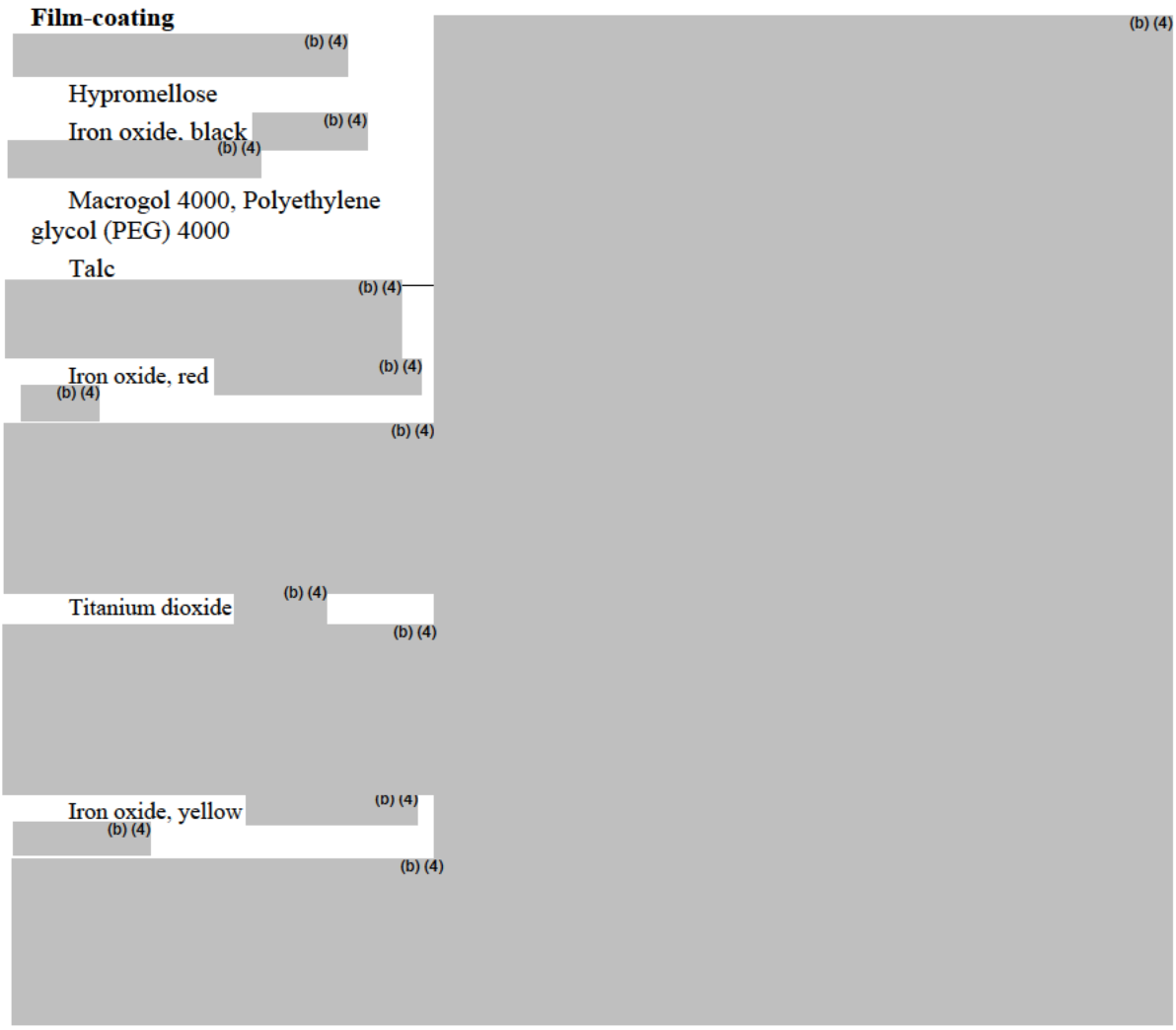
Bridging of changes between Piqray (Alpelisib 50 mg and 200 mg film-coated tablets, approved NDA) and Alpelisib 50 mg and 200 mg film-coated tablets (yellow shades)

A qualitative and quantitative comparison of the compositions of Piqray® (approved NDA) and Alpelisib 50 mg and 200 mg film-coated tablets (yellow shades) is provided in the following Table. The differences are highlighted in **bold** font. The minor modifications in the pigments used in the (b) (4) film-coating compositions and debossing to support the product differentiation of yellow shade formulation from Piqray® (approved NDA) have no detectable impact on formulation quality and performance.

A summary of the minor modifications considering the FDA "Scale-up and Post-Approval Changes - Immediate Release Solid Oral Dosage Forms (SUPAC IR): Chemistry, Manufacturing and Controls, In-vitro Dissolution Testing and In-vivo Bioequivalence Documentation" guidance is provided in Section 2.1.1.1, 3.2.P.2 (document 6004997_SM_A_P2_840).

Table **Composition of Piqray (approved NDA) and Alpelisib 50 mg and 200 mg film-coated tablets (yellow shades)**

Ingredients	Piqray® film-coated tablets (approved NDA)		Alpelisib film-coated tablets, (yellow shades)	
	Amount per 50 mg tablet (mg)	Amount per 200 mg tablet (mg)	Amount per 50 mg tablet (mg)	Amount per 200 mg tablet (mg)
Tablet core				
Alpelisib [1]	50.00	200.00	50.00	200.00
(b) (4)				
Microcrystalline cellulose (b) (4)				
Mannitol (b) (4)				
(b) (4)				
Sodium starch glycolate (b) (4)				
(b) (4)				
Hypromellose				
Magnesium stearate [2]				
(b) (4)				



Total weight of film-coated tablet:	127.00	500.00	127.00	500.00

[1] Alpelisib (b) (4)

(b) (4)

The changes in excipients, expressed as percentage (w/w) of the target total weight of the dosage form are described in Table below:

Table Description of SUPAC Level 1 changes between Piqray (approved NDA) and Alpelisib 50 mg and 200 mg film-coated tablets (yellow shades)

Ingredient	Function	50 mg film-coated tablets				200 mg film-coated tablets			
		Piqray® (Light pink, approved NDA) Amount per tablet in mg (A)	Alpelisib (Light yellow) Amount per tablet in mg (B)	% w/w difference out of the total target dosage form (A-B)	SUPAC Level classification	Piqray® (Light red, approved NDA) Amount per tablet in mg (C)	Alpelisib (Pale yellow) Amount per tablet in mg (D)	% w/w difference out of the total target dosage form (C-D)	SUPAC Level classification
Alpelisib [1]	Active ingredient	50.00	50.00	Nil	No change	200.00	200.00	Nil	No change
(b) (4)					No change				No change
Microcrystalline cellulose (b) (4)									
Mannitol, (b) (4) (b) (4)					No change				No change
(b) (4)					No change				No change
Sodium starch glycolate (b) (4) (b) (4)					No change				No change
Magnesium stearate [2]					No change				No change

Ingredient	Function	50 mg film-coated tablets				200 mg film-coated tablets			
		Piqray® (Light pink, approved NDA) Amount per tablet in mg (A)	Alpelisib (Light yellow) Amount per tablet in mg (B)	% w/w difference out of the total target dosage form (A-B)	SUPAC Level classification	Piqray® (Light red, approved NDA) Amount per tablet in mg (C)	Alpelisib (Pale yellow) Amount per tablet in mg (D)	% w/w difference out of the total target dosage form (C-D)	SUPAC Level classification
(b) (4)				(b) (4)	No change			(b) (4)	No change
					No change				No change
Macrogol 4000, Polyethylene glycol (PEG) 4000					No change				No change
Talc					No change				No change
Iron oxide, black (b) (4) (b) (4)					**SUPAC Level 1**				**SUPAC Level 1**
Iron oxide, red (b) (4) (b) (4)					**SUPAC Level 1**				**SUPAC Level 1**
Titanium dioxide (b) (4)					**SUPAC Level 1**				**SUPAC Level 1**
Iron oxide, yellow (b) (4)					**SUPAC Level 1** [12]				**SUPAC Level 1** [12]

Ingredient	Function	50 mg film-coated tablets				200 mg film-coated tablets			
		Piqray® (Light pink, approved NDA) Amount per tablet in mg (A)	Alpelisib (Light yellow) Amount per tablet in mg (B)	% w/w difference out of the total target dosage form (A-B)	SUPAC Level classification	Piqray® (Light red, approved NDA) Amount per tablet in mg (C)	Alpelisib (Pale yellow) Amount per tablet in mg (D)	% w/w difference out of the total target dosage form (C-D)	SUPAC Level classification
Total weight of film-coated tablet:		127.00	127.00			500.00	500.00		
[1] Alpelisib	(b) (4)	(b) (4)							

Based on the above discussion, it can be concluded that the change in pigments is minor and have no impact on formulation quality and performance of Alpelisib 50 mg and 200 mg film-coated tablets (yellow shades).

Manufacturing process development

Alpelisib 50 mg, 125 mg and 200 mg film-coated tablets (yellow shades) are manufactured [redacted] The manufacturing process for Alpelisib 50 mg, 125 mg and 200 mg (yellow shades) is based on the approved automated manufacturing process used for Piqray® (Prior Approval Supplement to the NDA #212526/S-002), which was optimized to consistently and reproducibly deliver a high quality commercial drug product.

The development history of Alpelisib film-coated tablets (Piqray®, approved NDA) is located in [Section 3, 3.2.P.2, (document 6003036_P2_M_840_1)]. The original manufacturing process was validated and commercialized for Piqray®. Subsequently, an alternative automated manufacturing process was developed and approved for the commercial production of Piqray® tablets utilizing a technologically advanced manufacturing line and different equipment capacities. Only the automated manufacturing process is used for the manufacture of Alpelisib 50 mg, 125 mg and 200 mg film-coated tablets (yellow shades) and its manufacturing process development is described in "Pharmaceutical Development" [3.2.P.2, (document 6003036_SM_A_P2_ RD01_840)] of Piqray® NDA.

Optimization of automated process for yellow formulation pre-validation campaign at commercial scale

Three development batches ('pre-validation') were manufactured at commercial scale, using the commercial equipment to demonstrate the robustness of the manufacturing process within the proposed process parameter ranges prior to formal process validation. [redacted] are approved for Piqray® film-coated tablets and applied to the three dosage strengths of Alpelisib 50 mg, 125 mg and 200 mg film-coated tablets (yellow shades). The [redacted] ranges as applied and approved for Piqray® 50 mg and 200 mg film-coated tablets, including the CPP [redacted] are applied to the corresponding Alpelisib 50 mg and 200 mg film-coated tablets (yellow shades). The [redacted] ranges for the bracketed Alpelisib 125 mg strength are based on the knowledge gained [redacted] throughout the development of Piqray® (approved NDA) and this PROS film-coated tablet formulation.

The pre-validation batches were manufactured at the commercial manufacturing site, Novartis Pharma Stein AG, Stein, Switzerland. [redacted] The pre-validation batch details are presented in Table 3-1, 3.2.P.2 (document 6004997_SM_A_P2_840).

The objective of this exercise was as follows:

a. To establish and demonstrate the Proven Acceptable Ranges (PAR) [redacted], which were adapted from the commercialized Piqray® process [redacted]
b. To establish and demonstrate the [redacted] process parameters for the bracketed 125 mg dosage strength
c. To demonstrate the Proven Acceptable Ranges (PAR) (already established and commercialized for Piqray®) are appropriate for the 50 mg and 200 mg dosage strengths [redacted]

Summary of process optimization is provided in Section 3.2.1, 3.2.P.2 (document 6004997_SM_A_P2_840).

Link: Sections 2.1 and 3, 3.2.P.2 (document 6004997_SM_A_P2_840) Page#: 9, 22

The FDA's Assessment: ***Adequate***

Since (a) the proposed Alpelisib Tablets (yellow shades) 50 mg, 125 mg and 200 mg and the approved Piqray (pink and red shades, Alpelisib Tablets 50 mg, 150 mg and 200 mg) have same core tablet composition (qualitatively and quantitatively) with only difference in pigments (yellow shade vs. pink and red shades) and debossing, (b) the manufacturing process of the proposed drug product is based on the approved manufacturing process used for Piqray, (c) the manufacturing site for the proposed drug product is the same as Piqray, therefore, the minor changes in pigment, debossing and manufacturing process are not expected to affect the drug product quality and in vivo performance. Therefore, bridging is not needed.

d. BIOWAIVER REQUEST

The Applicant's Position:

The NDA does contain a biowaiver request

Biowaiver request for Alpelisib 125 mg film-coated tablets

A biowaiver is requested from conducting an *in-vivo* bioavailability study in accordance with 21 CFR § 320.22(d)(2) and the Committee for Medicinal Products (CHMP) Guideline on the Investigation on Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1) for the Alpelisib 125 mg film-coated tablets based on the establishment of comparability with the highest strength (200 mg) of Piqray® (approved NDA) film-coated tablets.

The criteria summarized below supports the biowaiver as discussed with the Health Authorities.

- Pharmacokinetic data demonstrating linear pharmacokinetics of alpelisib, with respect to dose and time, in the tested dosage range of 30 mg to 450 mg under fed conditions (Section [2.7.1]);
- Information demonstrating that the proposed commercial formulations of Alpelisib 50 mg, 125 mg and 200 mg film-coated tablets are qualitatively the same and

compositionally proportional with respect to the active and inactive ingredients across strengths (Section 2.1.1, 3.2.P.2);

- The proposed commercial strengths are manufactured by the same manufacturing process at the same manufacturing site, controlled via the same specifications, and packaged in the same container closure system; and
- In-vitro dissolution data showing that the product exhibits similar dissolution profiles for the 125 mg test batch and 200 mg reference batch (Piqray®, approved NDA), meeting the criteria of the f1 and f2 test in multiple dissolution media (e.g. 0.1 N HCl, 0.01 N HCl, pH 4.5, pH 6.8, water and the registered batch release media (0.6% Cetyltrimethyl ammonium bromide in acetate buffer pH 4.5)). The dissolution profiles (n = 12) were generated using the same dissolution conditions. Please refer to Section [2.7.1] and "Dissolution Comparability Report" [General Report-ARD000060] for more details.

Link: General Report-ARD000060, "Summary of Biopharmaceutics Studies and Associated Analytical Methods" [2.7.1] and [Module 1] Page#: Page 17 of 3.2.P.2

[To the Applicant: Insert text here]

The FDA's Assessment: ***Adequate***

In the pre-NDA preliminary comments dated 07/06/2021, for a Type B meeting cross-referenced to IND 143387[3, 4], FDA conveyed the following comments under Question 7a with regards to the biowaiver request:

> 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

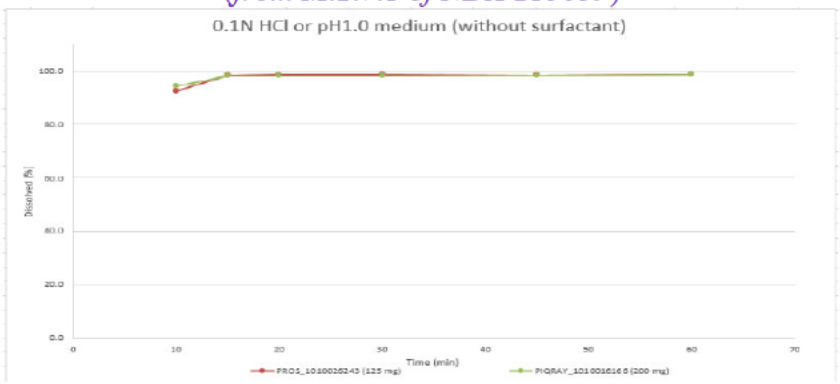
[3] IND 143387 Preliminary Comments dated 07/06/2021: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80600188&_afrRedirect=2209804884287209

[4] IND 143387 Meeting Request Cancellation dated 07/22/201: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80604ac2&_afrRedirect=2209851330080682

granting the biowaiver for this strength will be made during the NDA's review. In the current NDA 215039, the Applicant submitted a biowaiver request for the proposed middle strength of Alpelisib Tablets (*yellow shades*), 125 mg, against the approved Piqray Tablets, 200 mg, per 21 CFR 320.22(d)(2). The middle strength of 125 mg is developed as a bracketed strength between the proposed Alpelisib Tablets 50 mg and 200 mg, which are used in the retrospective chart review study (EPIK-P1).

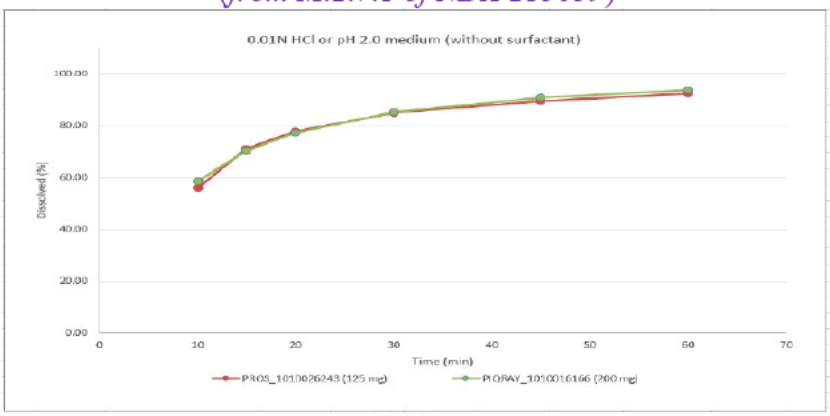
The comparative dissolution data profiles between the proposed middle strength of Alpelisib Tablets, 125 mg (batch 1010026234), and the approved Piqray Tablets, 200 mg (batch 1010016166), are provided and presented in the Figures 1 to 6 below. The used dissolution conditions are: USP Apparatus II Paddle, 75 rpm, 900 mL of 0.6% CTAB in acetate buffer pH 4.5 (QC medium), 0.1 N HCl (pH 1.0), 0.01 N HCl (pH 2.0), pH 4.5, pH 6.8 and water without surfactant.

Figure 1: Comparative dissolution profiles in pH 1.0 medium (without surfactant) (*from M.2.7.1 of NDA 215039*)



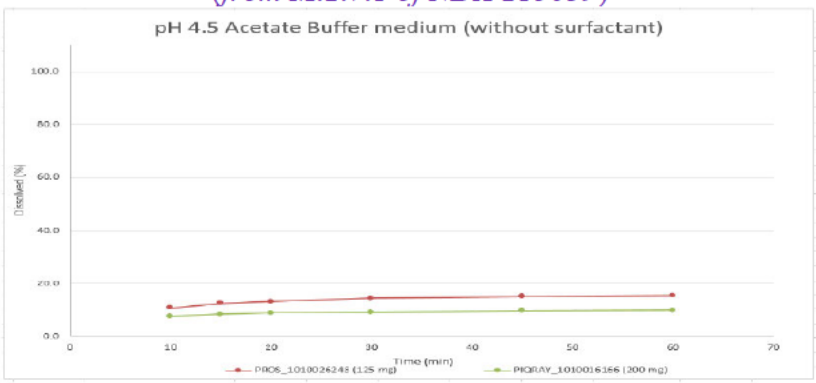
Source: Adapted from [Module 3.2.P.2]

Figure 2: Comparative dissolution profiles in pH 2.0 medium (without surfactant) (*from M.2.7.1 of NDA 215039*)



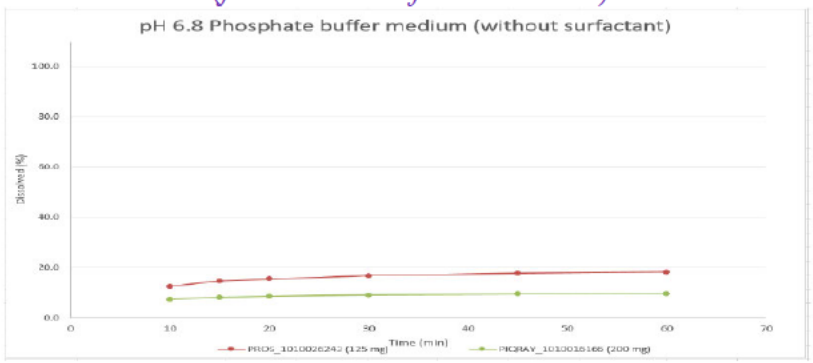
Source: [General Report-ARD000060-Section 3.2.P.2]

Figure 3: Comparative dissolution profiles in pH 4.5 medium (without surfactant) (*from M.2.7.1 of NDA 215039*)



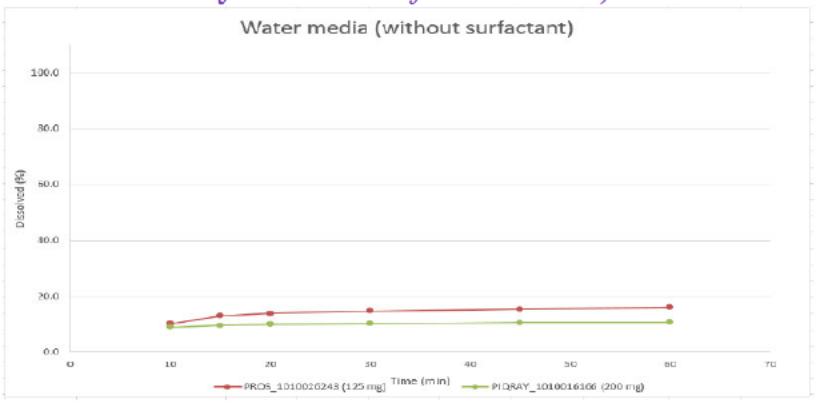
Source: [General Report-ARD000060-Section 3.2.P.2]

Figure 4: Comparative dissolution profiles in pH 6.8 medium (without surfactant) (*from M.2.7.1 of NDA 215039*)



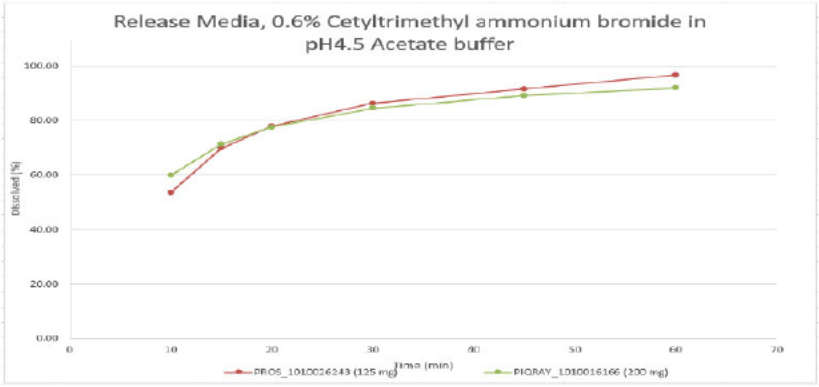
Source: [General Report-ARD000060-Section 3.2.P.2]

Figure 5: Comparative dissolution profiles in water (without surfactant) (*from M.2.7.1 of NDA 215039*)



Source: [General Report-ARD000060-Section 3.2.P.2]

Figure 6: Comparative dissolution profiles in QC medium (pH 4.5 with 0.6% CTAB) (*from M.2.7.1 of NDA 215039*)



Source: [General Report-ARD000060-Section 3.2.P.2]

Per 21CFR320.22(d)(2), the biowaiver request for the proposed middle strength of Alpelisib Tablets (*yellow shades*), 125 mg, is granted due to the following reasons:

a) Pharmacokinetic information/data of alpelisib have been reviewed in the approved NDA 212526, showing the linear pharmacokinetics of alpelisib with respect to dose and time in the tested dosage range of 30 mg to 450 mg under fed conditions.
b) The proposed Alpelisib Tablets (*yellow shades*), 50 mg, 125 mg and 200 mg, are compositional proportional with respect to the active and inactive ingredients across strengths.
c) The proposed Alpelisib Tablets (*yellow shades*), 50 mg, 125 mg and 200 mg, are manufactured using the same manufacturing process, at the same manufacturing site, controlled via the same specifications, and packaged in the same container closure system.
d) The one time point dissolution data support that the proposed Alpelisib Tablets (*yellow shades*), 50 mg, 125 mg and 200 mg have consistent dissolution during the stability testing.

The proposed Alpelisib Tablets (*yellow shades*), 50 mg, 125 mg and 200 mg have same core tablet composition compared to the approved Piqray® (*pink and red shades*, Alpelisib Tablets 50 mg, 150 mg and 200 mg), so that the difference in pigments and debossing are not expected to affect the drug product dissolution, quality and in vivo performance. The comparative dissolution in multi-media between the proposed middle strength of Alpelisib Tablets 125 mg and the approved Piqray® Alpelisib Tablets 200 mg is supportive to the biowaiver request.

e. DATA TO SUPPORT IVIVC AND/OR PBBM MODELING, IF APPLICABLE.

[To the Applicant: Provide summary of the objective of the model, model development and validation, and outcome. Insert additional text, graphs, and table here to support the information provided above as necessary]

Not applicable

Link: Page#:

[To the Applicant: Insert text here]

The FDA's Assessment: Choose an item.

Not applicable.

9. LABELING

USPI

Highlights: ***Adequate***

Compared to the approved package insert for PIQRAY®, the only change is removing the 150 mg dosage strength and replacing it with the new 125 mg dosage strength.

Section 2 (if relevant): ***Adequate***

The VIJOICE package insert includes instructions for patients unable to swallow tablets. This is new compared to the PIQRAY® package insert. The instructions direct the patient to place VIJOICE tablets in (b) (4) water for ~5 minutes, crush the tablets with a spoon and administer the dose within 60 minutes of preparation. The patient is instructed to rinse the glass with (b) (4) water and resuspend any remnants with a spoon and administer the rinse.

Section 3 Dosage Forms and Strengths: ***Adequate***

Compared to the PIQRAY® label, this section was updated for the 125 mg strength and changes to the appearance of the tablets to designate their strengths.

Section 11 Description: ***Adequate***

If the following excipients used in the drug product, include warning/declaration in the USPI:

- FD&C Yellow No.5 or No.6, as a color additive (21 CFR 201.20) is not used.
- Phenylalanine, as a component of aspartame (21 CFR 201.21) is not used.
- Sulfites (21 CFR 201.22) is not used.

This section is identical to PIQRAY® with the replacement of the tradename, 'VIJOICE', and description of the change of the film coats.

Section 16 How Supplied/Storage and Handling: ***Adequate***

The storage statement is identical to the PIQRAY® label. The different strengths are arranged in a tabular format compared to PIQRAY®, (b) (4) The same description of the container presentations is provided in both labels.

Manufacturer Information (Name and Address): ***Provided: Adequate***

Carton/Container Label ***Adequate***

The container configuration for VIJOICE™ is the same as for PIQRAY®. The labeling has the same storage statements, content information, manufacturer, and strength representation.

Representative Blister Card:

Representative Dose Pack:

3 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

Final Risk Assessments

[FDA will complete this section.]
To the Review Team: *Keep the appropriate Table; delete the rest*

SOLID ORAL

Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	Low	(b) (4)	Low	
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low		Low	
Content Uniformity	• Formulation • Container closure • Raw material • Process Parameters • Scale/equipment • Site	Low		Low	(b) (4) yields were observed for the new strength- 125 mg. Yields from validation/commercial batches should be evaluated during next inspection.
Moisture content	• Formulation • Container closure • Process parameters • Scale/equipment • Site	Medium		Medium	
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low		Low	
Dissolution – BCS Class II & IV	• Formulation • Container Closure • Raw materials • Process parameters • Scale/equipment • Site	Medium		Low	

Recommendation Page

[FDA will complete this section.]

Drug Substance: Approval

Primary Reviewer: Haripada Sarker Date: February 10, 2022
Secondary Reviewer: Haripada Sarker Date: February 10, 2022

Drug Product: Approval

Primary Reviewer: Olen Stephens Date: January 6, 2022
Secondary Reviewer: Xing Wang Date: February 16, 2022

Process and Facility: Approval

Primary Reviewer: Md Abdullah A Mahmud Date: February 8, 2022
Secondary Reviewer: Zhaoyang Meng Date: February 9, 2022

Biopharmaceutics: Approval

Primary Reviewer: Mei Ou Date: January 10, 2022
Secondary Reviewer: Mei Ou Date: January 10, 2022

Application Technical Lead: Approval

Xing Wang Date: February 25, 2022

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/

XING WANG
02/25/2022 09:56:37 AM

HARIPADA SARKER
02/25/2022 10:13:21 AM

OLEN M STEPHENS
02/25/2022 10:17:48 AM
DP recommendation: approval

MD ABDULLAH A MAHMUD
02/25/2022 10:52:01 AM

ZHAOYANG MENG
02/25/2022 11:00:47 AM

MEI OU
02/25/2022 11:15:09 AM