CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218466Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	218466
Applicant Name	Novartis Pharmaceuticals
Drug Product Name	Vijoice (alpelisib) granules
Dosage Form.	Granule
Proposed Strength(s)	50 mg
Route of Administration	Oral
Maximum Daily Dose	250 mg
Rx/OTC Dispensed	Rx
Proposed 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*. *This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).
Drug Product Description	Alpelisib 50 mg granules are an immediate release dosage form for oral administration. The drug product is white to almost white free flowing mixture of powder and granules. Alpelisib granules are packaged in [redacted] (b) (4) sachets contained in a cardboard-based box (secondary packaging).
Co-packaged product information	N/A
Device information:	N/A

Storage Temperature/ Conditions	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F), USP controlled room temprature conditions.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Raymond Frankewich	Haripada Sarker
	Drug Product/ Labeling	Olen Stephens	Shalini Anand/David Claffey
	Manufacturing	Jigarkumar Patel	Zhaoyang Meng
	Biopharmaceutics	Payal Agarwal	Anitha Govada
	Other (specify):	N/A	N/A
	RBPM	Janell Artis	
	ATL	Shalini Anand	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: An expiration dating period of **24 months** is granted for the drug product when stored at USP controlled room temprature conditions (20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)).

b. Additional Comments for Action: n/a

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends ***APPROVAL*** of NDA 218466 for the commercialization of Vijoice (alpelisib) granules, 50 mg. Based on our evaluation of the available information, the Applicant provided sufficient information to support an approval recommendation from the drug product quality perspective. The Applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and quality of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**N/A**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No

Comments: N/A

Additional Lifecycle Comments: N/A

Shalini Anand

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CHAPTER III: ENVIRONMENTAL

R REGIONAL INFORMATION

Alpelisib is an oral α-specific class I phosphatidylinositol-3-kinase (PI3K) inhibitor belonging to the 2-aminothiazole class of compounds. Alpelisib received accelerated approval from the Food and Drug Administration (FDA) on 05-Apr-2022 under the name Vijoice® for the 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.

The current Type 3 NDA submission for Vijoice is intended to introduce a new dosage form of alpelisib (i.e., granules), which is bioequivalent to the already approved dosage form (i.e., filmcoated tablets) for the treatment of selected patients with PROS who are prescribed a 50 mg dose. The new dosage form will not lead to an increased use of alpelisib as the indication, dosage levels, and treatment duration remain unchanged from that already approved by the FDA.

As such, pursuant to 21 CFR 25.31 (a) and in line with FDA's Guidance for Industry on Environmental Assessment of Human Drug and Biologics Applications (July 1998), Novartis claims a categorical exclusion from the requirement to submit an Environmental Assessment (EA) given that approval of the new dosage form of alpelisib for use in selected patients with PROS would not increase the use of the active moiety.

Furthermore, pursuant to 21 CFR 25.15 (d), Novartis confirms 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 an EA.

Assessment: Adequate; The applicant qualifies for an exemption from the requirement to conduct an environmental assessment due to the fact that approval of this application will not increase the use of the active moiety.

Primary Environmental Assessor Name and Date: Olen Stephens 11/02/2023

Secondary Assessor Name and Date: Shalini Anand 03/01/2024

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Shalini Anand

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate with minor comments; the labeling comments are focused on the new granule formulation unless there are changes to the tablet labeling.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling	Assessor's Comments
Product Title in Highlights		
Established name(s)[1]	Adequate	Alpelisib; this is a line extension
Route(s) of administration	Adequate	Oral; no change from previous formulation
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	Tablets: 50 mg, 125 mg, and 200 mg Oral Granules: 50 mg
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Adequate	(b) (4) o Pour the contents of one VIJOICE granules packet directly onto the tongue and swallow with approximately 2 to 4 ounces of water. If needed, rinse the mouth with additional water and swallow to ensure no particles remain in the mouth. o Pour the contents of one VIJOICE granules packet into a (b) (4) cup, (b) (4) • Discard the granules mixed with water, milk, apple juice, applesauce, or yogurt if they are not administered within 2 hours after preparation. • (b) (4)
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	"… (b) (4)
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	N/A	

If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Tablets: 50 mg, 125 mg, and 200 mg alpelisib Oral Granules: 50 mg alpelisib Product appearances are included in this section
Strength(s) in metric system	Adequate	See above
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	50 mg: Light yellow, unscored, round and curved with beveled edges film-coated tablet, debossed with "C7" on one side and "NVR" on the other side. 125 mg: Dark yellow, unscored, ovaloid and curved with beveled edges film-coated tablet, debossed with "Y7" on one side and "NVR" on the other side. 200 mg: Pale yellow, unscored, ovaloid and curved with beveled edges film-coated tablet, debossed with "CL7" on one side and "NVR" on the other side. 50 mg: White to almost white free flowing mixture of powder and granules equivalent to 50 mg alpelisib.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 11 (DESCRIPTION) Item	Items in Proposed Labeling	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Adequate	VIJOICE (alpelisib)
Dosage form(s) and route(s) of administration	Adequate	Film coated tablets and oral granules
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	kinase inhibitor
Chemical name, structural formula, molecular weight	Adequate	No change from the previous label for Vijoice
If radioactive, statement of important nuclear characteristics.	N/A	

Other important chemical or physical properties (such as pKa or pH)	Adequate	The original label had no change from the previous label for Vijoice, but had no physical properties of the API. The applicant was sent the following IR: “In Section 11 of the package insert, include important chemical or physical properties (such as pKa or pH) regarding the drug substance.” In response, the applicant added the following text, “The pH of a 1.0% (m/V) solution of alpelisib in water/ethanol (50:50 V/V) is approximately 6.2.”
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity”)	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Items in Proposed Labeling	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	Tablets and Granules
Strength(s) in metric system	Adequate	Tablets: 50 mg, 125 mg, and 200 mg alpelisib Oral Granules: 50 mg alpelisib
Available units (e.g., bottles of 100 tablets)	Adequate	Tablets: blisters with 28-tablets and blisters with 56 tablets Oral Granules: 28 packets
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	The applicant was instructed to include this information and the applicant responded in SDN 0004 to include an 'appearance' column in tables 13 and 14 to describe the visual identification clues of the FCTs and granules.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	Adequate	The new granule formulation is intended to be used immediately. The package insert instructs the healthcare provider to dispose of the granules prepared in water, milk, apple juice, applesauce, or yogurt if not administered within 2 hours of preparation.

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling	Assessor's Comments
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	USP Controlled Room Temperature
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	Adequate	The original NDA submission contained no information on the blister configuration or sachet. The applicant responded to an IR in SDN 0004 to verify the sachet and blister packs comply with 16 CFR 1700 and to update Tables 13 and 14 with CR statements for the containers.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	Distributed by Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Items in Proposed Labeling	Assessor's Comments about Carton Labeling
Established name[2]	Adequate	
Special preparation instructions (if applicable)	Adequate	The instructions are the same as in the package insert
Storage and handling information (if applicable)	Adequate	Store VIJOICE at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F)
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	Adequate	
Alphabetical listing of inactive ingredients (if applicable)	Adequate	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	Distributed by: Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

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Item	Items in Proposed Labeling	Assessor's Comments about Carton Labeling
Established name[3], (font size and prominence)	Adequate	DMEPA will comment on prominence and size
Strength(s) in metric system	Adequate	50 mg
Route(s) of administration	Adequate	Oral Granules
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	50 mg in the packet
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Not included on the sachet – there may not be room; the information is included on the carton
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

[3] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Items in Proposed Labeling	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	Adequate	Instructions for sample preparation are included on the carton and are the same as in the package insert.

Assessment of Carton and Container Labeling: Adequate pending resolution of the following comments: None

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Adequate; minor edits were communicated via information requests on November 8, 2023. The applicant responded in SDN 0004 with revised labels. The applicant submitted an updated label, changing the product title and product dosage form from (b) (4) to 'oral granules'. DMEPA and David Lewis (labeling expert) confirmed this is the current convention and the changes were accepted. Further labeling review will be negotiated through the clinical RPM.

Primary Labeling Assessor Name and Date: Olen Stephens 12/18/2023

Secondary Assessor Name and Date: David Claffey 3/11/2024

Olen Stephens

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David Claffey

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	VIJOICE®(alpelisib) Granules
NDA Number	NDA-218466-ORIG-1 505(b) (1) [associated with NDA-212526 and 215039 Tablets
Assessment Cycle Number	1
Drug Product Name/ Strength	VIJOICE®(alpelisib) Granules/ 50 mg
Route of Administration	Oral
Applicant Name	Novartis
Therapeutic Classification/ OND Division	Anticancer/Division of Oncology 2 (DO2)
Proposed Indication	Treatment of selected patients with PIK3CA-related overgrowth spectrum (PROS)
Proposed Dosage and Administration	Pediatric patients 2 to less than 18 years of age: 50 mg

Assessment Recommendation: **Adequate**

Assessment Summary:

NDA 218466 for a (Type 3) new dosage form seeks approval of Vijoice® (alpelisib) immediate release Granules for oral administration, 50 mg for the treatment of selected patients with PROS. This proposed new dosage form is intended to provide an alternative dosage form for patients prescribed Vijoice® (alpelisib) Granules, 50 mg i.e., pediatric patients 2 to less than 18 years of age or adult patients (b) (4) as per the approved/proposed label.

The applicant cross-references Piqray® (alpelisib) Film-coated Tablets (FCTs), 50 mg, 150 mg, and 200 mg intended for oral administration (approved on May 24, 2019 under NDA # 212526) for the treatment of selected patients with advanced or metastatic breast cancer and a differentiated product, Vijoice® (alpelisib) FCTs 50 mg, 125 mg, and 200 mg (approved on April 05, 2022 under NDA # 215039) for the treatment of selected patients with PROS. The proposed new dosage form, Vijoice® (alpelisib) Granules, 50 mg (b) (4) (b) (4) (b) (4)

This Biopharmaceutics review is focused on the 1) assessment of the adequacy of the proposed dissolution method and acceptance criterion for the proposed test product, the 2) evaluation of the need for *in vitro* bridging between the approved tablet dosage form and the proposed to-be-marketed oral granules.

and 3) the effect of using soft-food vehicles for administering oral granules on dissolution rate.

Reviewer's Assessment:

1) Dissolution Method and Acceptance Criterion:

The Applicant's proposed dissolution method and test conditions (900 mL of acetate buffer with 0.6% CTAB at pH of 4.5 using USP Apparatus 2 (paddle) at 75 rpm) with dissolution acceptance criterion of Q = (b)(4)% in 30 minutes is adequate for quality control of the proposed Alpelisib Granules, 50 mg at batch release and during stability testing.

2) Bridging to the Final-To-Be-Marketed Alpelisib Oral Granules:

The final TBM product was introduced in the pivotal clinical BE study (CBYL719F12101) in healthy subjects to evaluate the pharmacokinetic bioequivalence of the Alpelisib granule, 50 mg and Alpelisib FCT, 50 mg. The supporting PK/BE data will be assessed by the Clinical Pharmacology Reviewer, Office of Clinical Pharmacology.

3) Effect of Administration of Oral Granules with Soft-Food Vehicles (apple sauce, yoghurt, water, apple juice or milk):

The granule dosage form is available in stick packs and as per the proposed label, contents of the stick packs can be poured directly onto the patient's tongue and swallowed with water, mixed with soft food such as apple sauce or yogurt, or mixed with liquids such as water, apple juice, or milk. The granule formulation is comparable to the tablet formulation and has a short in-use period when exposed to soft foods, which can be administered immediately. Therefore, no *in vitro* dissolution studies of the proposed granule formulation in various soft food vehicles is needed. The *in vitro* compatibility studies for mixing the oral granules with applesauce, apple juice, milk or yoghurt will be evaluated in the Drug Product Reviewer's assessment.

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Dissolution	Medium	Alpelisib is a BCS Class II drug substance. API Particle Size can significantly impact the dissolution and thereby bioavailability	Low	API particle size is controlled in the DS release specifications. Adequate Dissolution QC specifications (developed a dissolution method that can reject batches with API particle size outside the defined specifications).

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
Original (SDN #1)	06/29/2023
Response to Information Request dated November 08, 2023 (SDN #5)	11/22/2023

Highlight Key Issues from Last Cycle and Their Resolution: n/a

Concise Description of Outstanding Issues *(list bullet points with key information and update as needed)*: n/a

B.1 BCS DESIGNATION

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

Solubility: Solubility of alpelisib granules is given in Table 1 across different pH conditions. Alpelisib exhibits pH dependent solubility (>3 mg/mL at pH 1.0, ≤ 0.4 mg/mL at pH 2 and ≤ 0.1 mg/mL above pH 2).

Table 1. Solubility profile of alpelisib at different pH conditions

Solvent		Solubility [mg/ml] of solution	Solubility [%] (m/V) (g/100 ml solution)	Description term*)
Water		0.017	0.002	ins
Buffer solutions1) *):				
	pH 1.0 (HCl 0.1N)	3.636	0.364	sls
	pH 2.0 (HCl 0.01 N)	0.423	0.042	vsls
buffer	pH 3.0 (citrate)	0.078	0.008	ins
buffer	pH 4.0 (acetate)	0.026	0.003	ins
buffer	pH 5.0 (acetate)	0.020	0.002	ins
buffer	pH 6.0 (phosphate)	0.019	0.002	ins
buffer	pH 6.8 (phosphate)	0.018	0.002	ins
Cetyltrimethyl ammonium bromide (CTAB) 0.6 % in acetate buffer pH 4.5		0.690	0.069	vsls
FeSSIF2)		0.318	0.032	vsls
FaSSIF3)		0.045	0.005	ins

1) *) according to USP
2) fed state simulated intestinal fluid (pH 5.0)
3) fasted state intestinal simulated fluid (pH 6.5)

Permeability: Permeability of alpelisib is high as per the clinical summary and biopharmaceutics report submitted.

Dissolution: Dissolution of the proposed product was found to be complete in the proposed dissolution medium: 900 mL of acetate buffer with 0.6% Cetyltrimethyl ammonium bromide (CTAB) at pH of 4.5. However, dissolution of granules is not rapid across the entire physiologic pH range. Refer to the dissolution profiles in the sections below.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: ADEQUATE.

Background

The alpelisib granules 50 mg strength has been formulated as an immediate release drug product for the treatment of selected patients with PROS who have difficulties

[1] NDA 212526-ORIG-1 Integrated Quality Assessment Biopharmaceutics Section- Date March 20, 2019

swallowing the FCTs whole (i.e., pediatric patients 2 to less than 18 years of age and adult patients [redacted]).

For administration, the granule dosage form (available in stick pack) can be poured directly onto the patient's tongue and swallowed with water, mixed with soft food such as apple sauce or yogurt, or mixed with liquids such as water, apple juice, or milk. The granule dosage form essentially has the same qualitative composition as the cores of the commercial alpelisib FCTs [redacted].

Dissolution Method

Alpelisib is a BCS Class II drug substance. The Applicant's proposed dissolution method test conditions as shown in Table 2 and acceptance criterion [NLT [redacted]% (Q) in 30 minutes] for batch release and stability testing, are same as that of the approved dissolution specifications for the Alpelisib FCTs. Based on the totality of the information and data provided (e.g., low solubility drug substance, high permeability, complete dissolution in the given pH conditions, controlled API particle size and relevant clinical BE study), the final QC dissolution method is deemed adequate for the proposed product.

Table 2. Dissolution Method and Acceptance Criterion for the proposed Alpelisib Granules, 50 mg

Apparatus	Speed	Medium/Temperature	Volume	Acceptance Criterion
USP Apparatus 2 (Paddle)	75 rpm	Acetate Buffer with 0.6% CTAB, pH 4.5	900 mL	Q = [redacted] % in 30 minutes

Selection of the Dissolution parameters

[redacted]

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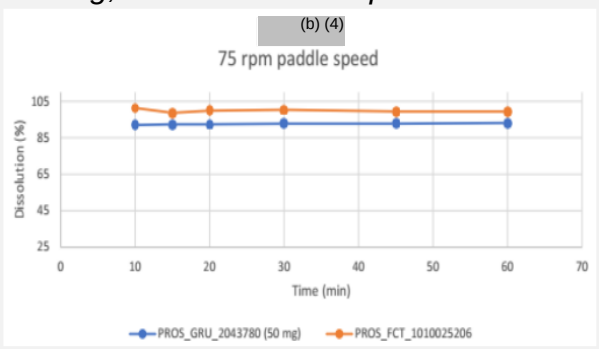
Dissolution Profile Comparison of FCT and Granules

Based on the IR response received on November 23, 2023, the Applicant submitted the *in-vitro* comparative dissolution study to evaluate the dissolution similarity among the approved FCT and the proposed Granule dosage form, using the proposed dissolution method in accordance with the recommendations provided in FDA Guidance for Industry, '*Immediate Release Solid Oral Dosage Forms Scale-Up and Post approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation'*.



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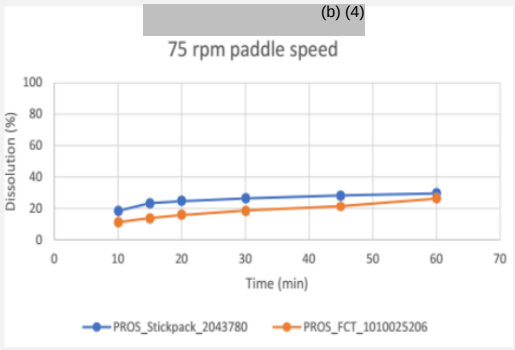
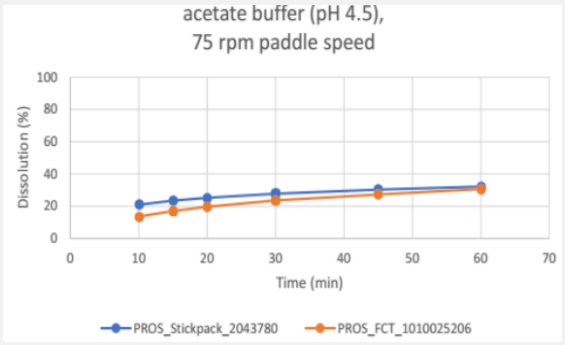
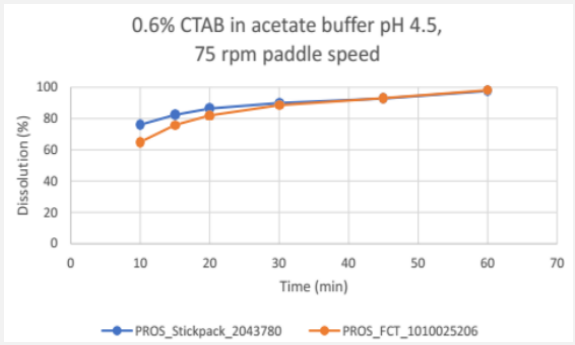


B.



C.



D.

Fig. 3 Dissolution profile comparison of Alpelisib granule, 50 mg as stick pack, and Alpelisib FCT, 50 mg, A: (b) (4) without surfactant, B: Acetate buffer, pH 4.5 without surfactant, C: (b) (4) without surfactant, D: proposed QC medium Acetate buffer, pH 4.5 with 0.6% CTAB

Based on the comparative multi-pH ((b) (4), pH 4.5, (b) (4)) dissolution study, the dissolution for the proposed Alpelisib granules, 50 mg (stick pack) was demonstrated to be similar (f2>50) to the approved Alpelisib FCT, 50 mg as shown in Figures 3 A, B, C and D.

As discussed in the previous section of this review, for administration, granules in stick packs can either be poured directly onto patients' tongue and swallowed with water or can be taken with a small volume of water, apple juice, milk, apple sauce or yogurt. The Applicant conducted compatibility studies of Alpelisib granules, 50 mg with these selected vehicles which will be reviewed by the DP reviewer.

Biopharmaceutics Risk Assessment and Mitigation

Considering the drug substance to be BCS Class II, the drug substance has pH-dependent solubility and low solubility at higher pH >4, and *in vitro* dissolution of highest strength does not show rapid dissolution at pH 4.5, the initial Biopharmaceutics risk is identified as medium for this drug product.

Discriminating Ability

The Applicant provided a detailed dissolution method development report. The Applicant justified the selection of each dissolution parameter (dissolution apparatus, dissolution medium, concentration of surfactant, and rotation speed). The Applicant was able to identify the potential critical biopharmaceutical attributes (CBAs) that can impact the product performance *in vivo* (Table 6). The discriminating ability of the selected dissolution method was verified towards these identified CBAs.

The drug substance particle size was identified to be most critical material attribute (CMA) for achieving the desired dissolution[2]. The increase of drug substance PSD of D(90) from target (b) (4) µm) used in batch # 2043779 to (b) (4) µm (three batches #32117430, #32117432, #32117433) resulted in a significant drop of the dissolution rate (Fig 4). DS PSD and batches with DS PSD of D90 = (b) (4) µm are either failing or only marginally meeting dissolution acceptance criteria of Q = (b) (4) % in 30 minutes at S2 stage. With the DS PSD to D90 = (b) (4) µm, the dissolution was passing either at S1 or S2 stage (based on S1 data). The proposed dissolution method was able to discriminate DS with PSD D90 difference of (b) (4) microns. Therefore, the Applicant proposed to (b) (4) the upper limit of the DS PSD to D90 (b) (4) µm.

The initially identified critical formulation variables (CFV's) such as (b) (4) and critical process parameters (CPP's) such as (b) (4) were demonstrated as non-significant variables for dissolution of drug product in the given fixed ranges.

This discriminating ability of the proposed dissolution method serves as a control for lifecycle management and hence mitigates the risk to low.

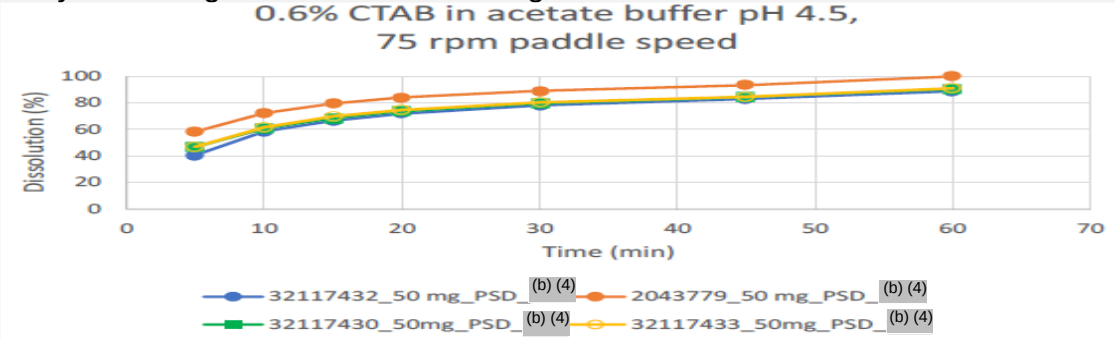


Fig. 4 Dissolution Profiles for 50 mg strength Granules in Sachet with Various PSD

[2] \\CDSESUB1\EVSPROD\nda218466\0004\m3\32-body-data\32p-drug-prod\byl719-granules\32p2-pharm-dev\pharmaceutical-development-manufacturingprocessdevelopment.pdf

Table 6. Potential critical bioavailability attributes of alpelisib granules in sachet:

Potential Critical Bioavailability Attribute (CBA)*	Variable	Control	Details / data supporting the discriminatory ability of the dissolution procedure
Critical material attribute	Drug substance particle size	Specifications for drug substance particle size are established (D(50) (b) (4) µm, D(90) (b) (4) µm).	Section 3.1.2 / 7.1.3.1 DS PSD affects dissolution, demonstrating the discriminatory power of the dissolution method. It is controlled by the DS PSD specification.
Potential critical formulation variable	(b) (4)		
Potential critical formulation variable			
Potential critical formulation variable			

Dissolution Acceptance criterion- Adequate

The acceptance criteria for dissolution of Alpelisib granules, 50 mg in stick pack are set by the Applicant to ensure that sufficient *in vitro* release can be achieved with adequate discriminating ability. The Applicant proposed dissolution acceptance criterion of Q = (b) (4) % in 30 minutes for batch release and stability, which is found acceptable by this Reviewer.

Conclusion/Recommendation: Based on totality of information submitted, from a Biopharmaceutics perspective, the dissolution method using USP Apparatus 2 with 900 mL of pH 4.5 acetate buffer (with 0.6% CTAB) at 75 rpm and acceptance criterion of Q = (b) (4) % in 30 minutes proposed by the Applicant for batch release and stability testing for Alpelisib granules, 50 mg is deemed acceptable for NDA 218466 and recommended for **APPROVAL.**

B.6 IN-VITRO SOFT-FOOD INTERACTION STUDY (Oral Granules):

Assessment: For administration, the granule dosage form can be poured directly the onto the patient's tongue and swallowed with water, mixed with soft food such as apple sauce or yogurt, or mixed with liquids such as water, apple juice, or milk. The Applicant conducted compatibility studies of alpelisib granules with these selected vehicles to assess the stability of a drug product in proposed vehicles and ensuring patient safety. The

compatibility study will be reviewed by the DP reviewer. The drug's solubility is not expected to support the label claim, as the full dose intake is ensured through various administration methods. The granule formulation is comparable to the tablet formulation and has a short in-use period when exposed to soft foods, which can be administered immediately and therefore no *in vitro* dissolution studies of granules in various soft food vehicles is needed. To understand if there are any issues/concerns related to the administration of granules with soft food vehicles, the DP reviewer was reached out and no concerns regarding the administration of alpelisib granules with soft food vehicles was raised by the DP reviewer.

Refer to the proposed labeling and the respective Instructions for Use. Per the Drug Product Reviewer, the design, and the results of the study for the oral granules mixed with soft-food vehicles are acceptable/adequate.

B. 12. BRIDGING OF FORMULATIONS

Assessment: Adequate

The Applicant conducted a clinical BE study (CBYL719F12101) in healthy subjects to evaluate the pharmacokinetic bioequivalence of the Alpelisib granule, 50 mg and Alpelisib FCT, 50 mg dosage forms in the fed condition, and the effect of food on alpelisib 50 mg granules which will be reviewed by the OCP.

No formulation bridging is needed as same proposed 50 mg formulation is used in the clinical BE study.

B. 13 BIOWAIVER REQUEST

Assessment: N/A

Only one strength 50 mg of the Alpelisib Oral Granules is proposed for marketing in the current NDA and Clinical BE study was conducted using the proposed Alpelisib Granules 50 mg. No lower strengths for granules have been proposed by the Applicant.

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: N/A

Post-Approval Commitments

None

Lifecycle Management Considerations

None

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Payal Agarwal,

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Anitha Palamakula Govada

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SHALINI ANAND
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