CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218466Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	NDA 218466 (SDN 1)
Type/Category	Original NDA
Submission Date	6/29/2023
Submission Type	*Standard*
Brand Name	VIJOICE
Generic Name	Alpelisib
Dosage Form and Strength	Granules: 50 mg
Route of Administration	Oral
Approved Indication	VIJOICE is a kinase inhibitor indicated for the treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PIK3CARelated Overgrowth Spectrum (PROS) who require systemic therapy. This indication is approved under accelerated approval based on response rate and duration of response.
Approved Dosing Regimen	• Pediatric patients (2 to less than 18[1] years of age): 50 mg taken orally once daily with food. • Adult patients: 250 mg taken orally once daily with food.
Applicant	Novartis Pharmaceuticals Corp.
OCP Divisions	Division of Cancer Pharmacology II (DCPII)
OND Divisions	Division of Oncology 1 (DO1)
OCP Review Team	Hairat Sabit, Ph.D. (DCPII) Miyoung Yoon, Ph.D. (DPM)
OCP Team Leaders	Hong Zhao, Ph.D. (DCPII) Manuela Grimstein, Ph.D. (DPM)
OCP/DCPII Deputy Director	Stacy Shord, PharmD. (DCPII)

[1] Reviewer Notes: The current approved VIJOICE USPI defined the pediatric patients as “2 to less than 18 years of age). In the current review, same definition will be used to be consistent the VIJOICE USPI.

1. Contents

1. EXECUTIVE SUMMARY

Novartis submitted this Type 3 NDA for VIJOICE (alpelisib) granules (50 mg) to provide an alternative dosage form for patients with PROS prescribed VIJOICE 50 mg (i.e., pediatric patients 2 to less than 18 years of age or adult patients who require dose reduction to 50 mg as per the approved/proposed labeling). (b) (4)

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VIJOICE (alpelisib) Tablets received an accelerated approval based on response rate and duration of response on April 5, 2022, for the treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PROS who require systemic therapy. The approved recommended dosage of VIJOICE is 50 mg for pediatric patients (2 to less than 18 years of age) and 250 mg for adult patients, taken orally once daily with food.

The bioequivalence (BE) between the 50 mg granules formulation and the 50 mg tablets formulation when administered with a low-fat low-calorie (LFLC) meal has been demonstrated in Study CBYL719F12101 as the 90% confidence intervals (CIs) on the geometric mean treatment ratios (granules vs Tablets) for AUC_{inf}, AUC_{last} and C_{max} were all within the pre-specified BE boundary of (0.80, 1.25). The PBPK model predicted lack of food effect at 50 mg formulations based on the gastrointestinal physiology and alpelisib solubility and dissolution under fed and fasted conditions, corroborating the finding from the Study CBYL719F12101. Study CBYL719F12101 establishes BE between the proposed 50 mg granule formulation and previously approved 50 mg tablet formulation, supporting the approval of VIJOICE (alpelisib) granules, 50 mg for the approved VIJOICE indications.

1.1 Recommendations:

The Clinical Pharmacology review team has reviewed the information contained in NDA 218466. This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations and/or comments are summarized in **Table 1.**

Table 1. The Key Clinical Pharmacology Review Issues, Recommendations and Comments

Review Issue	Recommendations and Comments
Bioequivalence between granule and tablet formulations	VIJOICE (alpelisib) granules, 50 mg formulation is BE to VIJOICE (alpelisib) tablets, 50 mg formulation. For pediatric patients (2 to less than 18 years of age), the recommended dose of 50 mg can be administered as VIJOICE Tablets or VIJOICE Granules.
Food effect on granule formulation	PBPK modeling corroborates the finding from the Study CBYL719F12101 predicted no clinically relevant food effect on the PK of alpelisib 50 mg granules.
General dosing instructions	Adult patients: 250 mg taken orally, once daily with food at approximately the same time each

	day. The 50 mg granules can be used for patients who require dose reduction as needed. Pediatric patients (2 to less than 18 years of age): 50 mg taken orally once daily with food at approximately the same time each day. Dose can be administered as VIJOICE tablets or VIJOICE granules.
Labeling	FDA labeling revisions per FDA labeling guidance have been provided.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

For brevity, only information related to current submission is summarized (**Table 2**). For additional information, please refer to the clinical pharmacology reviews for the original and supplemental NDA 215039 submissions.

Table 2. Clinical Pharmacology Highlights in the VIJOICE USPI that are Relevant to the Current Submission

PK Characteristic	Recommendations and Comments in VIJOICE USPI
Tmax	2 to 4 hours (median)
$t_{1/2}$	8 to 9 hours
Effect of Acid	No clinically significant differences in the pharmacokinetics of alpelisib were observed when used concomitantly with ranitidine (H2 receptor antagonist) and administered with food as directed.
Food Effect	A high-fat high-calorie (HFHC) meal (985 calories with 58.1 g of fat) increased alpelisib AUC by 73% and Cmax by 84%, and a low-fat low-calorie meal (334 calories with 8.7 g of fat) increased alpelisib AUC by 77% and Cmax by 145% following a single alpelisib tablet dose of 300 mg. No clinically relevant differences in alpelisib AUC were observed between low-fat low-calorie and high-fat high-calorie meals.
Pharmacodynamic	The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of VIJOICE have not been characterized.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

- Pediatric patients (2 to < 18 years of age): 50 mg QD with food.
- Adult patients: 250 mg QD with food.

2.2.2 Therapeutic individualization

Not Applicable.

2.3 Outstanding Issues

There are no outstanding issues in this submission.

2.4 Summary of Labeling Recommendations

The approved labeling was updated to include the following:

- 50 mg granules formulation.
- For pediatric patients (2 to < 18 years of age), the recommended daily dose of 50 mg can be administered as VIJOICE tablets or VIJOICE granules.
- No clinically relevant food effect on alpelisib PK was observed with the VIJOICE 50 mg granules after a single 50 mg oral dose following a LFLC meal as compared to fasted administration.
- The Applicant initially stated [redacted (b) (4)]". The statement was removed by FDA per FDA guidance for Industry: *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Formats* (https://www.fda.gov/media/74346/download).
- Three methods to administer the granules formulation including pouring the granules onto tongue and swallowing with 2 to 4 ounces of water which was used in the clinical trials, and two additional methods (mixing of the oral alpelisib granules with apple juice, milk, applesauce or yogurt) which are supported by adequate compatibility and stability (refer to Biopharmaceutics review).
- Some editorial changes to align with the PIQRAY labeling.

3. Review of Study CBYL719F12101

Study Title: A single-center, randomized, open-label, three-period crossover study to investigate the BE of alpelisib granule and film-coated tablet formulation and the food effect of alpelisib granule formulation in adult healthy volunteers

Study Objectives:

- Primary Objective
  - To assess the BE (rate and extent of absorption) of the granule formulation of alpelisib as compared to the film-coated tablet formulation, both at a single oral dose of 50 mg in healthy volunteers in the fed state after a low-fat low-calorie (LFLC) meal.

- Secondary Objectives
  - To assess the food effect on the granule formulation at the 50 mg dose across fasted and fed states [after a low-fat low-calorie (LFLC) meal].
  - To evaluate the pharmacokinetics of a single oral dose of:

    - alpelisib film-coated tablet formulation in the fed state (Treatment A)
    - alpelisib granule formulation in the fed state (Treatment B)
    - alpelisib granule formulation in the fasted state (Treatment C)
  - To assess safety and tolerability in healthy volunteers of the different alpelisib formulations at 50 mg dose.

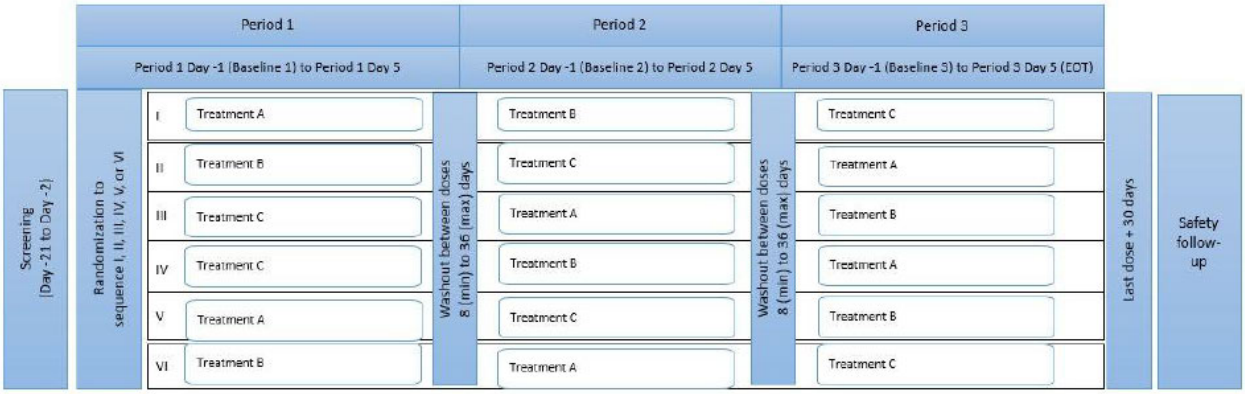
- Exploratory Objectives
  - To explore the palatability (taste, overall acceptance and ease of administration and acceptability) of the granules formulation of alpelisib.

Study Design:

This is a single-center, randomized, open-label, three-period six-sequence crossover study to investigate the BE of alpelisib granule and film-coated tablet formulations, as well as the food effect on the alpelisib granule formulation in adult healthy participants.

The study consisted of a screening period followed by Periods 1, 2, and 3 and a safety follow-up. Randomization occurred at the beginning of Period 1, whereby every participant who passed the screening were randomized to one of 6 sequences with 1:1:1:1:1:1 randomization ratio (**Figure 2**). Each sequence consisted of a permutation of three treatments in order: A, B and C (**Table 3**). Participants in Treatment A received a single oral dose of alpelisib FCT at 50 mg in the fed state (LFLC meal), participants in Treatment B received a single oral dose of alpelisib granule at 50 mg in the fed state, and those in Treatment C received a single oral dose of alpelisib granule at 50 mg in the fasted state. Alpelisib was administered with approximately 200 mL of still water. A standardized LFLC meal (~334 calories and ~8.7 g of fat) after overnight fasting (of at least 10 hours) was provided 30 min before the alpelisib dose for Treatments A and B. Participants in Treatment C was administered after overnight fasting. No food was allowed for at least 4 hours post the alpelisib dose.

Figure 2. Study Schema



(Data source: section 2.7.2 Summary of Clinical Pharmacology; Figure 2-1; SDN 1)

There was at least 8 days of washout between the dose administration (on Day 1) of each treatment period. A phone call for safety follow-up took place 30 days after the last administration of alpelisib.

Number of participants:
In total, 60 participants were randomized and received apelisib in the study, out of which 48 (80%) participants completed the study as per protocol. The primary reasons for discontinuation were adverse events (8 participants, 13%) and protocol deviation (3 participants, 5%).

Study Treatments:

Table 3. Study Treatments

Treatment	Dose and Formulation	Fasted or Fed State

A	Single oral dose of alpelisib film-coated tablet at 50 mg	Fed
B	Single oral dose of alpelisib granule at 50 mg	Fed
C	Single oral dose of alpelisib granule at 50 mg	Fasted

(Data source: Reviewer compiled based on section 2.7.2. Summary of Clinical Pharmacology; SDN 1)

Reviewer's Comments:

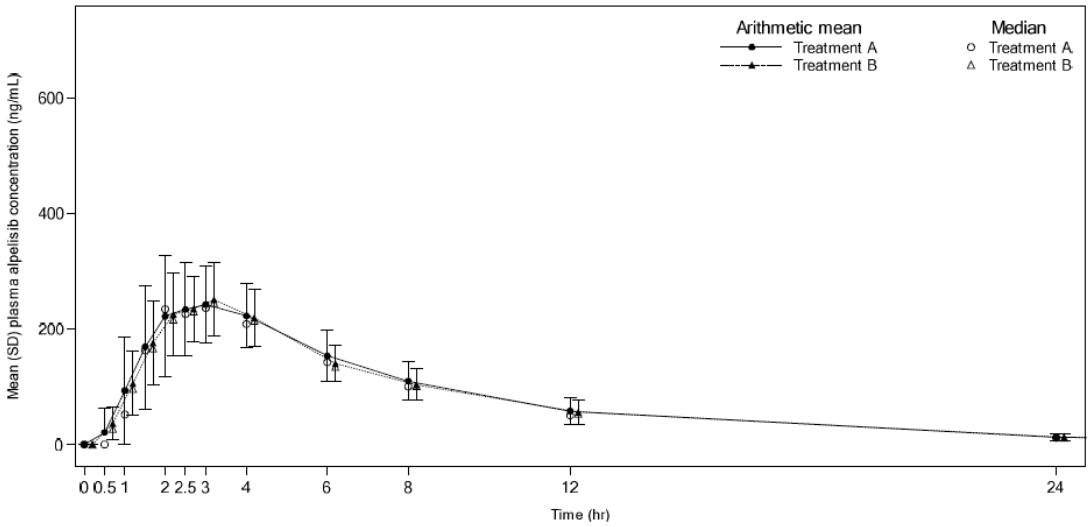
- *The Applicant's study design for the BE and food effect study is adequate from the clinical pharmacology perspective to address the following two questions:*
  1) *Whether the proposed alpelisib granules, 50 mg formulation is BE to VIJOICE FCT, 50 mg formulation under fed condition.*
  2) *The magnitude of food effect on alpelisib PK of VIJOICE granule formulation following LFLC meal as compared to fasted administration..The use of LFLC in the BE study is acceptable. Per VIJOICE USPI, no clinically relevant differences in alpelisib AUC were observed between LFLC and HFHC meals.*
  3) *The Applicant did not conduct a BE study under fasted conditions, which is considered acceptable as the granules formulation will be administered with food as the FCT formulation.*

PK Results:

1) BE between the 50 mg Granule and Tablet Formulations

The median and arithmetic mean (SD) alpelisib plasma concentration-versus time profiles of FCT (Treatment A) and granules (Treatment B) dosage forms following a single 50 mg dose under fed conditions are presented in **Figure 3**.

Figure 3. Median and arithmetic mean (SD) plasma concentration-time profiles for alpelisib



(Data source: Section 2.7.2 Summary of Clinical Pharmacology; Figure 2-2; SDN 1)

The 90% confidence intervals (CIs) on the geometric mean treatment ratios (granules vs Tablets) for AUC_{inf}, AUC_{last} and C_{max} were all within the pre-specified BE boundary of (0.80, 1.25) [**Table 4** (applicant's calculation) and **Table 5** (FDA's calculation)], demonstrating that VIJOICE® (alpelisib) granules, 50 mg is BE to VIJOICE® (alpelisib) tablets, 50 mg under fed conditions.

Table 4. BE Results (Granules vs Tablets; Fasted vs Fed) – Applicant Calculated

BE Comparison	Geo-mean Ratio [90% CI]		
	AUClast (ng*hr/mL) N = 48	**AUCinf (ng*hr/mL) N = 48**	**Cmax (ng/mL) N = 48**
Granules/Tablets*	0.98 (94.6, 102)	0.98 (95.2, 102)	0.95 (89.1, 101)
Fed/Fasted**	1.07 (102, 112)	1.07 (103, 111)	0.94 (88.1, 99.9)

*Both granules and tablets were given to the participants under fed condition.
**The fed condition in this food-effect study was LFLC consisted of ~20% fat and ~330 calories.
(Data source: Reviewer compiled based on Table 2-4 and Table 2-6 of section 2.7.2 Summary of Clinical Pharmacology; SDN 1)

Table 5. BE Results (Granules vs Tablets; Fasted vs Fed) – FDA's Assessment

BE Comparison	Geo-mean Ratio [90% CI]		
	AUClast (ng*hr/mL) N = 48	**AUCinf (ng*hr/mL) N = 48**	**Cmax (ng/mL) N = 48**
Granules/Tablets*	0.98 (94.4, 102)	0.98 (94.9, 102)	0.95 (89.2, 101)
Fed/Fasted**	1.06 (101, 112)	1.06 (102, 111)	0.94 (88.0, 99.9)

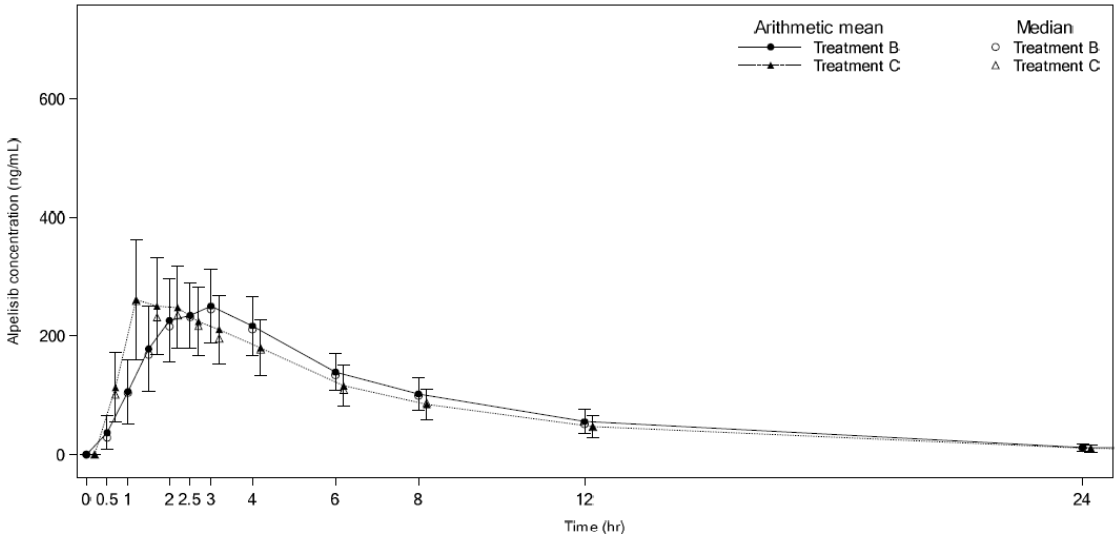
Reviewer's Comments:

- *The reviewer's calculated statistical analysis results (GMR, 90%CI) on C_{max}, AUC_{last} and AUC_{inf} are consistent with those of the Applicant's (Table 4 and Table 5).*
- *The reviewer agrees with the Applicant's conclusion.*

2) Food Effect on Granule Formulation

The median and arithmetic mean (SD) alpelisib plasma concentration-versus time profiles of granules formulation under fed (Treatment B) and granules formulation under fasted (Treatment C) conditions are presented in **Figure 4.**

Figure 4. Median and arithmetic mean (SD) plasma concentration-time profiles for alpelisib



(Data source: Section 2.7.2 Summary of Clinical Pharmacology; Figure 2-4; SDN 1)

The median Tmax with the granule formulation under fed condition was 2.5 hours, whereas the median Tmax was 1.0 hour under fasted condition. No clinically relevant food effect was observed with alpelisib granules on the rate (Cmax) or extent (AUC) of absorption. The statistical analysis of alpelisib PK parameters demonstrated that there is no clinically relevant food effect on the 50 mg alpelisib granule dosage form (**Table 4** and **Table 5**).

Reviewer's Comment:

- *The reviewer's calculated statistical analysis results (GMR, 90%CI) on C_{max}, AUC_{last} and AUC_{inf} are consistent with those of the Applicant's (**Table 4** and **Table 5**).*
- *The reviewer agrees with the Applicant's conclusion.*

Safety Results:
The study results show no new safety findings. There were no deaths, SAEs, or grade 3/4 AEs reported in the study (**Table 6**).

Table 6. Overview of adverse events (Safety set)

	All Participants N=60	
	All Grades nE, nS(%)	Grade >=3 nE, nS(%)
Adverse events	39,24 (40.0)	0, 0 (0.0)
Treatment-related	6,4 (6.7)	0, 0 (0.0)
SAEs	0, 0 (0.0)	0, 0 (0.0)
Treatment-related	0, 0 (0.0)	0, 0 (0.0)
Fatal SAEs	0, 0 (0.0)	0, 0 (0.0)
Treatment-related	0, 0 (0.0)	0, 0 (0.0)
AEs leading to discontinuation	9,8 (13.3)	0, 0 (0.0)
Treatment-related	2,2 (3.3)	0, 0 (0.0)
AEs leading to dose adjustment/interruption	0, 0 (0.0)	0, 0 (0.0)
AEs requiring additional treatment	9,9 (15.0)	0, 0 (0.0)

(Data source: Section 5.3.1.2 Study No. CBYL719F12101 – Study Report Body; Table 12-1; SDN 1)

Reviewer's Comment:

- *The reviewer agrees with the Applicant safety conclusions.*

Overall Conclusions:

Study CBYL719F12101 results demonstrate that

- there is no clinically meaningful difference in the exposure of alpelisib granules and film-coated tablet formulations under fed conditions.
- There is no food effect on granule formulation.

These results support the Applicant's proposed labeling update that recommended dosage of 50 mg QD can be administered as VIJOICE tables or VIJOICE granules.

4. Bioanalysis

BYL719 and BZG791 were detected using a validated analytical method 1600667, entitled "*Quantitative determination of BYL719 and BZG791 in K3EDTA Human Plasma by LC-MS/MS*". In this submission, the Applicant submitted the following method validation reports:

1) Method Validation Report; report No. DMPK R1600667
2) Method Validation Amendment 01 to 06

Validation Results in the Original Method Validation:

Validation item	Acceptance Criteria	Parameters / Results
Specificity	Interference of BYL719 and BZG791 ≤20% mean response (n≥3) of the LLOQ	fulfilled
	Interference of [M+6]BYL719 and [M+6]BZG791 ≤5% mean response (n≥3) of the LLOQ	fulfilled
Selectivity	Interference of BYL719 and BZG791 ≤20% mean response (n≥3) of the LLOQ	fulfilled
	Interference of [M+6]BYL719 and [M+6]BZG791 ≤5% mean response (n≥3) of the LLOQ	fulfilled
Matrix effect	Mean ISTD normalized matrix factor of BYL719 and BZG791 at 3 concentration levels	0.89 for BYL719 0.94 for BZG791
	Precision of ≤15%	fulfilled
Recovery	Mean Internal standard normalized recovery for BYL719 and BZG791 at 3 concentration levels	92.5% for BYL719 and 95.1% for BZG791
	Precision of ≤20%	fulfilled
Carryover	Response after injection in blank samples following each injection of the ULOQ ≤20% of the mean response observed for the LLOQ for BYL719 and BZG791	fulfilled
	Response after injection of [M+6]BYL719 and [M+6]BZG791 at the working concentration in blank samples following each injection of ULOQ ≤5% of the [M+6]BYL719 and [M+6]BZG791 mean response observed at the working concentration	fulfilled
Calibration	Deviation of ±15% (±20% at the LLOQ) for 75% of the C standards and 50% at each C standard level from the nominal values at a minimum of 6 different levels	fulfilled
Intra-day accuracy and precision	Mean bias within ±15% (±20% at LLOQ) of the nominal values	fulfilled
	Precision of ≤15% (≤20% at LLOQ)	fulfilled
Inter-day accuracy and precision	Mean bias within ±15% (±20% at LLOQ) of the nominal values	fulfilled

	Precision of ≤15% (≤20% at LLOQ)	fulfilled
Dilutions	Bias within ±15% of the nominal concentration for samples (5 times the ULOQ) diluted up to 10-fold (25500 ng/mL for BYL719 and 5100 ng/mL for BZG791)	fulfilled
	Precision ≤15%	fulfilled
Stability of	Stock solutions:	
BYL719 and BZG791	Mean bias ±10% and mean precision ≤15%	fulfilled
	Storage temperature	room temperature
	Number of hours	26
	Storage temperature	5±3°C
	Number of days	90
	Working solutions:	
	Mean bias ±10% and mean precision ≤15%	fulfilled
	Storage temperature	room temperature
	Number of hours	25
	Storage temperature	5±3°C
	Number of days	90
	Post-preparative stability in extracts on the autosampler:	
	Mean bias ±15%	fulfilled
	Storage temperature	5±3°C
	Number of hours	124
	Post-preparative stability in extracts on the shelf	
	Mean bias ±15%	fulfilled
	Storage temperature	room temperature
	Number of hours	04
	Freeze-thaw stability of spiked human plasma:	
	Mean bias ±15%	fulfilled
	Cycles:	5
	Storage temperature	-78±8°C, -20±5°C
	Dry Extract Stability	
	Mean bias ±15%	fulfilled
	Storage temperature	-20°C±5°C
	Number of hours	118
	Short-term stability in spiked human plasma:	
	Mean bias ±15%	fulfilled
	Storage temperature	At room temperature

	Short-term stability in spiked human whole blood	
	Mean bias ±20%	fulfilled
	Precision ≤15%	fulfilled
	Storage temperature	At room temperature and at+5°C±5°C
	Number of hours	2
	Long-term stability in spiked human plasma	
	Mean bias ±15%	fulfilled
	Storage temperature	-78±8°C, -20±5°C
	Number of days	145
Stability	Stock solutions:	
[M+6]BYL719	Mean bias ±10% and mean precision ≤15%	fulfilled
and[M+6]BZG791	Storage temperature	room temperature
	Number of hours	26
	Storage temperature	5±3°C
	Number of days	90
	Working solutions:	
	Mean bias ±10% and mean precision ≤15%	fulfilled
	Storage temperature	room temperature
	Number of hours	25
	Storage temperature	5±3°C
	Number of days	90
Batch Size Experiment	Accuracy within ±15% (≤20% and within ±20% at LLOQ) of the nominal values	fulfilled
	Precision of ≤15% (≤20% at LLOQ)	fulfilled
	Number of samples including Calibration Curve	165
Haemolysis and Lipemic effect	The precision must be ≤15% from the theoretical concentration for Haemolysis and Lipemic QC samples.	fulfilled
	The bias must be within ±15% from the theoretical concentration for Haemolysis and Lipemic QC samples.	fulfilled
Cross-check between Veeda Clinical Research and Sponsor	For incurred samples, at least 2/3 of the samples at greater than 3 times LLOQ must be within the target range: -20% ≤ normalized difference ≤+20%.	fulfilled
Special Issue	During Specificity experiment significant interference (i.e.65.5%) was observed at the RT of BZG791 in sample name ULOQ (Without ISTD) (BYL719) compared to mean response of LLOQ sample. Further, investigation was performed to evaluate effect of interference by preparing aqueous samples by drying and compare and interference was compared with the extracted samples. But in almost all investigation, significant interference was found in aqueous samples and also in extracted samples. Based on overall investigation, it was concluded that working standard of BYL719 itself having interference of BZG791. However, the results of Method Validation such as Precision & Accuracy batch, Matrix Factor all stability experiments for both BYL719 & BZG791 were found well within the acceptance criteria, therefore interference of working standard may not affect overall quantitation of BYL719 & BZG791. For detailed Investigation report along with conclusion, see Appendix C.	

(Data source: DMPK R1600667 Study Report in section 5.3.1.4; Page 11; SDN 1)

Key change in Amendment 01:

- Long-term stability in spiked Human plasma: 377 days at -78± 8°C, -20±5°C

Key change in Amendment 02:
- Long-term stability in spiked human plasma: 522 days at -78± 8°C, -20±5°C

Key change in Amendment 03:
- Long-term stability in spiked human plasma: 1217 days at -78± 8°C, -20±5°C

Key change in Amendment 04:
- Free-thaw stability of spiked human plasma: 3 cycles at -78± 8°C, -20±5°C

Key changes in Amendment 05:
- Short-term stability in spiked human plasma at room temperature: 12 hours
- Intra-day accuracy and precision: fulfilled.

Key change in Amendment 06:
- Cross validation between sites: fulfilled the requirement of 2/3 of all the samples the normalized differences (%) for spiked samples within ±15%.

Reviewer's Assessment on Bioanalytical Method and Method Validation*:*

The precision and accuracy of quality control and standard of the bioanalytical method were within the pre-specified acceptance limits. The Applicant also adequately validated the selectivity, specificity, matrix effect, recovery, freeze-thaw stability, dilution, short-term and long-term stability.

The Applicant has adequately validated bioanalytical method 1600667 for Study CBYL719F12101.

5. Appendix – PBPK Analysis

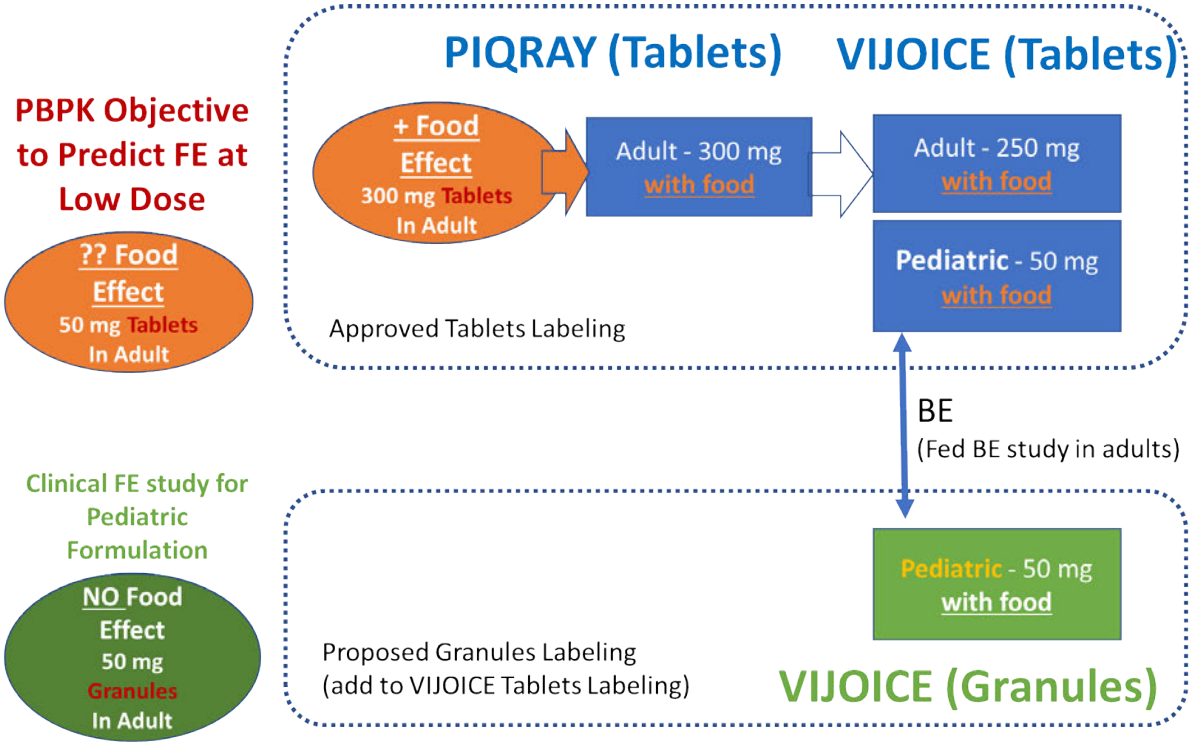
5.1 Executive Summary

This review memorandum summarizes the Applicant PBPK analysis of food effect on the PK of alpelisib submitted in the NDA 281466 (Report DMPK-R2170199). In this submission, a new dosage form (granules) was proposed for alpelisib 50 mg. The previously approved alpelisib products (Piqray and Vijoice) are film-coated tablets (FCTs). Alpelisib tablets (as Vijoice) is recommended to be taken with food, with the recommended dosage of 50 mg once daily with food for pediatric patients and 250 mg once daily with food for adult patients. In Study CBYL719F12101, a low fat low calorie meal (LFLC) did not affect the C_{max} or AUC of alpelisib administered as 50 mg granules. Further, the 50 mg granules formulation was demonstrated bioequivalent to the 50 mg FCT formulation under fed conditions (LFLC).

The Applicant conducted a PBPK analysis that provided mechanistic explanation for the lack of clinically relevant food effect at a lower dose of 50 mg administered as granules compared to

that observed at 300 mg administered as tablets. An overview of the available food effect data for alpelisib different formulations and dose levels is illustrated in **Figure 5**.

Figure 5. Overview of clinical food effect for alpelisib formulations and dose levels



Source: Illustration by FDA reviewer. Abbreviation: FE, food effect. Note that in the approved labeling, the recommended dose of PIQRAY Tablets is 300 mg taken orally once daily with food, whereas the recommended dose of VIJOICE Tablets is 50 mg and 250 mg taken orally once daily with food for pediatric patients and adult patients, respectively.

5.2 Methods

The PBPK analysis was conducted using the PBPK platform Gastroplus. The Applicant used a published PBPK model of alpelisib (Gajewska et al., 2020)[2], with modification. The inter-compartment distribution rate constants were modified to better capture the terminal phase of the clinical PK profile of alpelisib (200 mg and 300 mg with and without food), thus absorption description remained the same. The absorption of alpelisib was characterized using the software's ACAT (Advanced Compartmental Absorption) model, which describes human gastrointestinal physiology such as pH, transit times and volumes across the intestinal tract and their differences under fed and fasted conditions. Further, the model incorporated alpelisib solubility and dissolution such as alpelisib pH-dependent solubility in vitro, dissolution parameters estimated using in vitro biorelevant solubilities in fasted-state simulated intestinal fluid (FaSSIF) and fed-state simulated intestinal fluid (FeSSIF) with constant dissolution rate, and bile acid concentration-dependent solubilities. In vitro, the decrease in alpelisib solubility

[2] Gajewska M, Blumenstein L, Kourentas A, et al (2020) Physiologically based pharmacokinetic modeling of oral absorption, pH, and food effect in healthy volunteers to drive alpelisib formulation selection. The AAPS Journal 22:134

reached a plateau at 0.02 mg/ml when pH was greater than/or equal to 5.0. Further, the solubility of alpelisib in vitro in FeSSIF increased substantially to 0.32 mg/ml, suggesting that solubility of alpelisib would have a significant increase under fed condition.[3] Simulations were conducted for alpelisib in tablets for all doses. The PBPK analysis to predict food effect at 50 mg tablet was considered relevant for the 50 mg granule formation for the purpose of providing mechanistic support considering that the 50 mg granule formulation was shown bioequivalent to the 50 mg tablet formulation under fed conditions (Study CBYL719F12101).

5.3 Results

The Applicant's PBPK model reasonably captured the clinical food effect on the PK of alpelisib observed at 200 mg (Study CBYL719A2109) and 300 mg (Study CBYL719A2103) in healthy participants administered as FCT. Based on the PBPK analysis of alpelisib absorption kinetics, alpelisib dissolves fast, both under fed and fasted states, while extensive precipitation follows under fasted conditions. Under fed conditions, alpelisib dissolution is slower. But due to the high drug solubility in the presence of bile acids, higher amount of the dose is dissolved and absorbed as expected from the enhanced solubility in FeSSIF**Error! Bookmark not defined.**. Consistent with these, parameter sensitivity analysis showed that alpelisib fraction absorbed is sensitive to the factors such as reference solubility, and intestinal permeability. In addition, alpelisib absorption was shown to be sensitive to small intestine fluid volume and transit time.

Taken all these together, the amount of dissolved alpelisib as well as the fraction of alpelisib absorbed are predicted to be higher compared to those without food at the dose shown food effect (FDA reviewer predicted the amount dissolved and the fraction absorbed values using the Applicant submitted model). The differences in the amount dissolved and fraction absorbed between fed and fasted conditions are predicted to be diminished as alpelisib dose decreases. The Applicant's PBPK analysis in this submission predicted positive food effect for 150 mg or higher doses of alpelisib. The PBPK prediction is consistent with the results of Study CBYL719F12101, where there was no effect of a LFLC meal on the C_{max} and AUC of alpelisib with the 50 mg granules.

5.4 FDA Assessment on PBPK Modeling Results

In general, FDA has not confirmed the performance of PBPK analysis to reliably predict the effect of food on the PK of a drug in a prospective manner. However, in the case of alpelisib, FDA considers that the Applicant PBPK analysis provided a reasonable mechanistic support to the food effect assessment of the new dosage form for alpelisib 50 mg. The PBPK model predicted lack of food effect at 50 mg based on the gastrointestinal physiology and alpelisib solubility and dissolution under fed and fasted conditions, corroborating the finding from Study CBYL719F12101.

[3] FDA's Assessment in Section 6.3 of the Comprehensive Clinical Pharmacology Review of NDA212526. Electronic Action Package available at Drugs@FDA

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