CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214876Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

This is a corrected review that does not change the overall recommendations/conclusions of the original review dated 04/18/2023.

NDA or BLA Number	214876
Link to EDR	\\CDSESUB1\evsprod\NDA214876\0020
Submission Date	06/30/2022 (SDN 20)
Submission Type	Standard review
Brand Name	ZEJULA®
Generic Name	Niraparib
Dosage Form and Strength	Tablets in 100, 200, and 300 mg strengths
Route of Administration	Oral
Proposed Indication	• Maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. • Maintenance treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*mut) recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete response to platinum-based chemotherapy.
Applicant	Glaxosmithkline, LLC (GSK)
Associated IND	IND 100996
OCP Review Team	Yixuan Dong, Ph.D., Salaheldin Hamed, Ph.D. (TL)
OCP Final Signatory	Stacy S Shord, PharmD, Deputy Director, Division of Cancer Pharmacology II

Table of Contents

1. EXECUTIVE SUMMARY

This application is a re-submission from GSK requesting the approval of ZEJULA® (niraparib) tablets, 100, 200, and 300 mg for 1) maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and 2) maintenance treatment of adult patients with deleterious or suspected deleterious g*BRCA*mut recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete response to platinum-based chemotherapy. The reference drug is ZEJULA® (niraparib) capsules, approved on March 27, 2017 under NDA 208447.

To support this NDA, the applicant submitted results of a relative bioavailability (BA) and bioequivalence (BE) study (Stage 1 and 2 of Study 3000-01-004, which is a single-dose, two-period, two-treatment, two-way, crossover study in patients with advanced solid tumors) comparing the bioavailability of the proposed tablets formulation and the approved capsules formulation in patients with advanced solid tumors. The applicant also conducted a food effect study (Stage 3 of Study 3000-01-004, a single-dose, two-period, two-treatment, two-way, crossover study in patients with advanced solid tumors) characterizing the effect of the intake of a high-fat high-calorie meal (total calories of 800-1000 with 150 calories from protein, 250 calories from carbohydrates, and 500-600 calories from fat) on the bioavailability of the proposed tablets formulation. Results from this study shows that the proposed tablets and the approved capsules, at a single dose of 300 mg, have similar area under the curve (AUC) and maximum plasma concentration (C_{max}) and that administration with a high-fat meal increases the AUC and C_{max} of the tablets formulation (Table 1).

Table 1: Summary of Relative BA and Food Effect Findings

Study	Parameter	Geometric Mean Ratio (90% CI)
BA/BE (stage 1, capsules – tablets sequence)	AUC_{inf}	91 (85, 98)
	C_{max}	95 (84, 116)
BA/BE (stage 2, tablets – capsules sequence)	AUC_{inf}	96 (92, 100)
	C_{max}	96 (91, 102)
Food effect (stage 3)	AUC_{inf}	128 (116, 141)
	C_{max}	111 (94, 132)

(Source: Reviewer's independent analysis)

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II has reviewed GSK's NDA requesting the approval of ZEJULA® (niraparib tablets) and recommends the proposed product for approval from a clinical pharmacology perspective.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Not applicable.
General dosing instructions	The proposed dosing regimen of this product is based on the approved recommended dosage for the reference drug.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The results of the food effect study suggests that concomitant administration of a high-fat meal will not have a clinically meaningful impact on the pharmacokinetics of niraparib. The proposed tablets formulation can be taken with or without food. The proposed dosing regimen of this product is based on the approved recommended dosage for the reference drug.
Labeling	Subsection 12.3 of the labeling was updated to include the effect of a high fat meal on the AUC and Cmax of the tablet formulation.
Bridge between the to-be-marketed and clinical trial formulations	A relative BA/BE study was conducted. The PK exposure was comparable between ZEJULA® (niraparib) tablets and the reference drug product.
Other (specify)	None.

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

The clinical pharmacology of niraparib has previously been described in detail in the clinical pharmacology review of the original NDA 208447 submission. Refer to the clinical pharmacology review of the original NDA 208447 (DARRTS, Reference ID: 4068706).

2.2 Dosing and Therapeutic Individualization

Refer to the clinical pharmacology reviews of the original NDA 208447 and supplements (DARRTS, Reference IDs: 4068706 and 4366075).

2.3 Outstanding Issues

None

2.4 Summary of Labeling Recommendations

Subsection 12.3 of the labeling was updated to include the effect of a high fat meal on the AUC and C_{max} of the tablet formulation.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

The current NDA for ZEJULA® (niraparib) tablets was submitted referencing ZEJULA® (niraparib) capsules developed by GSK (NDA 208447) which was initially approved on March 27, 2017 under NDA 208447.

Table 2 summarizes the clinical study 3000-01-004 that is intended to support the proposed NDA.

Table 2: Summary of Clinical Pharmacology Study 3000-01-004

Stage (N)	**Study Objective**	**Study Design**	**Treatments (Dose, Dosage Form, Route)**	**Subjects (M/F) Age: mean (Range)**
1 (N=29)	To assess bioavailability of niraparib tablets, 300 mg, compared to the approved capsules, 100 mg, under fasted conditions in patients with advanced solid tumors	Randomized, open-label, single-dose, two-period, two-treatment, two-way, crossover study	A: Niraparib tablets, 1 × 300 mg B: Niraparib capsules, 3 × 100 mg	29 patients (11/18) Age: mean 63 years (28 to 88)
2 (N=168)				168 patients (72/96) Age: mean 63.5 years (26 to 87)
3 (N=28)	To assess the effect of food on the relative bioavailability of niraparib tablets in patients with advanced solid tumors	Randomized, open-label, single-dose, two-period, two-treatment, two-way, crossover study	A: Niraparib tablets, 1 × 300 mg (fed) B: Niraparib tablets, 1 × 300 mg (fasted)	28 patients (17/11) Age: mean 61 years (28 to 79)

- Stage 1 and Stage 2 evaluated the PK of the proposed tablets (300 mg strength) in comparison to the reference product (100 mg capsules) in patients with advanced solid tumors. The reported results indicate that niraparib C_{max} and AUC of the proposed tablets are similar to those of the capsules following a single dose of 300 mg (See **Table 1**).

- Stage 3 evaluated the effect of food on the relative BA of the proposed niraparib tablets in patients with solid tumors. The reported results indicate that food intake increases C_{max} and AUC by 11% and 28%, respectively (see **Table 1**) and delays median T_{max} (range) from 4.9 h (min, max: 3, 7) in the fasted state to 6.0 h (min, max: 1, 11) in the fed state. These changes in PK exposure are not clinically meaningful, which is consistent with the effect of food on the approved capsules formulation. The administration instruction regarding food intake in proposed labeling is the same as that in the reference drug labeling (ZEJULA may be taken with or without food).

3.2 General Pharmacology and Pharmacokinetic Characteristics

Please refer to the ZEJULA® USPI and the clinical pharmacology review of the original NDA 208447 (DARRTS, Reference ID: 4068706).

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The results of the relative BA/BE study (Stage 1 and 2 of Study 3000-01-004) showed that niraparib tablets is equivalent, in terms of AUC and C_{max}, to the reference capsules following a single 300 mg dose (**Table 3**, **Figure 1**, and **Figure 2**).

The bioequivalence of the two formulations is demonstrated in Study 3000-01-004 (Stage 1 and 2) which was a multicenter, open-label, 2-stage, randomized-sequence, single-crossover study to assess the relative BA and BE of niraparib tablets formulation relative to the capsules formulation in patients with advanced solid tumors.

In Stage 1, all 29 patients completed the study. Due to the short 7-day washout between study periods, significant carryover (baseline concentration >5% of Cmax) resulting from incomplete washout of niraparib was observed in 6 patient PK profiles in Period 2. These patients were excluded from the bioavailability evaluation. In addition, PK data from one patient were also excluded from the analysis due to the thaw of the PK samples during transit. In stage 2, 60 out of 168 patients receiving the study drug were excluded from the BE evaluation due to adverse events, significant carryover, and protocol deviations. One hundred eight (108) patients who completed both periods and had sufficient and accurate PK data were included for the analysis.

To verify the PK results, a linear mixed effects model was used by the reviewer to analyze the fixed effects (formulation, period, and sequence) and the random effects (subjects nested within a sequence) on the PK parameters (AUC_{0-t}, AUC_{inf}, and C_{max}). The geometric mean ratio of test (tablets) to reference (capsules) along with the 90% confidence interval fell within 80% to 125%.

Table 3: Analysis of Relative Bioavailability and 90% Confidence Intervals for Niraparib PK Parameters (Stage 1 and 2)

Stage	Parameter	Treatment	Geometric LS Mean	Ratio (Test/ Reference)	90% CI for Ratio of Geometric LS Means
1	C_{max} (ng/mL)	Capsules (R)	462. 4	1.0	0.8, 1.1
		Tablets (T)	438.9		
	AUC_{0-t} (hr•ng/mL)	Capsules (R)	16168	0.9	0.8, 1.0
		Tablets (T)	14615		
	$AUC_{0-\infty}$ (hr•ng/mL)	Capsules (R)	17281	0.9	0.8, 1.0
		Tablets (T)	15748		
2	C_{max} (ng/mL)	Capsules (R)	537.8	1.0	0.9, 1.0
		Tablets (T)	518.9		
	AUC_{0-t} (hr•ng/mL)	Capsules (R)	17656	1.0	0.9, 1.0
		Tablets (T)	17043		
	$AUC_{0-\infty}$ (hr•ng/mL)	Capsules (R)	19399	1.0	0.9, 1.0
		Tablets (T)	18695		

(Source: reviewer's independent analysis)

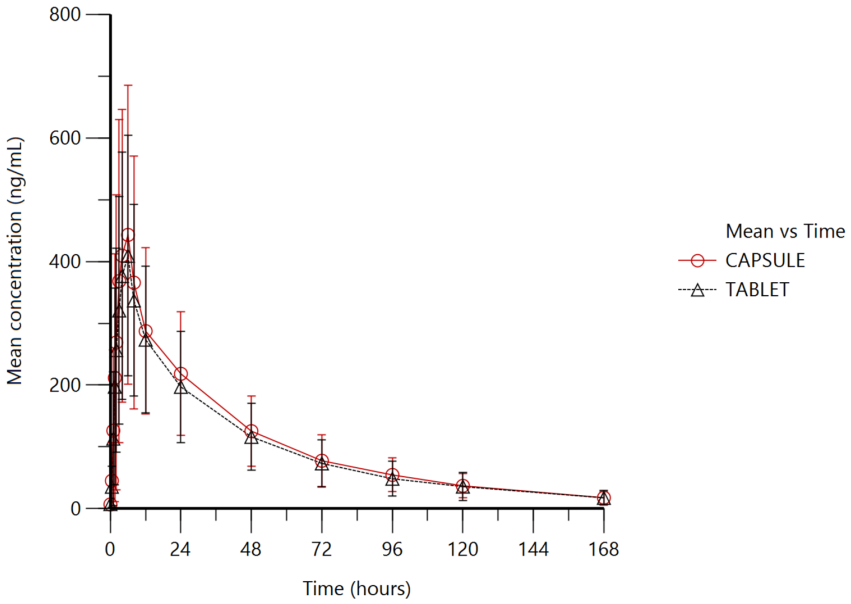

Figure 1: Mean (±SD) Niraparib Concentration-Time Profiles by Treatment (Stage 1 PK Phase, N=22)

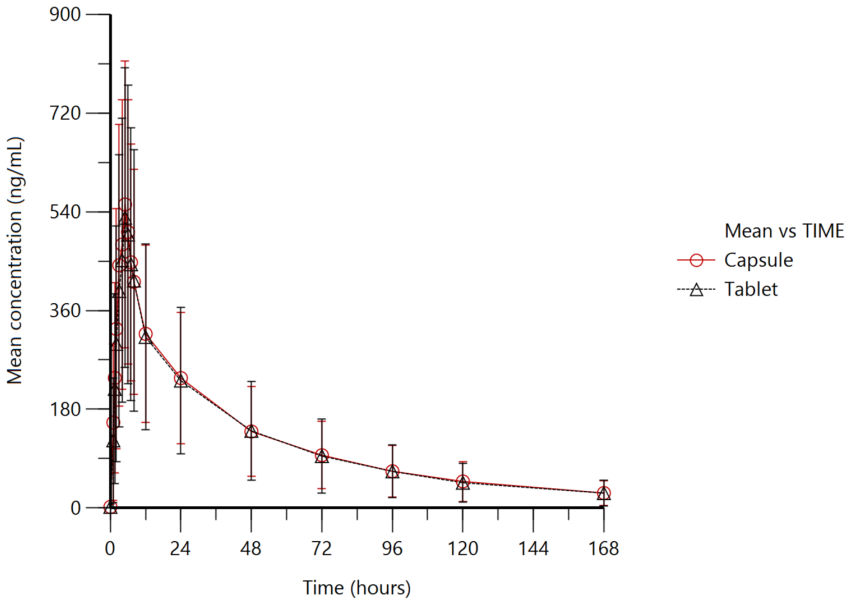

Figure 2: Mean (±SD) Niraparib Concentration-Time Profiles by Treatment (Stage 2 PK Phase, N=108)

In Stage 1, 19 (65.5%) patients receiving niraparib experienced at least 1 TEAE and 2 (6.9%) patients had Grade ≥3 TEAEs. No serious TEAEs, TEAEs leading to study drug discontinuation or interruption, or TEAEs leading to death were reported. In Stage 2, 125 (74%) patients receiving

niraparib experienced at least 1 TEAE and 36 (21%) patients had Grade ≥3 TEAEs. 26 (16%) patients had serious TEAEs, 5 (3%) patients had TEAEs leading to treatment discontinuation, and 3 (1.8%) patients had TEAEs leading to death. TEAEs of any grade and serious TEAEs occurring in Stage 1 and 2 are summarized in **Table 4**. Overall, the AE profiles of niraparib tablets were consistent with the known effects of the approved niraparib capsules.

Table 4: Treatment-Emergent AE in Stage 1 and 2 of Study 3000-01-004

	Stage 1		**Stage 2**	
	Tablet (N=29)	**Capsule (N=29)**	**Tablet (N=156)**	**Capsule (N=152)**
Any TEAE[#]	9 (31)	12 (41)	86 (55)	73 (48)
Nausea	1 (3.4)	5 (17)	17 (11)	13 (8.6)
Vomiting	1 (3.4)	2 (6.9)	10 (6.4)	9 (5.9)
Fatigue	1 (3.4)	2 (6.9)	12 (7.7)	8 (5.3)
Back pain	1 (3.4)	1 (3.4)	5 (3.2)	2 (1.3)
Hypomagnesaemia	1 (3.4)	0	--	--
Constipation	--	--	18 (12)	11 (7.2)
Anemia	--	--	9 (5.8)	8 (5.3)
Dehydration	--	--	6 (3.8)	5 (3.3)
Decreased appetite	--	--	4 (2.6)	3 (2.0)
Headache	--	--	7 (4.5)	2 (1.3)
Abdominal pain	--	--	5 (3.2)	4 (2.6)
Serious TEAE occurring in ≥ 2 patients	0	0	10 (6.4)	10 (6.6)
Abdominal pain	--	--	2 (1.3)	1 (0.7)
Constipation	--	--	2 (1.3)	1 (0.7)
Vomiting	--	--	0	2 (1.3)
Pulmonary embolism	--	--	1 (0.6)	0
Sepsis	--	--	1 (0.6)	1 (0.7)

[#]Only TEAEs occurring in ≥ 5% patients in Stage 2 are included in the table.

Reviewer's comments:
The design and conduct of Study 3000-01-004 (Stage 1 and 2) are adequate to evaluate the relative BA and BE of the proposed tablets formulation and the approved capsules formulation. Niraparib was administered under an overnight fasted state. Per ZEJULA® USPI, ZEJULA can be taken with or without food. In Stage 3 of the study, the effects of high-fat meals on the exposure of niraparib tablets were evaluated. Administration with a high-fat meal increased the PK exposures of niraparib (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) by up to 31%; however, the increase in niraparib exposure is not considered clinically meaningful (see section 3.3.4 for details). Therefore, administration without regard to food is acceptable.

FDA analysis of niraparib PK results in Study 3000-01-004 (Stage 1 and 2) was consistent with the Applicant's analysis. The proposed tablets formulation met bioequivalence criteria in all pair-wise comparisons to the approved capsules formulation. Therefore, no clinically meaningful

differences in niraparib exposure are expected when the same total dose of niraparib is administered, regardless of dosage form.

Conclusions and Recommendations:

Based on the results of Study 3000-01-004 (Stage 1 and 2), the proposed tablets formulation met bioequivalence criteria to the approved capsules formulation when administered as a single 300 mg dose. Therefore, the recommended dosage of niraparib may be delivered using either dosage form.

3.3.2 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Study 3000-01-004 (Stage 3) was a single cohort, randomized-sequence, 2-period, single dose, crossover study to assess effect of a high-fat meal on the PK of the niraparib tablets formulation in patients with advanced solid tumors. The patients received a 300 mg dose of niraparib tablets either following a 10-hour overnight fast (reference) or following consumption of a high-fat meal (test, total calories of 800-1000 with 150 calories from protein, 250 calories from carbohydrates, and 500-600 calories from fat), with a 14-day washout period between periods. Twenty-eight (28) patients were given at least one dose of the study drugs and 19 patients completed all PK assessments in both a fasted and fed state and were included in the food effect evaluation. In addition, one additional patient was removed from $AUC_{0-\infty}$ calculation due to >20% extrapolation and 3 additional patients were removed from AUC_{0-t} calculation as last time point samples at 168 hours were not collected or were collected out of the 24-hour sampling window.

The statistical evaluation of the PK parameters, C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, is presented in **Table 5**. The geometric LS mean ratios for the fed to fasted comparison were 1.1, 1.3, and 1.3 for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively. The 90% CIs for all key PK parameters were outside the limit of 0.8 to 1.25. However, the modest increase in exposure following a high-fat meal is not likely to be clinically meaningful. The exposure-response relationship for safety characterized in the original NDA 208447 submission (Reference ID: 4068706) indicates that a doubling in exposure increased the frequency of any Grade thrombocytopenia, the most frequent adverse reaction, by only 10% (see **Figure 3**). In addition, the concentration-over-time profiles are comparable under fasted and fed conditions as shown in **Figure 4**.

Table 5: Analysis of BE and 90% Confidence intervals for Niraparib PK Parameters (Stage 3)

Parameter	Treatment	Geometric LSM	Ratio (Test/ Reference)	90% CI of Ratio of Geometric LSM
C_{max} (ng/mL)	Fasted (reference)	711	1.1	0.9, 1.3
	Fed (test)	791		
AUC_{0-t} (hr•ng/mL)	Fasted (reference)	20059	1.3	1.2, 1.5
	Fed (test)	26361		
$AUC_{0-\infty}$ (hr•ng/mL)	Fasted (reference)	23637	1.3	1.2, 1.4
	Fed (test)	30234		

(Source: reviewer's independent analysis)

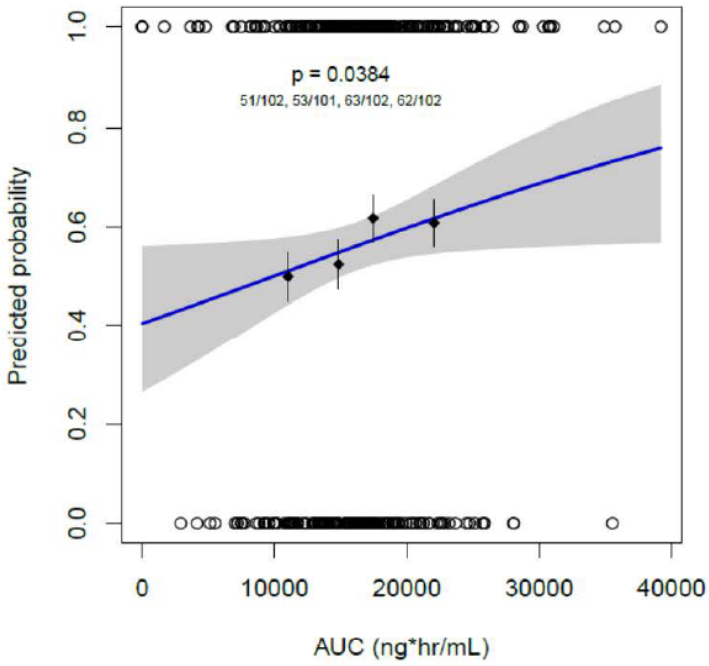

Figure 3. Predicted probability of any Grade thrombocytopenia by AUC by AE status

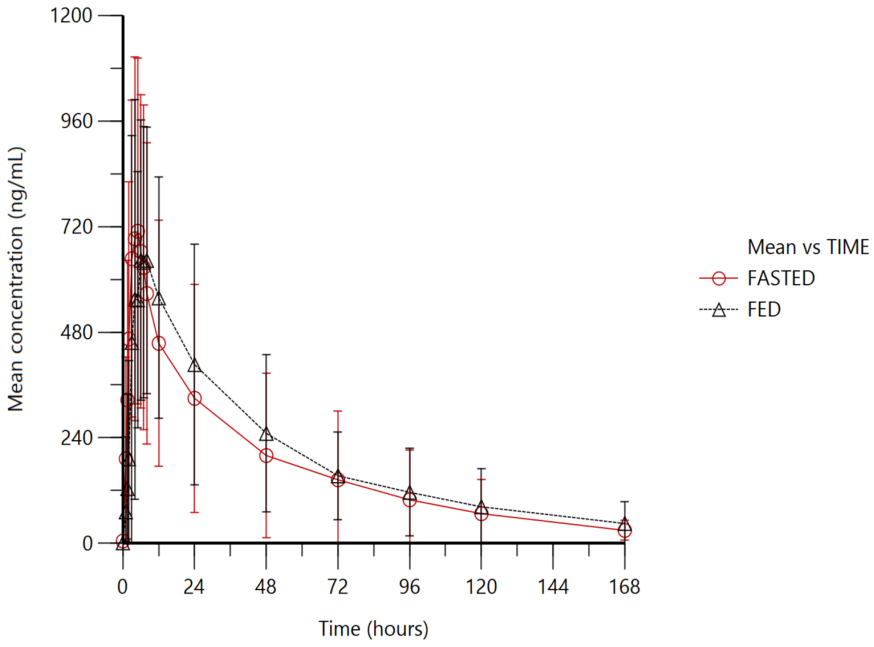

Figure 4: Mean PK profiles of niraparib tablet under fasted (red line) and fed (black line) conditions.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

The methods (BAC-KB-L010 and BAC-KB-L012) for the determination of concentrations of niraparib in human plasma (K3EDTA) were developed and validated using a protein precipitation extraction procedure and LC-MS/MS. The method used for pivotal BE study (Stage 2) and food effect study (Stage 3) is similar as that used for pilot BE study (Stage 1) with updates on calibration range, LLOQ, QC concentrations, stability data. To cross-validate between the two assays, 100 Stage 1 samples were randomly selected and reanalyzed for niraparib only using BAC-KB-L012. For the cross-validation, niraparib data from both assays was compared and the results for over two-thirds of the samples that were selected for reanalysis were acceptable (within ±20.0% difference between the original and reanalysis values). Laboratory Method BAC-KB-L012 was used for the remainder of the study.

The highest C_{max} (2020 ng/mL) in Stage 1 was not covered by the calibration range of 1 ng/mL to 500 ng/mL but can be covered by the dilution QC (10000 ng/mL). The standard curve for Stage 2 and 3 spanned a range of concentrations from 5 ng/mL to 2500 ng/mL, which covered the highest C_{max} values in both stages (2100 ng/mL and 2070 ng/mL in Stage 2 and 3, respectively). QC samples ($n \geq 2$) at low, medium, high, and/or dilution concentrations (3, 40, 400, and 10000 ng/mL for stage 1, and 15, 150, 2000 ng/mL for stage 2 and 3) were included in each run. The accuracy and precision of the QC samples were well below the 15% limit for the accepted runs. The stability of QC samples was assessed at room temperature (24 hours), freeze thaw cycles (up to 7 cycles), and at -20°C and -80°C for long-term stability (up to 231 days and 1026 days, respectively). The bias of all the stability samples was within the 15% acceptance criteria. The method validation and in-study performance for plasma samples were acceptable based on the current Bioanalytical Method Validation Draft FDA Guidance for Industry.

The summaries of the validation data for pilot BE study (Stage 1) and pivotal BE study (Stage 2) and food effect study (Stage 3) are presented in **Table 6 and 7**, respectively.

Table 6: Bioanalytical Method Validation for Pilot BE Study (Stage 1)

Analytical Validation Report	**KB-0044-RB-CV-RPT-01 and KB-0047-RB-CL-RPT-01**
This analytical method was used in the following studies:	KB-0164-RB-CS
Short description of the method	LC-MS/MS
Analyte	Niraparib and M1
Internal standard (IS)	M002151 and D5-M1
Calibration range	1.00 to 500 ng/mL
Linearity	Linear, $1/x^2$, R^2: Niraparib 0.9984-0.9996; M1 0.9987-0.9996
Lower limit of quantification (LLOQ)	1.00 ng/mL
Standard curve concentrations (ng/mL)	1.00, 2.50, 5.00, 20.0, 50.0, 100, 250, and 500
QC concentrations (ng/mL)	1.00 (LLOQ QC), 3.00 (low QC), 40.0 (mid QC), 400 (high QC), and 10,000 (dilution QC)
Between-run accuracy (%)	Niraparib: -1.8 → -1.0 M1: 2.7 → 6.0
Between-run precision (%)	Niraparib: 2.1 → 6.7 M1: 2.4 → 4.7
Within-run accuracy (%)	Niraparib: -6.6 → 4.0 M1 : 1.3 → 7.0
Within-run precision (%)	Niraparib: 1.6 → 6.7 M1: 1.2 → 6.0
Matrix factor (analyte and IS) CV% of IS normalized matrix factor	Niraparib: 0.982, CV: 2.3% Niraparib IS: 0.977, CV: 2.1% Niraparib normalized by IS: 0.999, CV: 6.1% M1: 1.01, CV: 2.9% M1 IS: 1.02, CV: 1.7% M1 normalized by IS: 1.02, CV: 2.9%
Short-term stability of the stock solution and working solutions	Stock solutions Niraparib - Confirmed up to 24 hours, observed change 2.4% at room temperature. M1 - Confirmed up to 24 hours, observed change 0.8% at room temperature. Working solutions Niraparib - Confirmed up to 23 hours, observed change within ±1.5% at room temperature. M1 - Confirmed up to 23 hours, observed change within ±1.9% at room temperature.

Long-term stability of the stock solution and working solutions	Stock solutions Niraparib - Confirmed up to 334 days, observed change 4.8% at -20°C. M1 - Confirmed up to 238 days, observed change -9.6% at -20°C. Working solutions Niraparib - Confirmed up to 485 days, observed change ±5.9% at -20°C. M1 - Confirmed up to 210 days, observed change ±6.2% at -20°C.
Short-term stability in plasma at room temperature (QC)	Confirmed up to 22 hours, observed change within ±11.7% for niraparib and within ±13.5% for M1
Post-preparative stability (dry extract stability)	Confirmed up to 6 days refrigerated, observed change within ±8.8% for niraparib and within ±7.0% for M1
Long-term stability in plasma	Niraparib - Confirmed up to 546 days, observed change 4.3% at -80°C. M1 - Confirmed up to 546 days, observed change 8.0% at -80°C
Autosampler storage stability	Confirmed up to 6 days refrigerated
Freeze and thaw stability (-80°C)	Niraparib and M1 were stable after 4 cycles
Dilution integrity	10,000 ng/mL diluted 40-fold Niraparib: Accuracy -3.1%, Precision 2.1% M1: Accuracy 1.0%, Precision 1.7%

Table 7: Bioanalytical Method Validation for Pivotal BE Study (Stage 2) and Food Effect Study (Stage 3)

Analytical Validation Report	**Test Site Study No. KB-0167-RB-CV** **Test Site Report No. KB-0167-RB-CV-RPT-01** **Test Site Validation Report No. KB-0179-RB-CL-RPT-02**
This analytical method was used in the following studies:	KB-0164-RB-CS
Short description of the method	LC-MS/MS
Analyte	Niraparib
Internal standard (IS)	M002151
Calibration range	5.00 to 2,500 ng/mL
Linearity	Linear, 1/x2, R2: 0.9959-0.9995
Lower limit of quantification	5.00 ng/mL
Standard curve concentrations (ng/mL)	5.00, 10.0, 25.0, 50.0, 100, 250, 500, 1,000, and 2,500
QC concentrations (ng/mL)	5.00 (LLOQ QC), 15.0 (low QC), 150 (mid QC), and 2,000 (high QC), 12,500 (dilution QC)
Between-run accuracy (%)	-2.7 → 1.5
Between-run precision (%)	3.3 → 5.7
Within-run accuracy (%)	-6.0 → 4.4
Within-run precision (%)	1.1 → 8.8
Matrix factor (analyte and IS) CV% of IS normalized matrix factor	Niraparib: 0.812, CV: 2.2% Niraparib IS: 0.813, CV: 1.5% Niraparib normalized by IS: 1.01, CV: 2.6%
Short-term stability of the stock solution and working solutions	Stock solutions Niraparib - Confirmed up to 24 hours, observed change 2.4% at room temperature. Working solutions Niraparib - Confirmed up to 24 hours, observed change -1.4% at room temperature.
Long-term stability of the stock solution and working solutions	Stock solutions Niraparib - Confirmed up to 428 days, observed change 5.8% at -20°C. Working solutions Niraparib - Confirmed up to 508 days, observed change -1.8% at -20°C.
Short-term stability in plasma in-ice (QC)	Confirmed up to 24 hours, observed change within ±4.7%
Post-preparative stability (dry extract stability)	Confirmed up to 6 days refrigerated, observed change within ±2.7%
Long-term stability in plasma	Niraparib - 1026 Days at -80°C 231 Days at -20°C
Autosampler storage stability	Confirmed up to 6 days refrigerated.
Freeze and thaw stability (-80°C/In-ice)	Niraparib was stable after 7 cycles at -80°C/in-ice.
Dilution integrity	12,500 ng/mL diluted 100-fold, Accuracy -2.4%, Precision 3.5%

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/

YIXUAN DONG
04/27/2023 01:38:59 PM

SALAHELDIN HAMED
04/27/2023 01:40:20 PM

STACY S SHORD
04/27/2023 04:42:53 PM

Office of Clinical Pharmacology Review

NDA or BLA Number	NDA 214876
Link to EDR	\\cdsesub1\evsprod\NDA214876
Submission Date	06/16/2020
Submission Type	*Standard Review*
Brand Name	ZEJULA®
Generic Name	Niraparib
Dosage Form and Strength	Immediate release tablets (100 mg, 200 mg, and 300 mg)
Route of Administration	Oral
Proposed Indication	The maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy. The maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. (b) (4)
Applicant	GlaxoSmithKline, LLC (GSK)
Associated IND	*IND 100996 and* (b) (4)
OCP Review Team	*Salaheldin S. Hamed, Ph.D.* *Pengfei Song, Ph.D.*

Review Memo

ZEJULA is approved as 100 mg strength capsules for oral administration. In this NDA submission, GSK is seeking approval for a tablet formulation (100 mg, 200 mg, and 300 mg strengths). To support approval, the applicant submitted results from study 3000-01-004, which is an open-label, randomized sequence, multicenter, single-crossover study to assess the relative bioavailability and bioequivalence of niraparib tablet formulation compared to niraparib capsule formulation in patients with advanced solid tumors. The study was conducted in fasted state. Of note, the applicant did not submit information to characterize the effect of food intake on the bioavailability of the proposed tablet formulation.

Given that the oral capsules are administered with or without regard to food, the Agency expressed concern that food intake may affect the bioavailability of the proposed tablet formulation. Food intake due to formulation changes may alter niraparib exposure and, consequently, adversely affect its safety and/or efficacy profile.

Given the lack of characterization of food effect on the tablet formulation, the proposed dosage form may not be labeled “without regard to food intake”. Additionally, an alternate labeling recommendation (i.e., administration in the fasted state alone) may result in substantial medication errors and may not be sufficient to address the above concerns. In response, the applicant submitted a protocol to assess the effect of food intake on the bioavailability of the proposed tablet formulation; however, the Applicant indicated that study results would not be available for review until Q3 2021.

In an advice letter issued on 1/13/2021, the Agency informed the applicant that food-effect study will be required prior to approval of the proposed niraparib tablet formulation, in order to ensure adequate guidance on dosing/administration in labeling. Given that PDUFA date for the current application is April 16, 2021, the applicant’s proposal to submit topline data from a food-effect study in Q3 2021 would not be sufficient to fulfill this timeline. As a result, the applicant officially withdrew the submission on January 29th, 2021.

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/

SALAHELDIN HAMED
02/02/2021 08:46:29 AM

PENGFEI SONG
02/05/2021 08:54:46 AM