CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214876Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	214876
Applicant Name	GLAXOSMITHKLINE LLC
Drug Product Name	ZEJULA (niraparib)
Dosage Form.	Tablet
Proposed Strength(s)	100 mg, 200 mg, 300 mg
Route of Administration	Oral
Maximum Daily Dose	300 mg
Rx/OTC Dispensed	Rx
Proposed Indication	ZEJULA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated: • for 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. • for the maintenance treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.
Drug Product Description	• Tablets: 100-mg gray, oval-shaped, film-coated tablet debossed with “100” on one side and “Zejula” on the other side. • Tablets: 200-mg blue, oval-shaped, film-coated tablet debossed with “200” on one side and “Zejula” on the other side. • Tablets: 300-mg green, oval-shaped, film-coated tablet debossed with “300” on one side and “Zejula” on the other side.
Co-packaged product information	N/A
Device information:	N/A

Storage Temperature/ Conditions	Store and dispense in the original bottle. Store at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Raymond Frankewich	Paresma Patel
	Drug Product/ Labeling	Tefsit Bekele	Xing Wang
	Manufacturing	Yifan Wang	Zhaoyang Meng
	Biopharmaceutics	Min Kang	Anitha Govada
	Microbiology	N/A	
	Other (specify):	N/A	
	RBPM	Kristine Leahy	
	ATL	Xing Wang	
Consults	None		

2. Final Overall Recommendation - *Approval*

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The applicant provided sufficient information to assure the identity, strength, purity, and quality of the proposed drug product. All associated manufacturing, testing, packaging facilities were deemed acceptable. Based on the OPQ review team's evaluation of the information provided in the submission, OPQ recommends APPROVAL of NDA 214876 for ZEJULA (niraparib) tablets, for oral use.

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**

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

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): Yes
Comments: The post-approval change management protocol is acceptable from the CMC perspective.

Additional Lifecycle Comments: None

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	ZEJULA	Adequate
Established name(s)	Niraparib	Adequate
Route(s) of administration	For oral use	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Tablets: 100 mg, 200 mg, 300 mg	Adequate
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	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	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)	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Tablet	Adequate
Strength(s) in metric system	• 100-mg gray, oval-shaped, film-coated tablet debossed with "100" on one side and "Zejula" on the other side. • 200-mg blue, oval-shaped, film-coated tablet debossed with "200" on one side and "Zejula" on the other side. • 300-mg green, oval-shaped, film-coated tablet debossed with "300" on one side and "Zejula" on the other side.	Change to: • Tablets: 100-mg gray, oval-shaped, film-coated tablet debossed with "100" on one side and "Zejula" on the other side. • Tablets: 200-mg blue, oval-shaped, film-coated tablet debossed with "200" on one side and "Zejula" on the other side. • Tablets: 300-mg green, oval-shaped, film-coated tablet debossed with "300" on one side and "Zejula" on the other side.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Strength is expressed based on base content	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Provided as shown above	Adequate
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 labeling term (e.g.,	N/A	

single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.		

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Pproprietary name: ZEJULA Established name: Niraparib	Adequate
Dosage form(s) and route(s) of administration	Tablet and orally available	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Each ZEJULA tablet contains 159.3 mg, 318.7 mg, or 478.0 mg of niraparib tosylate monohydrate equivalent to 100 mg, 200 mg, or 300 mg, respectively, of niraparib free base as the active ingredient.	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	The inactive ingredients in the core tablet are crospovidone, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and silicon dioxide. The film-coating consists of Opadry II Gray (100 mg), Opadry II Blue (200 mg), or Opadry II Green (300 mg).	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	
Pharmacological/ therapeutic class	poly (ADP-ribose) polymerase (PARP) inhibitor	Adequate
Chemical name, structural formula, molecular weight	**Chemical name**: 5β,20-2-{4-[(3S)-piperidin-3-yl]phenyl}-*2H*-indazole 7-carboxamide 4-methylbenzenesulfonate hydrate **Structural formula**: $C_{26}H_{30}N_4O_5S$ **Molecular weight**: 510.61 amu	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	N/A	
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	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Film-coated tablets	Adequate
Strength(s) in metric system	100 mg, 200 mg, and 300 mg	Adequate
Available units (e.g., bottles of 100 tablets)	Bottle of 30 tablets	Adequate
Identification of dosage forms, e.g., shape, color, coating,	Oval-shaped, film-coated tablets	Adequate

scoring, imprinting, NDC number	• Gray for 100 mg • Blue for 200 mg • Green for 300 mg NDC numbers are included	
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.)	Store in the original container	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store in the original container at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].	Adequate
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	N/A	

natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."		
Include information about child-resistant packaging	(b) (4)	

1.2.5 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	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	GlaxoSmithKline (b) (4)	Adequate

2.0 PATIENT LABELING

Assessment patient Labeling: Patient Labeling is adequate from the product quality perspective.

3.0 CARTON AND CONTAINER LABELING

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Item	Information Provided in the NDA	Assessor's Comments about Container Label
Proprietary name, established name, and dosage form (font size and prominence	Proprietary name: Zejula Established name: Niraparib	Adequate
Dosage strength	100 mg, 200 mg and 300 mg	Adequate
Route of administration	-	
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Each 100-mg tablet is equivalent to 159.3 mg of niraparib tosylate monohydrate	Adequate
Net contents (e.g. tablet count)	30 tablets	Adequate
"Rx only" displayed on the principal display	Provided	Adequate
NDC number	Provided	Adequate
Lot number and expiration date	Space provided	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature]. Store in original package	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Provided	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Container Label
Name of manufacturer/distributor	Trademarks owned or licensed by GSK. Mfd for GSK, (b) (4) (b) (4)	Adequate
Medication Guide (if applicable)	N/A	
No text on Ferrule and Cap overseal	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	N/A	

Assessment of Carton and Container Labeling: Adequate.

Overall Assessment and Recommendation:

The container labels and prescribing information comply with all regulatory requirements, and they are recommended for approval from a CMC perspective pending revision of what is noted in the Assessor's Comments column above.

Primary Labeling Assessor Name and Date: Tefsit Bekele January 04, 2023

Secondary Assessor Name and Date Xing Wang

TEFSIT
BEKELE

Digitally signed by TEFSIT BEKELE
Date: 1/20/2023 01:19:37PM
GUID: 5acb2d81000268cc7ce97540eb0a1791

Xing
Wang

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Date: 1/20/2023 02:17:30PM
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NDA Number	NDA 214876-RESUB-20; 505(b)(1)
Submission History	Original Submission: 6/16/2020 Response to FDA's IR #1: SDN-15, dated 10/20/2020 Original NDA was withdrawn on 2/5/2021 Re-Submission: SDN-20, dated 6/30/2022 Response to FDA's IR #2: SDN-32 dated 02/03/2023
Drug Product Name/ Strength	ZEJULA® (Niraparib) Tablet / 100 mg, 200 mg, 300 mg
Route of Administration	Oral
Applicant Name	GlaxoSmithKline LLC (GSK)
Therapeutic Classification/ OND Division	DO1
RLD/RS Number	NDA 208447, ZEJULA® (Niraparib) Capsule, 100 mg; Approved by FDA on 3/27/2017, GlaxoSmithKline LLC
Proposed Indication	For 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-base chemotherapy.

Review Summary: The Applicant submitted this 505(b)(1) NDA seeking approval for ZEJULA® (Niraparib) Tablets, 100 mg, 200 mg and 300 mg. The currently approved Niraparib 100 mg (free base) Capsule is an immediate-release, hard gelatin capsule with a starting dose of 300 mg once daily.

This reviewer also notes that the Applicant had originally submitted the application dated 6/16/20 which was later withdrawn on 1/29/21 due to inadequate food-effect study. In the current re-submission, the original Niraparib developer (GSK) is proposing a new dosage form, an immediate-release, film-coated tablet, that utilize the same active pharmaceutical ingredient (API) with three strengths, 100 mg, 200 mg, and 300 mg. The Niraparib Tablets is proposed to be made from (b) (4) API and excipients, and the new formulation and manufacturing process were selected to produce a tablet that has a comparable in vitro performance to that of the capsule, and the three strengths are compositionally proportional. The proposed indication and recommended dose for the tablet remains the same as for the capsule. The Applicant stated the reasons for the newly proposed changes (tablet dosage form with additional strengths) are (i) an improved patient compliance and convenience by having the 300 mg strength, (ii) improved amenability [e.g., hot and humid climates] as a tablet dosage form, and (iii) significantly improved manufacturing efficiency associated with the (b) (4).

This Biopharmaceutics Review focuses on evaluation of (1) the in vitro dissolution method and acceptance criterion as a quality control (QC) test for the proposed drug product, Niraparib Tablets, 100 mg, 200 mg, and 300 mg, (2) the bridging of the formulations between (i) the listed drug product [Capsule, 100 mg] to the newly proposed drug product [Tablet, 100 mg, 200 mg, 300 mg] as well as (ii) the two manufacturing sites (b) (4), and (3) the acceptability of biowaiver for the lower strengths, 100 mg and 200 mg.

In Vitro Dissolution Method and Acceptance Criterion: ADEQUATE

The proposed in vitro dissolution method and dissolution acceptance criterion shown in the table below are approved for the Quality Control (QC) testing of Niraparib Tablets, 100 mg, 200 mg and 300 mg, for batch release and stability testing:

Apparatus	Speed	Volume/ Temp	Medium	Acceptance Criterion
USP 2 (Paddle)	**60 rpm**	**900 mL/ 37 °C**	**100 mM Citrate buffer (pH 4.6)**	**Q = (b) (4) % at 30 minutes**

Biowaiver Request: ACCEPTABLE

The Applicant's submitted biowaiver request as per the 21 CFR 320.22(d)(2) to support the approval of the proposed 100 mg and 200 mg strengths is based on the following: (1) The 100 mg and 200 mg Niraparib Tablets are in same dosage form (as the 300 mg) but in different strengths, (2) Bioavailability of the 300 mg has been measured (Pivotal/ BE study: 3000-01-004), (3) Evidence to support proportional similarity of the 100 mg, 200 mg and 300 mg in the active and inactive ingredients, and (4) The in vitro dissolution profiles of the 100 mg, 200 mg and 300 mg strengths are similar (f_2-value ≥ 50). The Applicant's biowaiver request for the lower strengths (100 mg and 200 mg) is granted.

Formulation Bridging: ACCEPTABLE

The to-be-marketed formulation (registration batches M10723) remains the same as the clinical formulation (BE Study 3000-01-004). The two sites where Niraparib Tablets will be manufactured ((b) (4) (b) (4)) have been adequately bridged via the Comparative In Vitro Dissolution Study.

Post-Approval Change Management Protocol (PACMP)[1]: ACCEPTABLE

(b) (4)

Overall Recommendation: From the Biopharmaceutics perspective, NDA 214876 for the proposed ZEJULA® (Niraparib) Tablets, 100 mg, 200 mg and 300 mg, is **Adequate** and recommended for **Approval**.

[1] M.3.2.R.5. Comparability Protocol (dated 2/3/2023; SDN-32): \\CDSESUB1\EVSPROD\nda214876\0032\m3\32-body-data\32r-reg-info\r5-change-mgmt-protocol-alternative-mfg-and-testing.pdf

BIOPHARMACEUTICS ASSESSMENT

1. List of Submissions Reviewed:

eCTD sequence #	Received date	Document
01	06/16/2020	Original NDA submission
015	10/20/2020	Quality/Response to Quality/Biopharmaceutics IR #1
017	11/04/2020	Quality/Response to Quality/Biopharmaceutics IR #1 with CMC Module 3 Updates
020	06/30/2022	Re-submission of NDA
032	02/03/2023	Quality/Response to Quality/Biopharmaceutics IR #2 with M.3.2.R.5. Comparability Protocol/ PACMP Updates

2. Solubility and Permeability:

Solubility: Niraparib tosylate monohydrate is lowly soluble (<1.2 mg/mL) in aqueous media across the physiologic pH (pH 1-6.8) range, as described in Table 1.

Table 1: Solubility vs pH with theoretical sink volumes for Niraparib Tablets

Media pH	Tablet Strength (mg)	Solubility (mg/mL)	Sink Volume [a] (mL)
1.0 – 1.2	100	1.10	273
	200		545
	300		818
4.4 – 4.6	100	1.06	283
	200		566
	300		849
6.8	100	1.04	288
	200		577
	300		865

[a] Sink volume is defined as the volume of dissolution media that is at least three times greater than the volume at the saturation point of niraparib (expressed as free base)

Permeability: The apparent permeability (P_{app}) of niraparib free base was determined to be 14.9 ± 1.4E-6 cm/s by the unidirectional Caco-2 permeability test and was assessed have high permeability based on the co-dosed high-permeability reference compound minoxidil. Also, the total mass balance recovery of niraparib free base in Caco-2 cells was > 90% indicating ≥ 90% absorption in humans with no significant efflux.

Reviewer's comments: Based on the above submitted data/information, Niraparib tosylate monohydrate exhibits low solubility and high permeability. However, the Applicant did not request BCS designation for the drug product, therefore BCS classification is not evaluated in the current review.

3. Formulation

The three strengths (100 mg, 200 mg and 300 mg) of the proposed immediate-release, film-coated, oral tablets are manufactured using (b) (4) (b) (4) (b) (4) The formulations of the two strengths are compositionally proportional with respect to the active and inactive ingredients, differing only by the film coatings (Opadry II Gray Film Coating is used for 100 mg Tablet, Opadry II Blue Film Coating is used for 200 mg Tablet, and Opadry II Green Film Coating is used for 300 mg Tablet, as described in Table 2 and 3 below).

Table 2: Composition of Niraparib Tablets, 100 mg, 200 mg and 300 mg

Components	Quality Standard	Function	Amount per Tablet (mg)			% Composition
			100 mg Tablet	200 mg Tablet	300 mg Tablet	
(b) (4)						
Niraparib tosylate monohydrate[a] (free base)	In-House	Active	159.3	318.7	478.0	(b) (4)
Microcrystalline cellulose	USP-NF, Ph.Eur, JP					(b) (4)
Lactose monohydrate	USP-NF, Ph.Eur, JP					
Povidone	USP-NF, Ph.Eur, JP					
Crospovidone	USP-NF, Ph.Eur, JP					
Silicone dioxide	USP-NF, Ph.Eur, JP					
Magnesium stearate	USP-NF, Ph.Eur, JP					
(b) (4)						
Film Coating						
Opadry® II Gray	Non-compendial[b]					(b) (4)
Opadry® II Blue	Non-compendial[b]					
Opadry® II Green	Non-compendial[b]					
Total Tablet Weight (mg)						(b) (4)

Abbreviations: JP=Japanese Pharmacopoeia; MW=molecular weight; N/A=not applicable; NF=National Formulary; Ph.Eur=European Pharmacopoeia; USP=United States Pharmacopeia.

[a] Niraparib drug substance is supplied as the tosylate salt monohydrate. The molecular conversion factor from the niraparib (free base) to niraparib tosylate monohydrate is: MW (niraparib tosylate monohydrate/MW niraparib free base = 510.61/320.39 = 1.594)

[b] Details of individual coating components are provided in Table 2.

Table 3: List of Ingredients in Opadry® II Gray, Opadry® II Blue, and Opadry® II Green Coating Systems

Tablet Strength	Coating Material	Components	Amount per Tablet	% w/w of Film Coat
100 mg	Opadry® II Gray	(b) (4)		
200 mg	Opadry® II Blue			
300 mg	Opadry® II Green			

Abbreviations: CFR=Code of Federal Regulations; FCC=Food Chemicals Codex; JP=Japanese Pharmacopoeia; NF=National Formulary; Ph.Eur=European Pharmacopoeia; USP=United States Pharmacopeia.

4. Dissolution Method Development[2]

The Applicant's proposed dissolution method is summarized in Table 4 below:

Table 4: Proposed dissolution method parameters for Niraparib Tablets

Apparatus	Speed	Volume/ Temp	Medium	Acceptance Criterion
USP 2 (Paddle)	**60 rpm**	**900 mL/ 37 °C**	**100 mM Citrate buffer (pH 4.6)**	**Q = (b) (4) % at 30 minutes**

During the early development stages (IND 100996) of Niraparib Tablets, two Type C meetings[3] with CMC were held where clarifications regarding the proposed comparative dissolution method parameters were made by the FDA for the Applicant to support the biowaiver request of the lower strengths.

(b) (4)

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(b) (4)

[redacted]

Reviewer's comments: The Applicant supported the proposed dissolution method [Apparatus 2 (Paddle), 900 mL in 100 mM Citrate Buffer (pH 4.6) at 60 rpm] with adequate scientific justifications for the selection of each testing parameter. Given the low solubility of Niraparib tosylate monohydrate, it was especially critical to ensure that the Applicant's proposed dissolution method has the discriminating ability, and the Applicant was able to demonstrate this by testing the dissolution performance against the varying levels of the identified quality attributes (e.g., [redacted] (b) (4)

(b) (4) Others [stressed storage condition]) as described above in section 4.4. The proposed dissolution method was adequately able to demonstrate discriminating ability against batches containing (b) (4) as well as batches placed under a stressed storage condition;

(b) (4)

(b) (4)

(b) (4)

Based on the Applicant's adequate demonstration of discriminating ability of the proposed dissolution method described above in section 4.4 and based on the feedback from the Drug Product Reviewer with regards to the API-PSD that there are appropriate control measures for PSD, the deemed risk of the proposed drug product is mitigated from biopharmaceutics perspective. The Applicant's proposed dissolution method is acceptable for quality control at drug release and on stability.

5. Dissolution Data and Acceptance Criterion:

Table 9: Batch List of 100 mg Niraparib Tablets with dissolution data of a selected registration batch manufactured at (b) (4) (M10740)

Batch No.	KH17/0075	KH18/0174	M10740	M10747	M10748	CT-C19004	CT-C19005	CT-C19006
Site of DP Manufacture	(b) (4)							
Date of Manufacture	17 Aug 2017	22 Jan 2018	13 Nov 2018	13 Nov 2018	13 Nov 2018	06 Sep 2019	09 Sep 2019	10 Sep 2019
Batch Size (tablets)	(b) (4)							
API Batch number(s)	(b) (4)							
Site of API Manufacture								
Use	Clinical PK	Development	Clinical, Registration, Stability	Clinical, Registration, Stability	Clinical, Registration, Stability	Clinical, Stability	Clinical, Stability	Clinical, Stability

Test lot M10740, 100 mg Niraparib Tablets, Test Medium (0.1 M Citrate Buffer, pH 4.5)

	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min
1	(b) (4)								
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									

Table 10: Batch List of 200 mg Niraparib Tablets with dissolution data of a selected registration batch manufactured at (b) (4) (M10795)

Batch No.	KH17/0076	KH18/0175	M10795	M10796	M10797	CT-C19007	CT-C19008	CT-C19009
Site of DP Manufacture	(b) (4)							
Date of Manufacture	17 Aug 2017	22 Jan 2018	15 Jan 2019	17 Jan 2019	15 Jan 2019	06 Sep 2019	09 Sep 2019	10 Sep 2019
Batch Size	(b) (4)							
API Batch number(s)	(b) (4)							
Site of API Manufacture								
Use	Clinical PK	Development	Clinical, Registration	Clinical, Registration	Clinical, Registration	Clinical	Clinical	Clinical

Test lot M10795, 200 mg Niraparib Tablets, Test Medium (0.1 M Citrate Buffer, pH 4.5)

	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min
1	(b) (4)								
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									

Table 11: Batch List of 300 mg Niraparib Tablets with dissolution data of the Biobatch manufactured at (b) (4) (M10723)

Batch No.	KH17/0077	KH18/0176	M10723	M10737	M10738	CT-C19001	CT-C19002	CT-C19003
Site of DP Manufacture	(b) (4)							
Date of Manufacture	17 Aug 2017	22 Jan 2018	06 Nov 2018	08 Nov 2018	09 Nov 2018	30 Aug 2019	02 Sep 2019	03 Sep 2019
Batch Size (tablets)	(b) (4)							
API Batch number(s)								
Site of API Manufacture								
Use	Clinical PK, Stability	Development	Clinical BE, Registration, Stability	Clinical, Registration, Stability	Clinical, Registration, Stability	Clinical, Stability	Clinical, Stability	Clinical, Stability

Ref lot M10723, 300 mg Niraparib Tablets, Test Medium (0.1 M Citrate Buffer, pH 4.5)

	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min
1	(b) (4)								
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									

Figure 9: Overall Dissolution Profile of Niraparib Tablets, 100 mg and 300 mg, from Release and Stability data

Reviewer's Comments: As discussed in Section 4 review assessment above, the deemed risk of Niraparib drug substance is not high despite the "low solubility" classification per BCS. Based on the (i) Tmax data which is reported to be about 5 hours and (ii) the dissolution data from the initial release and stability which show a rapid dissolution ((b) (4)% in 30 minutes) as described in Figure 9 above, the Applicant's proposed dissolution acceptance criterion of "Q= (b) (4)% in 30 minutes" is deemed acceptable.

6. Formulation Bridging:

The to-be-marketed formulation (registration batches M10723) remains the same as the clinical formulation (BE Study 3000-01-004). The two proposed commercial manufacturing facilities for this product, Niraparib Tablets ((b) (4)) have been adequately bridged via the Comparative In Vitro Dissolution Study using the QC dissolution method with f_2-value of >50 for all tested batches.

Figure 10: Dissolution Profile of Biobatch (M10723 from (b) (4)) vs All (b) (4) batches

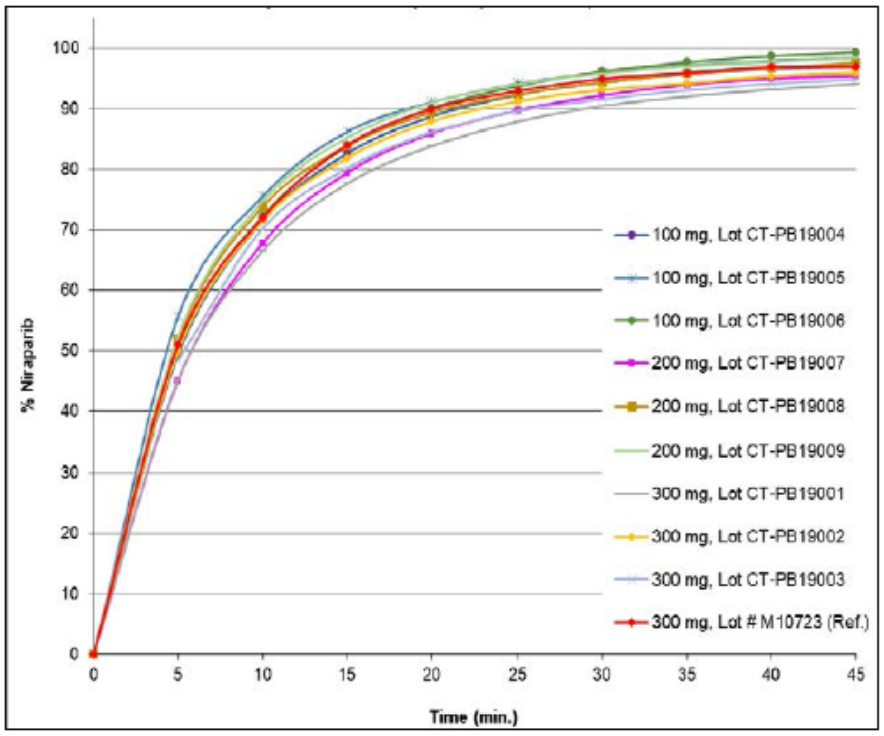


Table 12: Summary of f_2-results for Biobatch (M10723 from (b) (4)) vs. All (b) (4) batches

Reference Product	Test Product	f_2 Value
300 mg tablet (Biobatch) Lot M10723/ P138387-0197F004	100 mg tablet Lot CT-C19004/P138387-0219F001	90
	100 mg tablet Lot CT-C19005/P138387-0219F002	70
	100 mg tablet Lot CT-C19006/ P138387-0219F003	100
	200 mg tablet Lot CT-C19007/ P138387-0220F001	65
	200 mg tablet Lot CT-C19008/ P138387-0220F002	90
	200 mg tablet Lot CT-C19009/ P138387-0220F003	83
	300 mg tablet Lot CT-C19001/ P138387-0221F001	62
	300 mg tablet Lot CT-C19002/ P138387-0221F002	87
	300 mg tablet Lot CT-C19003/ P138387-0221F003	73

Reviewer's comments: In general, for bridging of distinctly located two manufacturing sites, the multipoint dissolution profile that is able to show that the dissolution performance performed at the two sites are comparatively similar (with f2-value > 50) using the QC dissolution method would serve as sufficient enough of evidence. The Applicant was able to show that the dissolution performance at the two sites is comparatively similar by comparing the dissolution profile data of Biobatch (M10723) manufactured at (b) (4) vs. all batches manufactured at (b) (4). From a Biopharmaceutics standpoint, the bridging of the drug product manufacturing at the above mentioned facilities is adequate.

7. Biowaiver Request:

The Applicant submitted the biowaiver for the lower strengths of Niraparib Tablets, 100 mg and 200 mg, with the supporting data as the following: (i) same dosage form that differ only in strengths, (ii) bioavailability of the higher strength (300 mg) has been measured [Pivotal BE Study: 3000-01-004], (iii) all strengths of the drug product (300 mg as well as 100 mg and 200 mg) meet an appropriate in vitro test approved by FDA [comparative in vitro dissolution study in multimedia with f_2-value >50, as described Table 14 and Figures 10-12], and (iv) evidence showing that the different strengths are proportionally similar in their active and inactive ingredients [drug product formulation compositions].

Based on the Applicant's submitted information that adequately supports the biowaiver requirements as required by the 21 CFR 320.22(d)(2), the biowaiver is granted for Niraparib Tablets 100 mg and 200 mg strengths.

Table 13: Comparative In Vitro Dissolution in Multimedia ((b) (4) batches)

Reference Product	Test Product	Dissolution Media f_2 Results			
		pH 1.2	pH 4.5	pH 6.8	pH 4.6[a]
300 mg tablet (Biobatch) Batch M10723/ P138387-0197F004	100 mg tablet Batch M10740/P138387-0197F001	54	61	59	74
	100 mg tablet Batch M10747/P138387-0197F002	50	63	57	67
	100 mg tablet Batch M10748/P138387-0197F003	61	68	74	69
	200 mg tablet Batch M10795/P138387-0195F001	79	92	97	77
	200 mg tablet Batch M10796/P138387-0195F002	88	85	94	71
300 mg tablet (Biobatch) (continued)	200 mg tablet Batch M10797/P138387-0195F003	85	71	80	66
	300 mg tablet Batch M10737/P138387-0197F005	68	92	65	96
	300 mg tablet Batch M10738/P138387-0197F006	66	97	81	91

[a] Dissolution profile overlay at pH 4.6 is presented in Figure 7.

Figure 11: Comparative Dissolution Profile in pH 1.2 (Biobatch vs. All other (b) (4) batches)

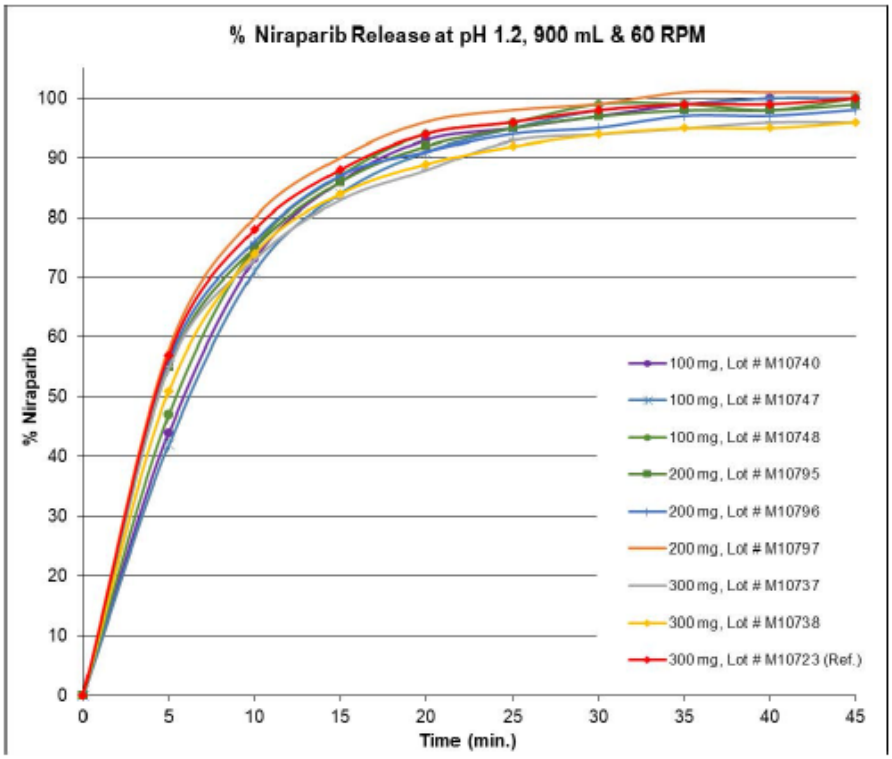


Figure 12: Comparative Dissolution Profile in pH 4.5 (Biobatch vs. All other (b) (4) batches)

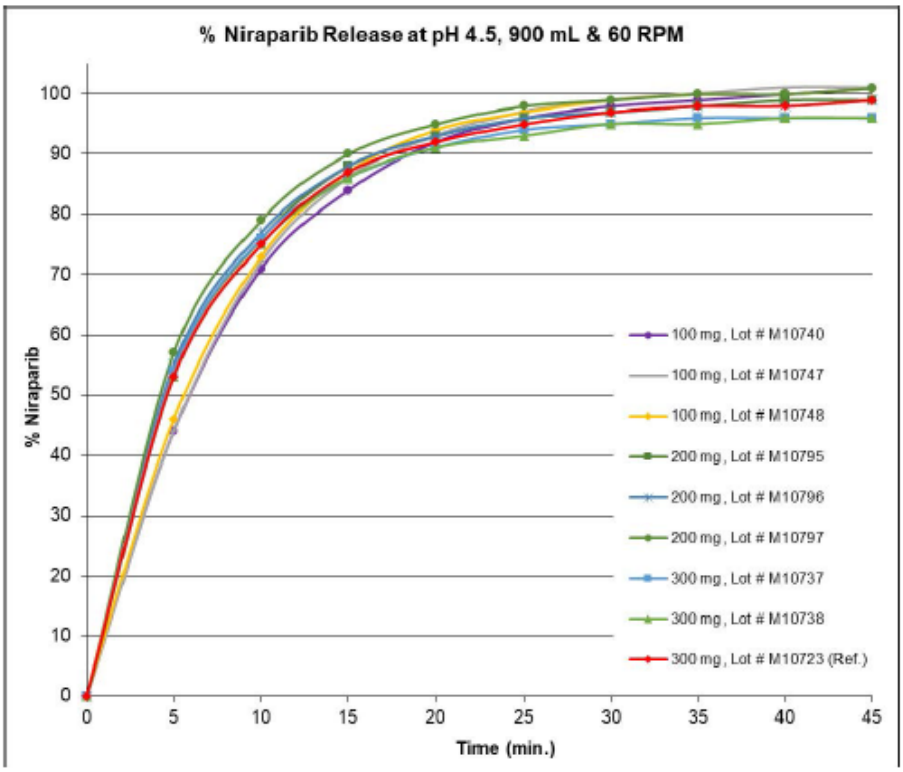
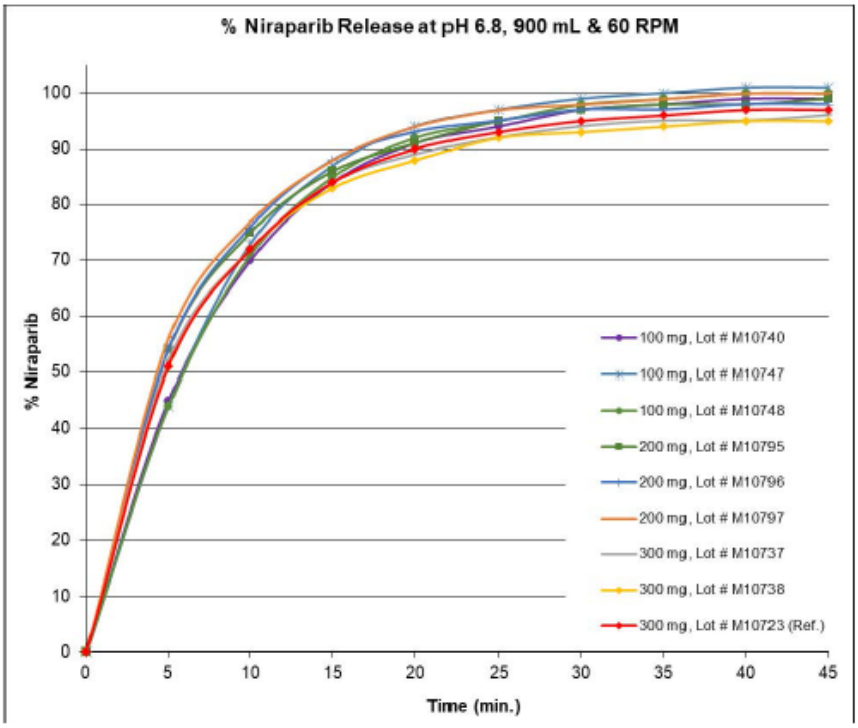


Figure 13: Comparative Dissolution Profile in pH 6.8 (Biobatch vs. All other (b) (4) batches)



8. Post-Approval Change Management Protocol (PACMP)[4]:

(b) (4)

[4] M.3.2.R.5. Comparability Protocol (dated 2/3/2023; SDN-32): \\CDSESUB1\EVSPROD\nda214876\0032\m3\32-body-data\32r-reg-info\r5-change-mgmt-protocol-alternative-mfg-and-testing.pdf

Min (Sammie) Kang

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Anitha Palamakula Govada

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/s/

XING WANG
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