CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214783Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA/BLA OPQ Review and Evaluation

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

NDA 214,783

Review # 01

OPQ RECOMMENDATION: APPROVAL

Drug Substance Retest Period:

- Belumosudil mesylate (b) (4): (b) (4) months
- Belumosudil mesylate (b) (4): (b) (4) months
- Storage conditions for both materials: (b) (4)

FDA Assessment: **Retest date of (b) (4) months may be granted when stored at the proposed storage condition of (b) (4) for the (b) (4) belumosudil drug substance. For the (b) (4) belumosudil drug substance, a retest of (b) (4) months may be granted when stored at the proposed (b) (4).**

Drug Product Expiration Dating Period: The proposed shelf life for the drug product is 24 months, when stored in the intended commercial container closure system at the following storage conditions: "Store at 20°C - 25°C (68°F – 77°F) with excursions permitted up from 15°C to 30°C (59°F to 86°F)" [See USP Controlled Room Temperature].

FDA Assessment: An expiration dating period of 24 months may be granted when stored at the proposed storage conditions.

Drug Name/Dosage Form	REZUROCK™ (belumosudil) tablets
Strength	200 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Indication	Treatment of patients 12 years and older with chronic graft-versus-host disease (cGVHD) after failure of at least (b) (4) of systemic therapy.
Applicant	Kadmon Pharmaceuticals, LLC
US agent, if applicable	N/A

[FDA will complete these sections.]

Submit Date(s)	09/30/2020
Received Date(s)	09/30/2020
PDUFA Goal Date	Original PDUFA Goal Date: May 30, 2021 Revised PDUFA Goal Date: August 30, 2021
Division/Office	OND/ Division of Hematologic Malignancies (DHM1)
Review Completion Date	6/2/2021
Established Name	belumosudil
(Proposed) Trade Name	REZUROCK
Pharmacologic Class	Rho-associated, coiled-coil containing protein kinase-2 (ROCK2) inhibitor
Recommendation on Regulatory Action	APPROVAL

Submit Date(s)	09/30/2020	
Received Date(s)		
PDUFA Goal Date		
Division/Office		
Review Completion Date		
Established Name		
(Proposed) Trade Name		
Pharmacologic Class		
Recommendation on Regulatory Action		

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Rohit V. Tiwari	Paresma Patel
Drug Product	Soumya Mitra	Anamitro Banerjee
Process and Facility	Djelila Mezaache	Rakhi Shah
Microbiology	Djelila Mezaache	Rakhi Shah
Biopharmaceutics	Kevin Wei	Om Anand
Regulatory Business Process Manager	Rabiya Haider	N/A
Application Technical Lead	Sherita McLamore	N/A
ORA Lead	N/A	N/A
Environmental	Soumya Mitra	Anamitro Banerjee

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

ORBIS Partner Agency Quality Review Team

Agency	PRIMARY REVIEWER	SECONDARY REVIEWER
HC Canada		
HSA Singapore		
TGA Australia		
Swissmedic Switzerland		
MHRA United Kingdom		

RELATED/SUPPORTING DOCUMENTS

DMFs:

[Applicant will complete]				[FDA will complete]	
DMF #	**Type**	**Holder**	**Item Referenced**	**Status**	**Comments**
(b) (4)	IV		(b) (4)	Adequate	Compendial excipient. DMF not reviewed
	IV			Adequate	Compendial excipient. DMF not reviewed.
	IV			Adequate	Compendial excipient. DMF not reviewed
	IV			Adequate	Compendial excipient. DMF not reviewed
	IV			Adequate	Compendial excipient. DMF not reviewed
	IV			Adequate	Mixture of compendial

					excipients (b) (4) DMF not reviewed
(b) (4)	III		(b) (4)	Adequate	Not reviewed per ONDP policy
	III			Adequate	Not reviewed per ONDP policy
	III			Adequate	Not reviewed per ONDP policy
	III			Adequate	Not reviewed per ONDP policy
	III			Adequate	Not reviewed per ONDP policy
	III			Adequate	Not reviewed per ONDP policy
	III			Adequate	Not reviewed per ONDP policy
	III			Adequate	Not reviewed per ONDP policy
	III			Adequate	Not reviewed per ONDP policy
	III			Adequate	Not reviewed per ONDP policy

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	125,890	Safety and efficacy data for GVHD (b) (4)
IND		
IND		
IND		

CONSULTS

[FDA will complete this section.]

N/A

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Evaluation of the Quality Information

DIFFERENCES IN M3 MODULE IN SUBMISSIONS TO DIFFERENT AGENCIES

#	TGA (Australia)	HC (Canada)	HSA (Singapore)	Swissmedic (Switzerland)	FDA (US)	MHRA (UK)
N/A	N/A	N/A	N/A	N/A	N/A	N/A

Other than changes in labeling that are specific to the territory, there are no changes in formulation, manufacturing, container closure system, presentation, etc. for belumosudil tablets in any of the territories including Australia, Canada, United Kingdom and Switzerland under Project Orbis. Dossiers subsequent to the original NDA submission on September 30, 2020 will contain (b) (4) will be submitted to FDA as an amendment.

1. EXECUTIVE SUMMARY

OPQ recommends **APPROVAL** of NDA 214783 for REZUROCK (belumosudil) Tablet, 200 mg. A comprehensive evaluation of the facilities associated with this application confirms that all sites are acceptable for the responsibility listed in the application. OPQ grants an **24-month expiration period** to the drug product when stored 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) with the following Post-Marketing Commitment :

PMC Number:

- Development and validation of an optimal and discriminating dissolution method for the Quality Control (QC) testing of REZUROCK™ (belumosudil mesylate) Tablets, 200 mg. Submit a Prior Approval Supplement to update the NDA to include the method in the drug product specifications.
- Dissolution acceptance criterion/criteria proposal, based on the data generated from the unexpired clinical and registration batches, and the first six commercial batches using the new dissolution method. Submit a Prior Approval Supplement to update the NDA to update the dissolution acceptance criterion in the drug product specifications.

Note: If six commercial batches have not been manufactured at the time of final report submission, dissolution acceptance criterion will be based on the data generated from the unexpired clinical and registration batches and from all available commercial batches

Interim Report Submission: 6 months after NDA approval

Final Report Submission: 12 months after NDA approval

The applicant, Kadmon Pharmaceuticals, submitted NDA 214783 as a 505(b)(1) NDA seeking accelerated approval for REZUROCK (belumosudil) tablets, 200 mg. Belumosudil mesylate is a once daily, orally bioavailable selective Rho-associated, coiled-coil containing protein kinase-2 (ROCK2) inhibitor that is indicated for the treatment of patients 12 years and older with chronic graft-versus-host disease (chronic cGVHD) after failure of at least (b) (4) of systemic therapy. Belumosudil is an NME that was granted Orphan and Breakthrough Therapy Designation (BTD) for the treatment of cGVHD under IND 125890. NDA 214783 was accepted as a rolling submission and was reviewed under RTOR, Project Orbis, and Product Quality Assessment Aid. The Project ORBIS partners (POP) for this NDA are Canada (Health Canada), Australia (TGA), Switzerland (Swissmedic) and England (MHRA).

The active pharmaceutical ingredient, Belumosudil mesylate, is a small achiral BCS Class IV molecule. It is a substituted quinazoline with 5 aminoindazole and a phenoxyacetamide component. Belumosudil mesylate is a white to yellow slightly hygroscopic powder with a melting range of 255-275°C. Belumosudil mesylate is practically insoluble in water (across all pHs) and in most of the common organic solvents. It is slightly soluble in methanol and DMF, and soluble in DMSO.

Belumosudil mesylate is manufactured by (b) (4) The applicant includes details of the impurity fate and purge studies, and clearly identifies IPCs, CQAs and CPPs. Polymorph screening revealed only one crystalline form.

The applicant included specifications for both (b) (4) drug substance. The specification for the (b) (4) drug substance includes tests for description, identification, water content, residue on ignition, related substance, assay, melting point, XRPD, (b) (4) content, residual solvents, (b) (4) content and (b) (4) content. The specification for the (b) (4) drug substance includes tests for description, identification, assay, related substances, water content and (b) (4).

The applicant provided up to (b) (4) months of long term (b) (4) and 6 months of accelerated (b) (4) stability data for the drug substance when stored in the commercial container closure system ((b) (4)) and requested a (b) (4)-month retest period for the (b) (4) drug substance and (b) (4) months for the (b) (4) drug substance when stored (b) (4). The available stability data

showed consistency over time and supports the proposed [redacted] month retest dates for the [redacted] drug substance, respectively.

The drug product, REZUROCK (belumosudil) Tablet, 200 mg, is an immediate-release, film-coated tablet for oral administration. The drug product formulation includes the 200 mg of the active (equivalent to 242.5 mg of the methane sulfonic acid salt), microcrystalline cellulose, hypromellose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The non-functional film coating [redacted] consists of polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide and yellow iron oxide. All excipients are compendial (or are composed of compendial excipients), are commonly used in solid oral dosage forms and fall below the limits specified in the FDA Inactive Ingredient Database for this route of administration. The drug product is presented as a as a pale-yellow, film-coated, oblong-shaped tablet, debossed with "KDM" on one side and "200" on the other with a recommended dose of 200 mg orally, once daily until disease progression or unacceptable toxicity.

REZUROCK drug product is manufactured by [redacted] at a commercial batch size of [redacted] kg which corresponds to [redacted] tablets. The drug product manufactured with a [redacted] formulation and targeted weight of [redacted] mg tablet weight [redacted]. The drug product is manufactured using conventional processes which include [redacted].

The biopharmaceutics review focused on the need for bridging of the pivotal clinical and commercial formulations and the acceptability of the proposed in-vitro dissolution method and acceptance criterion for the routine quality control testing of the proposed drug product.

Several different formulations (10 mg and 100 mg capsules and 200 mg tablets) used throughout development; however, only one tablet strength (200 mg) was used in the clinic. The components and composition of the 200 mg tablet used in clinical trials were essentially the same as the components and composition of the marketed formulation. Moreover, the manufacturing process used in the manufacture of clinical tablet is identical to that of the commercial tablet. The Applicant included a comparative bioavailability (BA) study to evaluate the relative BA of the tablet and capsule formulations in the Fed state (with food effect). The Applicant also submitted the in-vitro dissolution profile comparison between the capsule and tablet formulation. The results of the BA study demonstrated that there was no statistically significant difference in terms of exposure when subjects were administered belumosudil tablets or belumosudil capsules. Accordingly, no additional bridging studies were needed for the capsule formulation to the tablet formulation.

The dissolution method included a USP Apparatus II (paddles) at 100 rpm in 900 mL of 0.01M hydrochloric acid at 37°C. The Applicant originally proposed [redacted]. The proposed QC dissolution method showed limited discriminating and stability-indicating ability and the OPQ review team concluded that the proposed dissolution method was not adequate

because the paddle rotation speed (100 rpm) used in the proposed dissolution method is not justified. The Applicant was unable to generate sufficient data during the review cycle to support (b) (4) for the dissolution testing. The data submitted supported a single point dissolution acceptance criterion of Q=(b) (4)% in 20 minutes with the proposed method using a paddle speed of 100 rpm. Accordingly, the applicant was asked and agreed to develop a new discriminating and stability-indicating QC dissolution method (b) (4) as a part of a Post-Marketing Commitment. In the interim, the Applicant was asked and agreed to use the currently proposed dissolution method (i.e. USP Apparatus 2 at 100 rpm; 900 mL of 0.01N HCl) and adopt an acceptance criterion of Q=(b) (4)% in 20 minutes until a more optimal dissolution method is developed (i.e. fulfillment of the PMC).

The Applicant was asked to commit to the following as a part of the PMC:

- *To develop a new optimal and discriminating dissolution method (b) (4), and to submit the Interim Dissolution Method Development and Validation Report within 6 months of the NDA's action date for FDA's review and concurrence of the new dissolution method.*
- *To collect complete dissolution profile data for the unexpired clinical and registration batches, and all available commercial batches of the drug product using the new dissolution method. Based on the generated data, propose the dissolution acceptance criterion/criteria for the drug product. Submit the Final Report within 12 months of the NDA action date for FDA's review and concurrence of the new dissolution acceptance criterion/criteria*

The applicant requested a 24-month expiry for the drug product when stored under controlled room temperature (25°C/60%RH). In support of the proposed 24 month expiry the applicant included up to 48 months of long term (25°C/60% RH) and 6 months of accelerated (40°C/75% RH) data for three GMP batches of drug product packaged in the commercial container closure system. These batches were considered equivalent and representative of the proposed commercial product in formulation, manufacturing process, scale and manufacturing site (agreement Type B meeting 4/2019). Stability studies were conducted in accordance with the ICH 1A and Q1B and the available stability data shows consistency over time and supports the proposed expiry. Therefore, based on the available stability data provided, the applicant proposed, and the OPQ accepts the expiration dating period of **24-months** for the drug product when stored at stored under controlled room temperature.

Life Cycle Considerations:

Life-cycle considerations for this NDA are captured above in the PMCs

2. APPLICATION BACKGROUND

Belumosudil tablets for oral use is being submitted under NDA 214783 for approval for the treatment of patients 12 years and older with chronic graft-versus-host disease (cGVHD) after failure of at least (b) (4) of systemic therapy. Provided below is a summary of interactions with FDA as well as designations granted.

Belumosudil was granted Orphan Drug Designation for the treatment of cGVHD on October 5, 2017.

FDA granted Breakthrough Therapy Designation (BTD) for belumosudil for the "treatment of adult patients with cGVHD after failure of two or more lines of systemic therapy" by letter dated October 16, 2018. The BTD was granted in response to Kadmon's request dated August 17, 2018.

A face-to-face, initial BTD meeting (Type B) was held between FDA and Kadmon on May 1, 2019 to discuss Kadmon's drug development program for belumosudil.

A Type B CMC meeting was requested and granted for January 16, 2020. Preliminary responses received from FDA on January 10, 2020 were sufficient such that Kadmon chose to cancel the face-to-face meeting.

3. SUMMARY OF CMC SPECIFIC PRESUBMISSION AGREEMENTS

The Applicant's Position:

A list of meeting dates and agreements with FDA is provided below.

Meeting Date	Agreements with FDA	Kadmon Response
01-May-2019 (03-May-2019 Meeting Minutes)	Question 15: Does FDA agree with the drug substance proposed regulatory starting materials? FDA Response to Question 15: According to the information presented in the meeting package, (b) (4) appear acceptable starting materials of the drug substance. However, (b) (4) Provide in the NDA a risk assessment as per ICH Q11 guidelines in support of the designation of (b) (4) as starting material or (b) (4) .	No further discussion. Please also refer to Question 1 in this table (16-January-2020 (preliminary comments 10-January-2020) Meeting cancelled per sufficient preliminary response.
01-May-2019 (03-May-2019 Meeting Minutes)	Question 16: Does FDA agree with a change in the drug substance manufacturing process? FDA Response to Question 16: The change in the manufacturing process appears acceptable if the information provided in the NDA demonstrates comparable impurity profiles of the drug substance before and after this change.	No further discussion. .

01-May-2019 (03-May-2019 Meeting Minutes)	Question 17: Does FDA agree with Kadmon's proposed control strategy for potential genotoxic impurities and/or have any concerns about other structural alerts? FDA Response to Question 17: The proposed control strategy for potential genotoxic impurities appears reasonable, a final decision will be made during the NDA review according to the information provided in the application. Also, since you are proposing to change the manufacturing process for (b) (4), batch analyses (which includes (b) (4) content) of batches using the new process should be included in the NDA.	No further discussion.
01-May-2019 (03-May-2019 Meeting Minutes)	Question 18: Kadmon proposes to nominate three investigational batches, produced one per year between 2016 and 2018, as registration stability batches, submit data from these studies in the NDA, and propose the shelf-life based on the stability data generated for these batches, as well as supportive data from process validation batches produced in 2019. Does FDA agree with this approach? FDA Response to Question 18: Yes, it is acceptable. For further guidance refer to ICH Q1A.	No further discussion.
16-January-2020 (preliminary comments 10-January-2020) Meeting cancelled per sufficient preliminary response.	Question 1: Does the Agency agree with the designation of (b) (4), as the third regulatory starting material for the synthesis of KD025 drug substance? FDA Response to Question 1: The designation of (b) (4) as the third regulatory starting material appears reasonable. The acceptance criteria for the impurities arising from (b) (4) will be reviewed at the time of NDA submission that will also take into account the nonclinical evaluation of those impurities.	No further discussion. .
16-January-2020 (preliminary comments 10-January-2020) Meeting cancelled per sufficient preliminary response.	Question 2: Does the Agency agree with the proposed dissolution method development and parameters, the method's use for release & stability testing, and the method's use to set specifications for the NDA submission? FDA Response to Question 2: Based on the limited information provided, we do not agree with your proposed dissolution method [900 mL of 0.01M HCl using USP apparatus 2(paddle) (b) (4) rpm] because the discriminating ability of the method has not been adequately investigated and the meeting package has only limited dissolution data/justifications supporting the suitability of the proposed dissolution method. Please note that the discriminating ability of the dissolution method should be investigated towards	

	the critical material attributes (CMAs), critical process parameters (CPPs) and critical formulation variables (CFVs) affecting the dissolution. Submit a complete dissolution method development and validation report.	
12-March-2020 (19-March-2020 Meeting Minutes)	Question 8: Kadmon proposes to show drug substance stability and propose a retest date utilizing data from clinical batches and from process validation batches. In addition to long-term and accelerated stability data collected on multiple investigational batches, Kadmon proposes to submit supportive drug substance stability data (3 to 6 months) from process batches representative of the commercial process in the original NDA and provide additional data (6 to 9 months) at the Day 120 Safety Update. Does FDA agree with this approach? FDA Response to Question 8: FDA agrees with the approach. Any information submitted after 30 days of initial NDA submission may or may not be reviewed depending on internal review timelines and available resources. The Agency, however, reminds you that the review of a proposal to extend the retest period based on the accelerated stability data may take into account only the available long-term and accelerated stability data at the time of NDA submission.	Kadmon agreed with FDA's response.
12-March-2020 (19-March-2020 Meeting Minutes)	Question 9: Kadmon proposes to update the previously agreed upon plan to provide supportive drug product stability data in the NDA. In addition to long-term and accelerated stability data collected on multiple investigational batches, Kadmon proposes to submit supportive drug product stability data (3 months) from GMP batches representative of the commercial process (rather than from process validation batches) at the Day 120 Safety Update. Does FDA agree with this approach? FDA Response to Question 9: FDA agrees with the plan to submit 3 months of supportive drug product stability data from GMP batches representative of the commercial process at day 120. Be advised that data submitted 30 days beyond the original NDA submission will be reviewed as resources allow and the shelf life will be determined during and set based on available stability data in the initial submission.	Kadmon agreed with FDA's response.
03-September-2020 (Correspondence)	Question: Does the Agency agree with Kadmon's proposal to submit two batches of additional supportive data instead of three? FDA Response: Your proposal is acceptable. Please provide the date when the third batch will be available.	Kadmon agreed with FDA's response. Kadmon is currently scheduling manufacture of the third batch.

The FDA's Assessment: Choose an item.

[FDA will complete this section.]

4. ENVIRONMENTAL ASSESSMENT

The Applicant's Position:

Kadmon Pharmaceuticals, LLC (Kadmon) hereby requests a categorical exclusion from the requirement to prepare an Environmental Assessment (EA) under 21 CFR 25.31(b) for belumosudil (200 mg tablet) on the basis that the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion. Kadmon does not have any knowledge of any extraordinary circumstances that would warrant the preparation of an EA.

The FDA's Assessment: Choose an item.

[FDA will complete this section.]

5. FACILITIES

Drug substance manufacturing, packaging, and testing facilities are listed below:

---------- [Applicant to fill] ----------			[FDA to fill]
Site/address	**FEI/DUNS**	**Responsibility**	**Recommendation**
(b) (4)		(b) (4) (belumosudil mesylate) manufacturing, Release testing, Stability testing	Profile: CSN Approve-Based on Previous History
		Analysis of (b) (4) content in (b) (4) (belumosudil mesylate) drug substance	Profile: LCP Approve-Based on Previous History
		(b) (4) (belumosudil mesylate) (b) (4) Particle size analysis	Profile: CSN

(b) (4)			Approve-Based on Previous History

Drug product manufacturing, packaging, and testing facilities are listed below:

---------- [Applicant to fill] ----------			[FDA to fill]
Site/address	**FEI/DUNS**	**Responsibility**	**Recommendation**
(b) (4)		Belumosudil mesylate drug substance (b) (4) release and stability testing. Belumosudil drug product manufacturing, Release testing, Stability testing..	Profile: TCM Approve-Based on Previous History
		Labeling and secondary packaging of commercial batches	Profile: TCM NEN

*Updates or edits made to this flow diagram during the review cycle captured by the FDA reviewer in red colored fonts

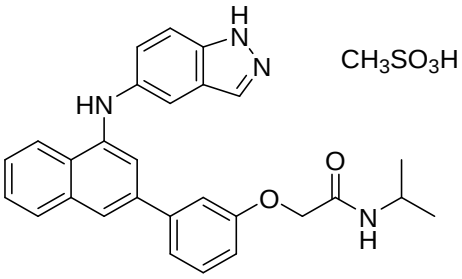
The FDA's Assessment: *Adequate*

[FDA will complete this section.]

A comprehensive evaluation of the facilities associated with this application shows that drug substance, drug product manufacturing and testing facilities are determined to be in acceptable state of compliance with regards to current good manufacturing practice (c-GMP). There are no significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facilities inspectional history and relevant experience.

6. DRUG SUBSTANCE

a. GENERAL DESCRIPTION AND STRUCTURE



USAN Name	Belumosudil mesylate

IUPAC Name	2-(3-(4-(1*H*-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-*N*-isopropylacetamide-methane sulfonic acid salt Acetamide, 2-[3-[4-(1*H*-indazol-5-ylamino)2-quinazolinyl]phenoxy]-*N*-(1-methylethyl)-,methanesulfonate (1:1) 2-{3-[4-(1*H*-indazol-5-ylamino)quinazolin-2-yl]phenoxy}-*N*-(propan-2-yl)acetamide methanesulfonate (1:1)
Molecular Weight	452.52 g/mole (free base); 548.62 g/mole (methane sulfonic acid salt)
Molecular Formula	$C_{26}H_{24}N_6O_2$ (free base) $C_{26}H_{24}N_6O_2$ CH_3SO_3H (methane sulfonic acid salt)
Solubility	The drug substance is practically insoluble across all pH and in most of the commonly used organic solvents. It is slightly soluble in methanol, slightly insoluble in dimethylformamide (DMF) and soluble in dimethyl sulfoxide (DMSO).
Polymorphism	None. One crystalline form only.
pK_a	1.57 and 5.33
LogD at pH 7.4	3.80

Additional information:

Laboratory codes: KD025, SLx-2119, (b) (4) (name used in manufacturing process)

CAS Registry Number: 911417-87-3 (free base); 2109704-99-4 (mesylate salt)

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

The provided information with respect to the physicochemical properties of belumosudil drug substance is adequate. It is noted that the drug substance is slightly hygroscopic (refer to application for details), practically insoluble under physiologic conditions and has limited solubility in organic solvents.

b. DRUG SUBSTANCE MANUFACTURING PROCESS

(b) (4)

(b) (4)

8. BIOPHARMACEUTICS

This Biopharmaceutics review is focused on the evaluation of the adequacy of the overall information/data supporting (i) the in vitro dissolution method and acceptance criteria as a quality control (QC) test, (ii) need for the bridging to the To-Be-Market (TBM) tablet products.

In Vitro Dissolution Testing:

The Applicant proposed a dissolution method [USP Apparatus 2 (Paddle), 100 rpm, 900 mL of 0.01N HCl] for the proposed drug product. The currently proposed dissolution method using a paddle speed of 100 rpm showed very rapid dissolution with limited discriminating and stability-indicating ability. The DOE batches used in the evaluation of discriminating ability of the proposed dissolution method showed significant slower dissolution than that of the clinical and registration batches. In addition, the dissolution data for the clinical and registration batches, with the use of a paddle rotation speed of 100 rpm, did not indicate any significant change, while the limited submitted data with the use of a paddle rotation speed of (b) (4) showed a decreasing trend in dissolution during the stability studies. The submitted data do not support the Applicant's claim of a better discriminating ability with the use of 100 rpm paddle speed and the proposed (b) (4)

Therefore, based on the data and information submitted during the current cycle, the following dissolution method and acceptance criteria are found acceptable only **on an interim basis**, for the proposed REZUROCK™ (belumosudil) Tablets, 200 mg, for batch release and stability testing:

USP Apparatus	Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criterion
2 (Paddle)	100 rpm	900 mL	37 °C	0.01M HCl	Q= (b) (4) % in 20 minutes

Bridging

To support the bridging of the capsule product (containing 100% API) to the tablet product, the Applicant evaluated the relative bioavailability (BA) between the tablets (200 mg) and capsules (2x100 mg) in the healthy subjects in a Fed State (Study KD025-106). The composition of the 200 mg (belumosudil) tablets used in clinical studies are same as for the commercial tablets except the debossing. The submitted data showed similar dissolution profiles between the plain (clinical products) and debossed (TBM) coated tablets. In addition, the manufacturing site, scale and process used for the clinical products is the same as that of the To-be-Market (TBM) product. Therefore, the batches used in the clinical studies and the registration batches/ To-be-Market (TBM) product are deemed adequately bridged.

RECOMMENDATION:

From a Biopharmaceutics perspective, NDA 214783 for REZUROCK™ (Belumosudil) Tablet, 200 mg, is recommended for **Approval with a Post-Marketing Commitment [PMC]**. The Applicant agreed to use the interim dissolution method and acceptance criterion until a more optimal dissolution method is approved. The Applicant agreed to a Post-Marketing Commitment [PMC Number XXXX] to develop a new dissolution method (b) (4). The Applicant agreed (IR response, dated 04/28/2021 (0073(73)) to provide the requested reports under a Prior Approval Supplements (PASs), 06 months (interim report) and 12 months (final report) post NDA approval.

a. BCS CLASSIFICATION

Applicant to fill:

FDA assessment (FDA to fill):

The Applicant submitted the solubility of belumosudil in buffers with various pHs and the submitted data indicated that belumosudil exhibited a pH-depended solubility and is insoluble at higher pHs. The Applicant submitted the in vitro permeability of belumosudil in Caco-2 cell lines and determined a bioavailability of 64% in the human absorption, metabolism, and excretion [hAME] study (KD025-108). The submitted in vitro and in vivo data indicated belumosudil is a low permeable drug substance (a potential substrate of efflux transporter (P-gp)).

Table 1. Solubility of belumosudil in buffers with various pHs (*Module 3.2.P.2. Pharmaceutical Development, Table 12, Page 15*)

Simulated Fluid	Solubility (mg/mL)
0.01M Hydrochloric acid (HCl), pH 2.0	1.433
0.1M Hydrochloric acid (HCl), pH 1.08	0.011
Phosphate buffer, pH 6.8	0.000
Fed State Simulated Intestinal Fluids (FeSSIF)	0.029
Fasted State Simulated Gastric Fluids (FaSSGF), pH 1.60	1.644
Fasted State Simulated Intestinal Fluids (FaSSIF), pH 6.5	0.003

Table 2. Permeability results of belumosudil in Caco-2 cell line (mean values ± SD) (*Module 4.2.2.2, ADME-KAD-200410-Cao-2, Table 1, Page 6*)

Compounds	P_{app} ($cm/s \times 10^{-6}$)		Recovery (%)		Efflux Ratio
	A→B	B→A	A→B	B→A	
KD025 (1 µM)*	<0.919	1.83±0.166	<32.7	33.1±5.15	>2.06
KD025 (10 µM)	0.294±0.0873	1.12±0.125	42.1±9.28	42.3±7.45	4.01±1.24
KD025 (100 µM)	0.276±0.0709	0.201±0.0681	49.8±7.20	68.6±8.22	0.727±0.121
Digoxin (5µM)	0.925±0.129	21.6±0.244	98.4±7.77	95.1±2.38	23.7±3.19
Atenolol (5µM)	0.566±0.0829	0.668±0.0857	84.3±1.78	95.5±4.15	1.19±0.172
Minoxidil (5µM)	4.75±0.182	7.73±0.396	86.5±0.815	93.6±4.11	1.63±0.141

* The concentration in the receiver was BLLOQ, the Papp, recovery and efflux ratio were calculated with cut-off of LLOQ (1 nM).

Reviewer's Assessment:

The Applicant has submitted sufficient data to support that belumosudil is a low soluble (see additional solubility data at 37°C below) and low permeable drug substance (as per BCS criteria).

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FDA assessment (FDA to fill):

In the further evaluation of the discriminating ability of the proposed dissolution method in the NDA submission, the Applicant identified the additional critical formulation variables (CFVs) (e.g., level of (b) (4)) and critical process parameters (CPPs) ((b) (4)) that might impact the drug product dissolution. The following QbD batches were manufactured for the further evaluation of the discriminating ability of the proposed dissolution method (USP Apparatus 2, 900 mL of 0.01N HCl).

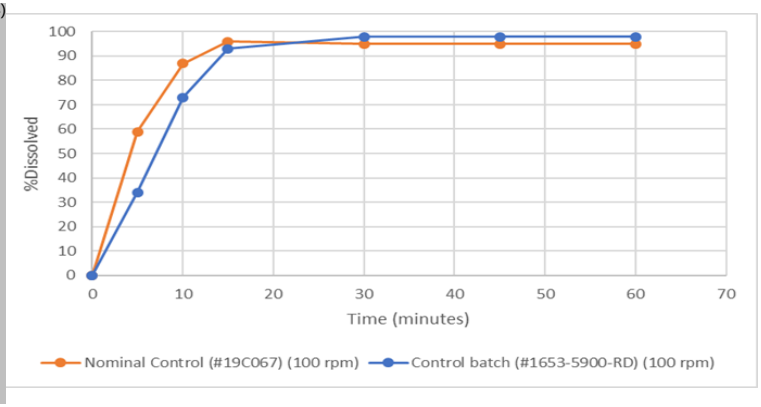
This Reviewer summarized the % change for the QbD batches studies as below:

Critical Attributes	Batch Number	Parameters (QbD)	Target controls	% of change
CFVs (b) (4)	1653-5907-RD	(b) (4)		
	1653-5914-RD			
CPPs	1653-5901-RD			
	1653-5924-RD			
	1653-5902-RD			
	1653-5908-RD			
	1653-5912-RD			
	1653-5913-RD			

A QbD batch #1653-5900 manufactured with the target parameters was used as control batch in the QbD study. However, the submitted data indicated that the control QbD batch #1653-5900-RD showed a (b) (4) while similar dissolution profiles were observed for these batches at a paddle speed of 100 rpm (shown in figure below). (b) (4) (*Biopharmaceutics IR dated 12/09/2020*).

Figure 2. Dissolution comparison of QbD control batch #1653-5900-RD and clinical batch #19C067 at (b) (4) 100 rpm
(*Plotted by the Reviewer, Data from Module 1.11.1, Table 15, Page 40, Table 63-64, Page 67*)

(b) (4)



The Applicant's IR response dated 12/23/2020 (Seq. 0029(29)):

The Applicant submitted a head-to-head comparison of the formulation composition, manufacturing process, equipment, equipment parameters. (b) (4) The Applicant submitted the testing results of the clinical batch and the QbD control batch as presented below:

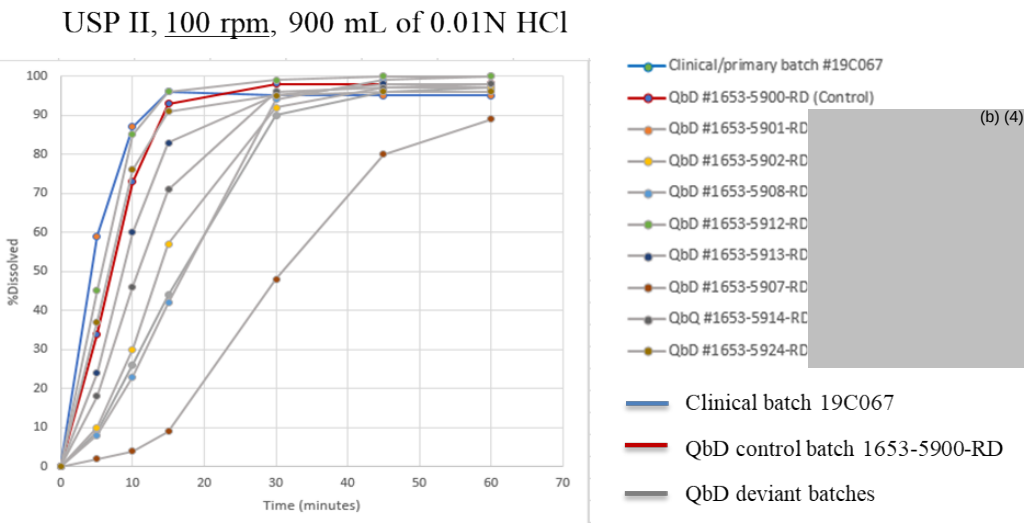
(b) (4)

Reviewer's Assessment:

This Reviewer plotted the dissolution profiles of the clinical batch and the QbD batches used in the further evaluation, as presented below in Figure 3*:*

Figure 3. Dissolution comparison of clinical batch #19C067 and QbD batches used in the discriminating studies
(*Data from Module 1.11.1, Table 15 (Page 40), Table 63-80 (Page 67-75)*)

(b) (4)



The dissolution method and acceptance criterion should be established based on the clinical and registration/commercial batches. As indicated by the dissolution profile comparison between the clinical batch (#19C067) and the QbD batches, (b) (4) *and ii) a very rapid dissolution (87%(mean) dissolved at 10 minutes) was observed for clinical batch (#19C067) and QbD batches with a paddle speed of 100 rpm. Therefore, the submitted data do not support the Applicant's claim of a better discriminating ability with the use of 100 rpm paddle rotation speed,* (b) (4) *. The Applicant was requested to submit additional dissolution data* (b) (4) *to determine an appropriate paddle rotation speed (Biopharmaceutics IR dated 12/31/2020).*

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(b) (4)

Reviewer's Assessment:

(b) (4)

while the proposed dissolution method using a paddle speed of 100 rpm does not reflect this trend, indicating that the proposed dissolution method with (b) (4) *may have limited stability-indicating ability.*

In addition, The Applicant submitted a comparison of the available PK information and data (e.g., AUCs C_{max} and T_{max},) from clinical batches #19C067 and #18E115 using three clinical studies (KD025-109/208/213) and claimed that the dissolution differences do not have any impact on the PK of drug product regarding the C_{max}, T_{max} and AUC.

Table 5. Comparison of clinical studies with clinical batches #19C067 and 18E115 (IR response dated 02/08/2021 (Seq. 0046(46))

Study	KD025-109	KD025-208	KD025-213
Batch	19C067	18E115	PK with 18E115
N for this Analysis	11 healthy subjects	2 subjects C1D1 (both on PPIs)	10 subjects (8 on PPIs)
Population	Subjects with normal hepatic function included	cGVHD	cGVHD
Dose	200 mg single dose; fed administration with standard breakfast	400 mg QD (200 mg QD and 200 mg BID included in the study but no subjects on either 200 mg regimen received batch 18E115); instructed to be taken with a meal or within 5 minutes of completing a meal	200 mg QD and BID; instructed to be taken with a meal or within 5 minutes of completing a meal

Reviewer's Assessment:

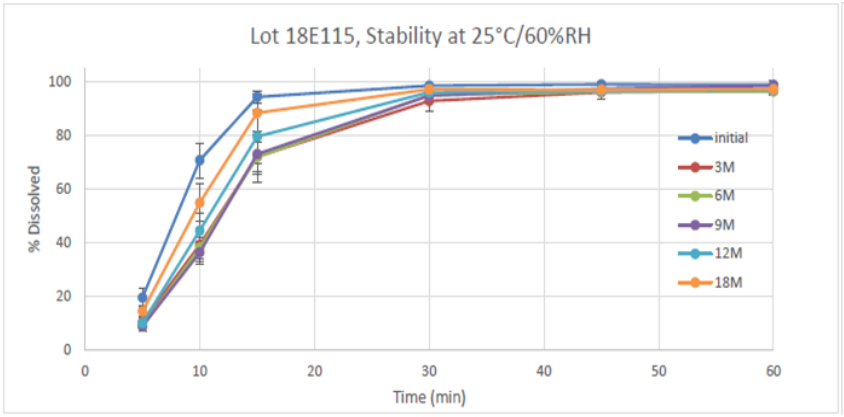
The submitted PK parameters for clinical batch #19C067 in Study KD025-109 (hepatic impairment study) are from the healthy subjects, while the submitted PK parameters for the clinical batch 18E115 in Study KD025-208/213 are from cGVHD patients. The

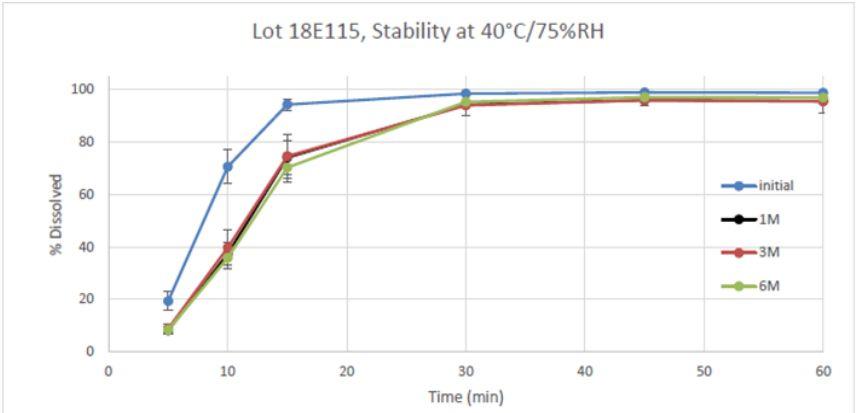
clinical pharmacology reviewer (meeting dated 12/03/2020) indicated that the cGVHD patients showed higher exposure (e.g., C_{max}, and AUC) than that in the healthy subjects. The comparability of submitted PK profiles for above batches cannot be determined due to the different study population (healthy vs. cGVHD), very limited number of subjects (only two subjects with PPIs in KD 0250213) and different administrative dosing from the submitted studies. In addition, the Applicant could not identify the root causes for the slower dissolution for clinical batch 18E115 compared to other clinical batches. In the IR responses the Applicant committed to continue evaluating the dissolution conditions (b) (4) *and submit the study result to the FDA.*

Stability/clinical batch #18E115

In addition, the submitted dissolution profile for the stability batch #18E115 showed a faster dissolution for samples stored under long term condition (25°C/60%RH) at 18M than that at 3M using the proposed dissolution condition (USP apparatus II (Paddles), 100 rpm, 900 mL of 0.01N HCl). Therefore, the Applicant was requested to provide the root cause of the change (increase) in the dissolution data observed at 18M stability time point for the clinical batch #18E1157 (*Biopharmaceutics IR dated 02/25/2021*).

Figure 7: Dissolution profile of registration/clinical batch #18E115 through stability study (*Module 1.11.1, CMC-PTR-004, Figure 20, Page 29; Figure 21, Page 30*)





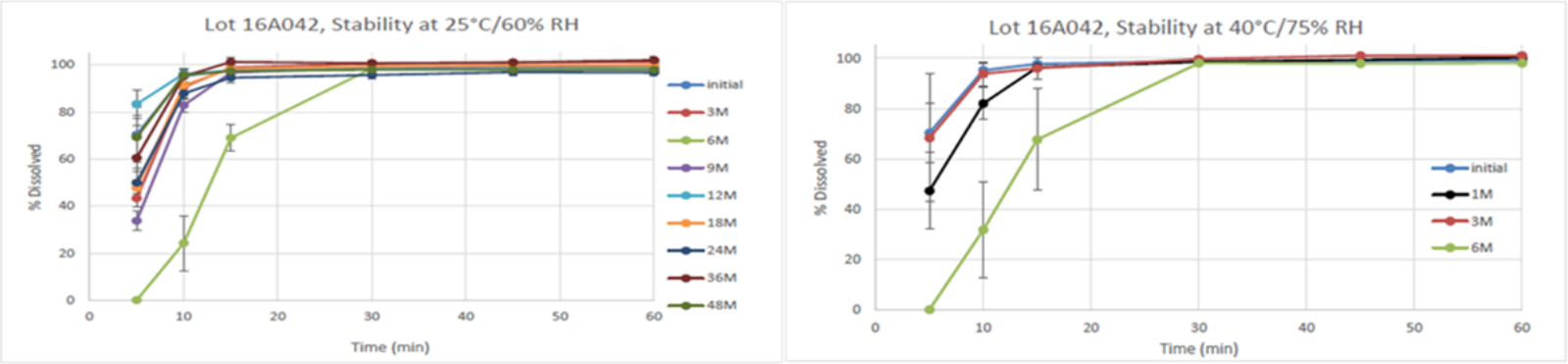
The Applicant's IR response dated 03/04/2021 (Seq. 0055(55))

The Applicant acknowledged that the % dissolution is slower at 3-month (average 10% (range 8-13%) than at 18- but could not identify a root cause for the counterintuitive trend. Instead, the Applicant committed to continue evaluating the dissolution conditions (b) (4) and submit the study result to the FDA.

Stability/clinical batch #16A042

The Applicant submitted the dissolution data from four registration/stability/clinical batches (16A042, 17C068, 18E115 and 19C067) (Module 1.11.1, page 3) using the proposed dissolution condition . Significantly slower dissolution profiles were observed for batch 16A042 at 6-month time point under both 25°C/60% RH and 40ºC/75% RH storage conditions (*Module 1.11.1, CMC-PTR-004, Figure 16-17, Page 26*).

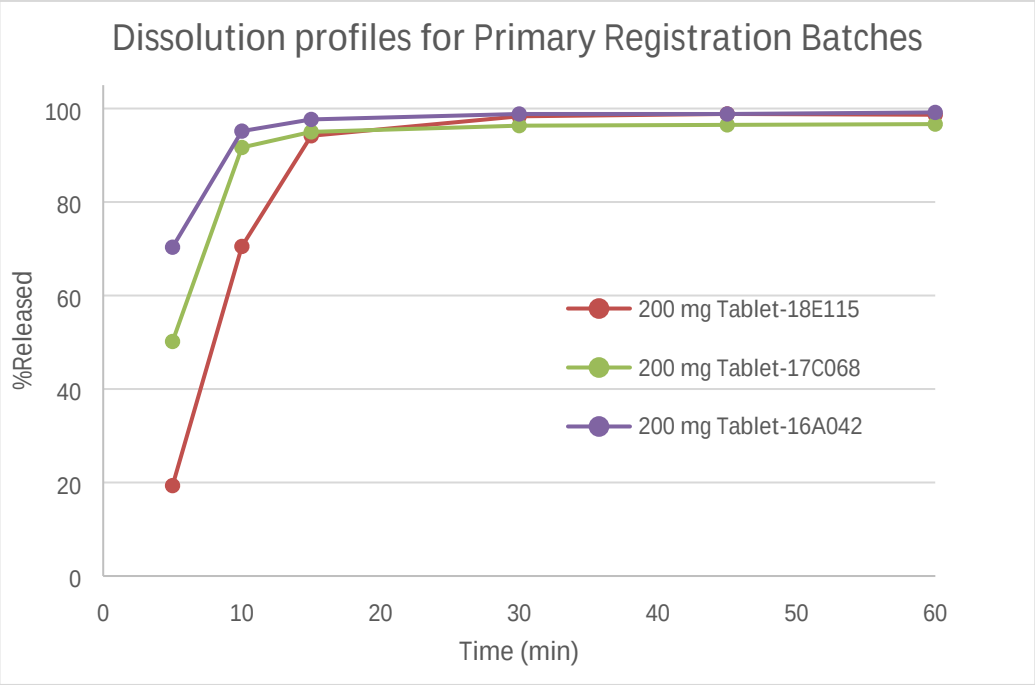
Figure 8. Dissolution profile of registration/clinical batch #16A042 through stability study



The Applicant's IR response dated 12/23/2020 (Seq. 0029 (29)):

The Applicant stated that the slower dissolution for the primary batch 16A042 observed at 6M time point is outlier in 48M of stability data and for all the primary and supportive stability batches. The Applicant attributed this anomaly of the slower dissolution point to a laboratory error rather than the product itself.

d. Justification for selection of the acceptance criteria (or criterion)



Applicant's comments:

Refer to Table 15 for detailed batch usage (stability and clinical studies).

FDA assessment (FDA to fill):

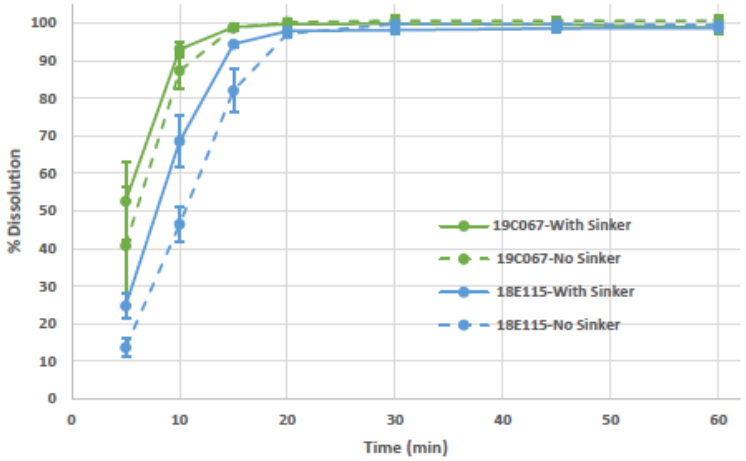
The Applicant has submitted the dissolution profiles (5, 10, 15, 30,45 and 60 minutes) for the registration/stability batches #16A042, #17C068, #18E115 and #19C067 and proposed (b) (4) for the proposed drug products. However, the submitted dissolution data do not support the proposed (b) (4) dissolution acceptance criteria. Therefore, for the current stability batches, using the proposed dissolution conditions, the Applicant was requested to submit a) complete dissolution profiles with additional time points (i.e., 5, 10, 15, 20, 25 and 30 minutes, etc.); and b) comparisons of the new dissolution profiles with the dissolution at the initial stability time point (*Biopharmaceutics IR dated 02/25/2021*).

In addition, the Applicant also reported an out of specification (OOS) dissolution results from supportive stability batch 20F220 at 3 months under long term storage condition (25°C/60%RH) (61% (mean) (n=24, Range: 48 to 78) at 15 minutes (data reported in *Module 3.2.P.8.3 Stability Data (0038 (38)), Table 11, Page 15*). The Applicant stated that they have initiated an investigation to identify the root cause for OOS dissolution results and committed to submit an investigation summary to the Agency upon completion.

The Applicant's IR response dated 03/04/2021 (Seq. 0055(55))

The Applicant submitted complete dissolution profiles and data (5, 10, 15, 20, 30,45 and 60 minutes) for the two clinical batches #19C067 and #18E115 using the proposed dissolution conditions (USP Apparatus II, 100 rpm, 900 mL of 0.01N HCl). In the response, the Applicant attributed the slow and variable dissolution to the potential tablet sticking/swirling. Therefore, the dissolution profile and data for these two clinical batches with the use a sinker were also submitted for a comparison.

Figure 9. Comparative dissolution profiles for batches 18E115 and 19C067



Reviewer's Assessment:

The submitted dissolution data support a single point dissolution acceptance criterion of Q= (b) (4) *% in 20 minutes with the interim method using a paddle speed of 100 rpm. An appropriate dissolution method and acceptance criterion(a) will be established based on the new dissolution method submitted in the PMC reports.*

Overall Summary of Dissolution Specifications (method and acceptance criterion)

Overall, the proposed QC dissolution method using a USP apparatus 2 (paddle) with a paddle rotation speed of 100 rpm showed limited discriminating ability. During the course of the NDA review, the Applicant could not generate adequate data and information to support an appropriate (b) (4) *for the dissolution testing of their proposed drug product. Instead, the Applicant committed to continue evaluating the dissolution conditions* (b) (4) *and to submit the study results to the FDA under a PMC, after their product is approved.*

According to the Applicant's IR response dated 04/28/2021 (0073(73)), the Applicant agreed to the following:

- *To use "On an Interim Basis", the currently proposed dissolution method (USP Apparatus 2 (paddle) at 100 rpm; 900 mL of 0.01N HCl[1]) with an acceptance criterion of Q=* (b) (4) *% in 20 minutes, and*
- *To a Post-Marketing Commitment (PMC). Specifically, to submit under a Prior Approval Supplement (PAS), the Interim and Final PMC Reports within 6 months and 12 months, respectively, from the NDA's action date.*

The specific goals of the PMC study are outlined below:

- *To develop a new optimal and discriminating dissolution method* (b) (4) *, and to submit the Interim Dissolution Method Development and Validation Report within 6 months of the NDA's action date for FDA's review and concurrence of the new dissolution method.*
- *To collect complete dissolution profile data for the unexpired clinical and registration batches, and all available commercial batches of the drug product using the new dissolution method. Based on the generated data, propose the dissolution acceptance criterion/criteria for the drug product. Submit the Final Report within 12 months of the NDA action date for FDA's review and concurrence of the new dissolution acceptance criterion/criteria.*

[1] At several locations in the Review document, the dissolution medium is mentioned as 0.01M HCl, which is same as 0.01N HCl.

	Applicant to fill:	FDA assessment:
The dissolution method is discriminating for:		
i) Particle size distribution (PSD)	Not applicable	Choose an item.
Link: Section 3.2.P.2.1		Page#: 1
ii) Polymorph/solid state form	Not applicable	Choose an item.
Link: Section 3.2.P.2.1		Page#: 1
iii) Formulation variations	Discriminating	Choose an item.
Link: Section 3.2.P.2.2		Page#: 15-16
iv) Manufacturing process variations	Discriminating	Choose an item.
Link: Section 3.2.P.2.2		Page#: 17-18

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

Link: Section 3.2.P.2.2, Section 3.2.P.2.3, and Section 3.2.P.5.4.

A timeline describing the development of belumosudil drug product from the initial IND to the to-be-marketed drug product is presented in Figure 7. Information about each batch of drug product manufactured to date, stability-registration studies, and use in clinical studies is also collected in Table 15.

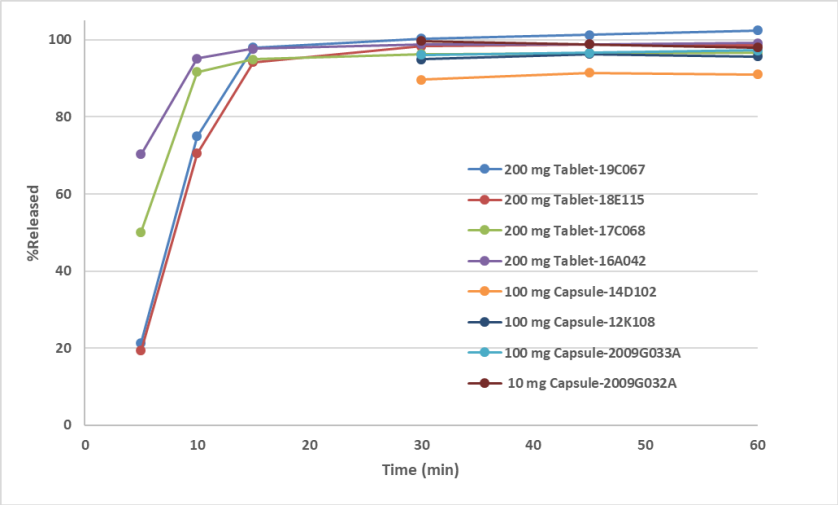
Historically, belumosudil drug product was developed as API in the capsule (no excipient) at two strengths: 10 mg and 100 mg. The analytical method used for this dosage form utilized USP type II (paddle) dissolution apparatus at a set rotation speed of 100 rpm. A 200 mg coated tablet formulation manufactured (b) (4) was then developed and used in clinical development. In order to maintain the analytical testing consistency and to allow direct comparison between tablet and capsule, the dissolution method used a similar dissolution apparatus with USP type II (paddle) and a set rotation speed of 100 rpm (see

Figure 6) for capsule and tablet comparison.

The process uses standard techniques ((b) (4) and equipment routinely used for pharmaceutical solid dosage form manufacturing. These unit operations have remained essentially unchanged throughout the clinical development program and into the proposed commercial production. The

process was initially developed by [redacted] up to a scale of [redacted] kg. Kadmon continued development activities at [redacted], where a technical transfer was performed to transfer the process and scale-up the batch size to [redacted] kg, which is the proposed commercial batch size range.

Figure 6 Comparison of Release Profile between Tablets and Capsules



Multiple batches of tablets have been manufactured and placed on stability studies. The to-be marketed drug product is identical to the clinical batches of tablets and will be produced at the same scale, by the same manufacturer [redacted]. The to-be-marketed tablet will be debossed on both sides of the tablet. A minute adjustment to the formula was implemented by adjusting the amounts of [redacted] ([redacted] w/w%) and [redacted] ([redacted] w/w%) while maintaining the weights of the [redacted], as described in Section 3.2.P.2.2. The clinical batches provide primary stability data to support the proposed shelf-life.

A relative bioavailability study (Study KD025-106) demonstrated that there was no statistically significant difference in terms of exposure when subjects were administered belumosudil tablets or belumosudil capsules. Food decreases the rate and increases the extent of belumosudil absorption. Exposure (AUC and C_{max}) in the fed state is ~2 to 3x that in the fasted state, and t_{max} is delayed 0.5 to 2 hours. Belumosudil is recommended to be administered with food. Absolute bioavailability (64%) was determined in Study KD025-107. The tablet formulation has been used in both cGVHD studies (KD025-208 and KD025-213) supporting this NDA.

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Table 15 Drug Product Usage

Manufacturer	Drug Product	Batch # (Scale) Stability Status	Description	Phase 1	Phase 2
(b) (4)	**10 mg Capsule**	**2009G032A** (b) (4)	API (b) (4) in capsule (no excipient) No excipient	SLx-2119-09-01—SAD KD025-101—SAD/MAD	Not applicable
	100 mg Capsule	**2009G033A** (b) (4)		SLx-2119-09-01—SAD KD025-101—SAD/MAD	Not applicable
		12K108 (b) (4)		KD025-102—MAD KD025-103—Repeat Dose KD025-105—Food effect	KD025-205—Psoriasis KD025-206—Psoriasis
		14D102 (b) (4)		Not applicable	KD025-205—Psoriasis KD025-208—cGVHD
(b) (4)	**100 mg Capsule**	**117415/C/02** (b) (4)	API (b) (4) in capsule (no excipient)	KD025-106—Tablet vs Capsule PK and Tablet food effect	Not applicable
	200 mg Tablet Small Scale (b) (4)	**117415/C/01** (b) (4)	Immediate release tablet formula (b) (4) Dose strength:200 mg Core tablet weight: (b) (4) Coated tablet weight: (b) (4) Developed and clinically tested at (b) (4)		
(b) (4) **To-Be-Marketed Formula**	**200 mg Tablet Production Scale**	**16A042** (b) (4) **Primary stability—36M and 48M**	Immediate release tablet formula (identical as above) Formula/Process transferred (Q4 2015) from (b) (4) to (b) (4) for scale up and production at intended commercial scale	Not applicable	KD025-211—Psoriasis
		17C068 (b) (4) **Primary stability—36M**		KD025-107—DDI study—Full PK profile 200 mg QD and 200 mg BID KD025-108—hAME study with ^{14}C-belumosudil—Absolute Bioavailability	KD025-208—cGVHD KD025-207—IPF KD025-211—Psoriasis
		18E115 (b) (4) **Primary stability—24M**		Not applicable	KD025-208—cGVHD KD025-213—cGVHD KD025-207—IPF KD025-209—SSc
		19C067 (b) (4) **Supportive stability—12M**		KD025-109—Hepatic Impairment—PK *KD025-110 (TQT study)*	KD025-208—cGVHD KD025-213—cGVHD KD027-207—IPF
	200 mg Tablet Debossed Production Scale	**20F220** (b) (4) **Supportive stability—Initial**	Identical as above with 2 minor modifications: • Implementation of debossing on both sides of tablet • Minute change to formula: adjusting the amounts of (b) (4)	To be determined	To be determined
		20F221 (b) (4) **Supportive stability—Initial**		To be determined	To be determined

SAD: single ascending dose; MAD: multiple ascending dose; cGVHD: chronic graft vs host disease; IPF: idiopathic pulmonary fibrosis; SSc: systemic sclerosis; TQT: thorough QT

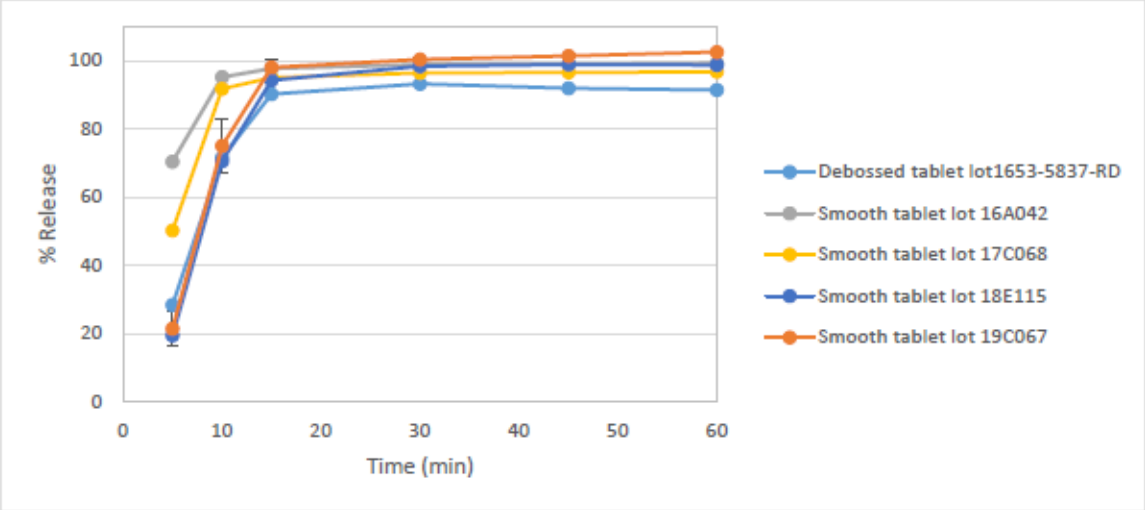
The FDA's Assessment: ***Adequate***

A capsule formulation (100% API) of 10 and 100 mg strengths (same capsule size) was used in the phase 1 studies (e.g., KD025-101, 102, 103, 105) and phase 2 clinical study KD025-208 (with both capsules and tablets) (cGVHD). The Applicant submitted a comparative bioavailability (BA) study KD025-106 to evaluate the relative BA of the tablet and capsule formulations in the Fed state (with food effect) (Regimen B: 200 mg belumosudil tablet in the fed state; Regimen C: 200 mg belumosudil as 2 × 100 mg capsules in the fed state). The study indicated that the average overall exposure for the Tablets was ~17% higher compared to the Capsules, but the result is not considered statistically significant (p = 0.2). As per the discussion with the clinical pharmacology reviewer (emails dated 12/03/2020), no additional bridging study for the capsule formulation to the tablet formulation is needed.

The clinical studies KD025-213 (safety and efficacy) and KD025-208 are considered pivotal clinical studies that are used for the approval of this NDA (cGVHD). The tablet products (200 mg) were used in the above pivotal studies and the drug-drug interaction (KD025-107), food effect (part of KD025-106) and mass balance (KD025-108) studies that are used for population PK analysis and the labeling claims.

The clinical and proposed TBM products only have very minor difference: the clinical batches were plain (coated, but not debossed) while proposed commercial TBM product are debossed tablets. The submitted data showed similar dissolution profiles between the plain and debossed coated product using the proposed dissolution conditions.

Figure 10. Dissolution profile comparison for the plain coated and the debossed tablet



In addition, the manufacturing site, process and batch size used for the clinical products is the same to that of the To-be-Market (TBM) product. Therefore, the batches used in the clinical studies and the registration batches/ To-be-Market (TBM) product are deemed adequately bridged.

c. BIOWAIVER REQUEST

The Applicant's Position:

The NDA does not contain a biowaiver request.

A biowaiver is not needed for belumosudil tablets, 200 mg, because the formulation and manufacturing process for the clinical/primary stability, supportive stability, and commercial products are essentially identical.

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

Biowaiver is not needed because this is a single strength product and this strength (200 mg) was used in the clinical studies.

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

We have not conducted IVIVC or PBBM modeling. A PBPK modeling effort has been initiated with the purpose of identifying drug-drug-interaction liabilities. A fit for purpose first order absorption model will be used to describe the absorption of belumosudil. An advanced dissolution and absorption metabolism model will also be explored to describe food effects, formulation effects, and drug-drug interactions with proton pump inhibitors. No data are available at the time of submission.

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

No IVIVC or PBBM modeling was submitted

Appendix. Biopharmaceutics Information Requests

Biopharmaceutics Information Request dated 12/09/2020:

- (b) (4)

rpm.

- (b) (4)
- Investigate and provide a root-cause analysis for the significant slow dissolution for primary batch 16A042 at 6M time point with supporting data and discuss any corrective actions that you took to avert such changes in the dissolution of the proposed drug product.

Biopharmaceutics Information Request dated 12/31/2020:

- At this stage, we have determined that your proposed dissolution method [USP apparatus II (Paddles) at 100 rpm in 900 mL of 0.01N HCl] is not adequate. We consider that the paddle rotation speed, 100 rpm, used in the proposed dissolution method is not justified because the dissolution profile data generated using a paddle rotation speed of 100 rpm, show very rapid dissolution. The submitted data indicated that (b) (4)
- (b) (4). If change in the paddle rotation speed alone does not result in an optimal suitable/discriminating dissolution method for your proposed drug product then you are recommended to develop a new suitable/discriminating dissolution method for your proposed drug product by altering apparatus, medium, volume etc.
- The dissolution method has not been shown to be discriminating to the critical attributes that has potential to affect in vitro/in vivo dissolution. In addition, the discriminating ability of the proposed dissolution method has not been adequately investigated. We found that the variants used to evaluate the discriminating ability of the proposed dissolution method are inadequate because the variant-formulations used are significantly different from the target drug product formulation (for example, (b) (4)).

- For a proper assessment of the discriminating ability of the proposed dissolution method, The testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) drug product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical material attributes (CMAs), critical formulation variables (CFVs), and critical process parameters (CPPs) (e.g., ± 10-20% change to the specified limit values or ranges for these variables). Once you optimize the dissolution method parameters then demonstrate that the dissolution method is discriminating to the critical attributes that has potential to affect in vitro/in vivo dissolution of you proposed product, Belumosudil Tablet.
- Provide a head-to-head comparison of manufacturing parameters and the testing results of the GMP clinical batches 18E115, 17C068, 16A042, and the QbD control batch 1653-5900-RD (e.g., tablet hardness, thickness, (b) (4)).

Biopharmaceutics Information Request dated 01/27/2021:

- (b) (4)
- The submitted data demonstrated that the clinical batch #18E115 showed a slower dissolution than the dissolution of the clinical batch #19C067. Provide root cause of slower dissolution profile of the clinical batch #18E115. In addition, provide a head to head comparison of the available pharmacokinetic (PK) information and data (e.g.,

AUC and C_{max}, T_{max}, T_{half} mean PK profiles etc.) obtained while using these clinical batches #18E115 and #19C067, showing that the above clinical batches are bioequivalent, or sufficient justifications with supporting data demonstrating that the dissolution differences do not have any impact on the PK of the drug product.

- Please note that until the dissolution conditions are accepted by the FDA, we recommend that you collect complete dissolution profile data (individual, mean, SD, plots, 5, 10, 15, 20, 30, 45 and 60 minutes, etc.) for the clinical and registration batches of the proposed drug product at release and on stability using both paddle rotational speeds, (b) (4).

Biopharmaceutics Information Request dated 02/25/2021:

- The submitted dissolution profile for the stability batch #18E115 showed a faster dissolution for samples stored under long term condition (25°C/60%RH) at 18 months than that of the samples at 3 months. Investigate and provide a root-cause analysis for the faster dissolution during the stability study.
- In addition, provide complete dissolution profile with additional time points (i.e., 5, 10, 15, 20, 25 and 30 minutes, etc.) for current stability batches using the proposed dissolution conditions and comparisons with the dissolution profile at the initial stability time point. Provide the root cause for any observed change in the dissolution profiles and include the measures that will be implemented to resolve it.
- In your IR response dated 02/08/2021 (Seq. 0046(46)), you indicated that the age of stability batch #18E115 was 18 months when the study (*IND 125890, seq. 0077/ SDN82, Module 1.6.2, Type B meeting package dated 12/16/2019, Figure 11, page 51*) was performed. However, the submitted profile data showed a faster dissolution than that of the same batch (clinical batch #18E115) at the same age (18 months) submitted in your dissolution method development report (*NDA 214783, 1.11.1, CMC-PTR-004, Figure, Page 18*). Explain the discrepancy in the dissolution profiles of the same batch at same age. Investigate and provide a root-cause for the slow dissolution for batch #18E115 at 18-month time point submitted in your dissolution method development report.

Biopharmaceutics Information Request dated 04/23/2021:

1. We acknowledge that, in the IR response letter dated 1/22/2021(Seq. 0035(35)), you committed to provide dissolution data for GMP clinical batches using paddle speeds between (b) (4) rpm, evaluate the discriminating ability for critical quality attributes that may impact dissolution and in vivo performance, and consider changes in apparatus, medium and volume.

   Therefore, submit a formal Post-Marketing Commitment (PMC) proposal to develop an optimal and discriminating dissolution method for the Quality Control (QC) testing of REZUROCK™ (belumosudil mesylate) Tablets (b) (4). In your formal PMC request include the

following PMC description and the PMC Schedule Milestones, to be submitted under a Prior Approval Supplement (PAS), the Interim and Final PMC Reports within 6 months and 12 months, respectively, from the NDA's action date:

PMC Description:

- Development and validation of an optimal and discriminating dissolution method for the Quality Control (QC) testing of REZUROCK™ (belumosudil mesylate) Tablets, 200 mg.
- Dissolution acceptance criterion/criteria proposal, based on the data generated from the unexpired clinical and registration batches, and the first six commercial batches, using the new dissolution method.

PMC Schedule Milestones:

- Submission of Interim PMC Report 6 months after NDA approval (as part of a Prior Approval CMC Supplement to the NDA)
- Submission of Final PMC Report 12 months after NDA approval (as part of a Prior Approval CMC Supplement to the NDA)

Note that until a new revised dissolution method is found acceptable by FDA, the currently recommended dissolution method and acceptance criterion will be used for batch release and stability testing **on an interim basis**.

2. Based on the information and data submitted in the current submission, we determined that the proposed dissolution conditions [USP Apparatus II (Paddle), 100 rpm, 900 mL of 0.01N HCl] can be used for the dissolution method for the Quality Control (QC) testing of REZUROCK™ (belumosudil mesylate) Tablets, 200 mg, only on an interim basis. In addition, the submitted dissolution data do not support your proposed dissolution acceptance criteria of (b) (4) for the proposed drug product, therefore the proposed acceptance criteria are not acceptable. Based on the data provided, the following new **interim** dissolution acceptance criterion is recommended for your proposed drug product: **NLT (b) (4) % (Q) in 20 minutes**.

Note that the dissolution testing may require Stage 2 testing and occasionally Stage 3 testing. Please revise your drug product specifications and stability protocol accordingly and submit a copy of the updated drug product specifications table.

9. LABELING

USPI

Highlights: ***Adequate***

The information provided is acceptable.

Section 2 Dosage and Administration (if relevant): ***Adequate***

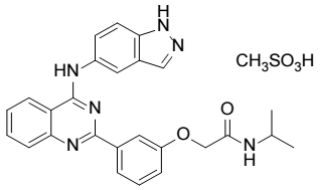
(b) (4)

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

Each 200 mg tablet is a pale-yellow oblong tablet debossed with "KDM" on one side and "200" on the other side.

Section 11 Description: ***Adequate***

Belumosudil is a (b) (4) . The active pharmaceutical ingredient is belumosudil mesylate with chemical name is 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-*N*-(propan-2-yl) acetamide methanesulfonate (1:1). The molecular formula is $C_{27}H_{28}N_6O_5S$ and the molecular weight is 548.62 g/mol. The chemical structure is as follows:



REZUROCK (b) (4) 200 mg free base equivalent to 242.5 mg of belumosudil mesylate) (b) (4) contains the following inactive ingredients:

(b) (4) Microcrystalline cellulose, hypromellose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate.

(b) (4) Polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide and yellow iron oxide.

(b) (4)

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

REZUROCK 200 mg tablets are supplied as pale-yellow oblong tablets containing 200 mg of belumosudil (equivalent to 242.5 mg belumosudil mesylate). Each tablet is debossed with "KDM" on one side and "200" on the other side and is packaged as follows: 200 mg tablets in 30 count (b) (4) bottle: NDC (b) (4)

Stored at room temperature, 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C and 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

(b) (4) in original container to protect from moisture. (b) (4) securely (b) (4) each time after opening. (b) (4)

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

Kadmon maintains quality oversight of the drug product.

Carton/Container Label ***Adequate***

The proposed carton and container labels submitted in the original NDA did not include equivalency statement for the salt. The following comment was sent from the Agency to include equivalency statement on the container and carton labels.

"Include equivalency statement indicating the name and strength of both the active ingredient (mesylate salt) and the active moiety next to Contents as recommended below: Each Tablet contains: Belumosudil 200 mg (equivalent to 242.50 mg of Belumosudil Mesylate)"

The Applicant revised both the container and carton labels by including the equivalency statement in the updated labels as per Agency's request. Refer to the updated the labeling section 1.14.1.3 in this application submitted via amendment SDN 63 (eCTD 0063) dated 03/22/2021.

Final Risk Assessments

SOLID ORAL

Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	Low	All deemed to be acceptable	Low	--
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low	Adequate data provided	Low	--
Content Uniformity	• Formulation • Container closure • Raw material • Process Parameters • Scale/equipment • Site	Low	Meet specs	Low	--
(b) (4)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	Low	Meet specs	Low	--
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low	Meet specs	Low	--
Dissolution – (low solubility, low permeability) BCS Class II or IV	• Formulation • Container Closure • Raw materials • Process parameters • Scale/equipment • Site	High	Meet the revised dissolution acceptance criterion (Q= (b) (4) % in 20 minutes)	Medium	

Recommendation Page

[FDA will complete this section.]

Drug Substance: Approval

Primary Reviewer: Rohit Tiwari Date: March 17, 2021

Secondary Reviewer: Paresma Patel Date: March 17, 2021

Drug Product: Approval

Primary Reviewer: Soumya Mitra, Ph.D. Date: March 29, 2021

Secondary Reviewer: Anamitro Banerjee, Ph.D. Date: March 29, 2021

Process and Facility: Approval

Primary Reviewer: Djelila Mezaache Date: March 16, 2021

Secondary Reviewer: Rakhi Shah Date: April 27, 2021

Biopharmaceutics: Approval

Primary Reviewer: Kevin Wei, Ph.D. Date: May 28, 2021

Secondary Reviewer Om Anand, Ph.D. Date: May 28, 2021

Application Technical Lead: Approval

Sherita D. McLamore Date: June 2, 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/

SHERITA D MCLAMORE
06/02/2021 02:42:32 PM

ROHIT V TIWARI
06/02/2021 02:53:09 PM

PARESMA R PATEL
06/02/2021 02:54:14 PM

SOUMYA MITRA
06/02/2021 02:56:35 PM

ANAMITRO BANERJEE
06/02/2021 05:22:00 PM

DJELILA N MEZAACHE
06/03/2021 07:04:38 AM

RAKHI B SHAH
06/03/2021 09:04:36 AM

LINYI WEI
06/03/2021 09:08:16 AM

OM ANAND
06/03/2021 09:18:09 AM