CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215814Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	215814
Applicant Name	Forma Therapeutics, Inc
Drug Product Name	REZLIDHIA® (olutasidenib)
Dosage Form.	Capsule
Proposed Strength(s)	150 mg
Route of Administration	Oral
Maximum Daily Dose	300 mg
Rx/OTC Dispensed	Rx
Proposed Indication	Indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation.
Drug Product Description	Olutasidenib is an orally bioavailable, small-molecule mutant IDH1 (mIDH1) inhibitor. It is an NME and a small chiral BCS Class IV molecule that was granted Orphan for the treatment of adult patients with relapsed or refractory AML. The drug product is presented as an immediate-release, white opaque hard gelatin capsules that are imprinted with "OLU 150" on the capsule cap. The drug product formulation includes the (b) (4) drug substance, microcrystalline cellulose NF, croscarmellose sodium NF, (b) (4) magnesium stearate NF filled into size 00 white opaque hard gelatin capsules that are imprinted with "OLU 150" on the capsule cap. All excipients in the drug product formulation are compendial and commonly used in solid oral dosage forms. The QTPP for the drug product was established based on the properties of the drug substance, characterization of the drug product and the intended patient population. The CQAs include particle size and typical CQAs for this dosage form.

	The recommended dosage of REZLIDHIA is 150 mg orally every 12 hours, until disease progression or unacceptable toxicity.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	20 °C - 25 °C USP CRT		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Rajan Pragani	Hari Sarker
	Drug Product/ Labeling	Yang Nan	Sherita McLamore
	Manufacturing	Zhaoyang Meng	Bogdan Kurtyka
	Biopharmaceutics	Kevin Wei	Kevin Wei
	Microbiology	N/A	N/A
	Other (specify):	N/A	N/A
	RBPM	Dahlia Walters	
	ATL	Sherita McLamore	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: The proposed product has a **36-month expiry** when stored at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].

b. Additional Comments for Action

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends APPROVAL of NDA 215814 for the commercialization of REZLIDHIA® (olutasidenib) capsules, 150 mg. Based on our evaluation of the available information, the applicant provided sufficient information to support an approval recommendation from the product quality perspective. The applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and strength of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.

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

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**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): No

Comments: N/A

Additional Lifecycle Comments: N/A

CHAPTER III: ENVIRONMENTAL

R. REGIONAL INFORMATION

Environmental

Assessment: *Adequate*

Olutasidenib is a new molecular entity. Dr. Xiaoqin Wu from ONDP's Environmental Team provided the following assessment on May 17, 2022:

"The EA team reviewed the categorical exclusion. The submitted materials are sufficient to support the applicant's claim for categorical exclusion, and therefore an EA is not required."

CHAPTER IV: LABELING

ASSESSMENT OF LABELING

This module includes an assessment of product-quality information in the Prescribing Information (PI), FDA-Approved Patient Labeling, and the Container Label and Carton Labeling. Refer to the working version of the labeling (the review team may have edited and commented on the applicant's proposed labeling).

Assessment of Product Quality-Related Information in the PI:
Adequate

HIGHLIGHTS OF PRESCRIBING INFORMATION

Information provided in the submission

The original draft PI is provided in this link.

Assessment: Acceptable.
This section includes required proprietary trade name (REZLIDHIA), established name (olutasidenib), dosage form (capsules), route of administration (oral) and strength (150 mg).

FULL PRESCRIBING INFORMATION

SECTION 2 DOSAGE AND ADMINISTRATION

Information provided in the submission
Refer to the submission.

Assessment: Acceptable.

SECTION 3 DOSAGE FORMS AND STRENGTHS
Information provided in the submission

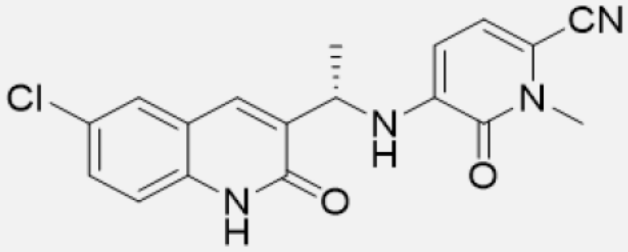
3 DOSAGE FORMS AND STRENGTHS
Capsules: 150 mg opaque white capsules imprinted with "OLU 150"

Assessment: Acceptable.

SECTION 11 DESCRIPTION
Information provided in the original submission

11 DESCRIPTION

Olutasidenib is an inhibitor of isocitrate dehydrogenase 1 (IDH1) enzyme. The chemical name is (S)-5-((1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)amino)-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile. The chemical structure is:



The molecular formula is C18H15ClN4O2 and the molecular weight is 354.79 g/mol. Olutasidenib is practically insoluble in aqueous solutions between pH 1.2 and 7.4.

(b) (4)

Assessment

The descriptions for the capsule shell and black printing ink are not complete. The Applicant is advised to revise the last paragraph as follows:

REZLIDHIA (olutasidenib) is available as hard gelatin capsules for oral administration. Each capsule contains 150 mg olutasidenib and the following ingredients: croscarmellose sodium, microcrystalline cellulose, and magnesium stearate. The capsule shell contains gelatin and titanium dioxide. Each capsule is printed with black ink containing ferrosoferric oxide, propylene glycol and shellac.

The Applicant accepted the recommendation on October 6, 2022 by email.

SECTION 16 HOW SUPPLIED/STORAGE AND HANDLING

Information provided in the submission

16 HOW SUPPLIED/STORAGE AND HANDLIN

16.1 How Supplied

(b) (4)

16.2 Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Assessment

There is no child-resistant language for the bottle. Also, it is generally not necessary to have sub-sections (16.1 and 16.2). We recommend the Applicant to revise this section as follows:

How Supplied

Capsule strength	Description	Package Configuration	NDC Number
150 mg	White hard gelatin capsules with black ink print "OLU 150"	White high density polyethylene (HDPE) bottle with child resistant closure Each bottle contains 30 capsules.	#####-###-##

Storage

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].

The Applicant accepted the recommendation on October 6, 2022.

END OF THE PI (AFTER SECTION 17)

Information provided in the submission

Manufactured for COMPANY, ADDRESS, CITY, STATE ZIPCODE

Assessment
There is no detailed information about the manufacturer. The Applicant is advised to include detailed description of manufacturer information (street address, city, state, and zip code).

On October 6, 2022, the Applicant revised the manufacturer information as follows:

Manufactured by Metrics Contract Services, 1240 Sugg Pkwy, Greenville, NC 27834
REZLIDHIA™ is a trademark of (b) (4) Pharmaceuticals, Inc.
For more information go to www.REZLIDHIA.com or call 1-800-983-1329

Assessment of Product Quality-Related Information in Patient Labeling

CMC related Information provided in the Medication Guide

How should I store REZLIDHIA?

- Store REZLIDHIA at room temperature (b) (4) 68°F to 77°F (20°C to 25°C).
- **Keep REZLIDHIA and all medicines out of the reach of children.**

What are the ingredients in REZLIDHIA?
Active ingredient: olutasidenib
Inactive ingredients: (b) (4)
(b) (4)

Manufactured for COMPANY, ADDRESS, CITY, STATE ZIP CODE
COMPANY, the COMPANY logo, and REZLIDHIA™ are trademarks of COMPANY.
© 2021 COMPANY
For more information go to www.DRUG.com or call 1-800-XXX-XXXX.

Assessment
Storage conditions are acceptable. However, the inactive ingredients are not correctly described. Also there is no detailed information about manufacturer. The Applicant is recommended to include manufacturer information and revise the inactive ingredients as follows:

Inactive ingredients: *croscarmellose sodium, microcrystalline cellulose, and magnesium stearate. The capsule shell contains gelatin and titanium dioxide. Each capsule is printed with black ink containing ferrosoferric oxide, propylene glycol and shellac.*

The Applicant accepted the recommendation on October 6, 2022. Also, the Applicant updated the manufacturer information.
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Assessment of Product Quality-Related Information in the Container Labels and Carton Labeling

Container Labels

Information provided in the submission on September 20, 2022

(b) (4)

[redacted]

Assessment
The Applicant revised the original container label per DMEPA comments. The proposed container label is acceptable.

Carton Labeling:
The Applicant did not submit carton labeling.

ITEMS FOR ADDITIONAL ASSESSMENT
None

Yang Nan

Digitally signed by Yang Nan
Date: 10/06/2022 04:41:33PM
GUID: 520bd6c90002b3b0320380334e69a817

Sherita McLamore

Digitally signed by Sherita McLamore
Date: 10/07/2022 12:13:52PM
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BIOPHARMACEUTICS

NDA: 215814 [505(b)(1)]
Drug Product Name/Strength: REZLIDHI® (Olutasidenib) Capsule, 150 mg
Route of Administration: Oral
Proposed Indication: Relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation.
Applicant Name: Forma Therapeutics, Inc
Submission Date: 02/15/2022
Primary Reviewer: Kevin Wei, Ph.D.
Secondary Reviewer: Kevin Wei, Ph.D.
Recommendation: Approval

EXECUTIVE SUMMARY

Forma therapeutics, Inc. submitted this NDA 215814 for Olutasidenib Capsules, 150 mg, indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation. This Biopharmaceutics review focuses on the evaluation of the adequacy of the overall information/data supporting (i) in vitro dissolution method and acceptance criterion as quality control (QC) test, and (ii) need for bridging between the clinical and To-Be-Marketed (TBM) drug products.

In vitro dissolution methods and acceptance criterion:

Olutasidenib is a low soluble drug substance as per the BCS criteria. The Applicant proposed to implement a dissolution method of USP apparatus 2 (paddle) with JP cage sinkers at 65 rpm in 500 ml of pH 2.2 McIlvaine's Buffer with 1.25% Sodium dodecyl sulfate (SDS) and set an acceptance criterion of Q=(b)(4)% in 45 minutes. The submitted method development data support the selected dissolution parameters and indicate that the proposed dissolution method is discriminating towards API particle size ((b)(4) (b)(4)). Therefore, the proposed dissolution method is deemed acceptable. The submitted dissolution data for clinical, registration and stability batches showed high variability, and if the dissolution acceptance criterion is tightened to Q=(b)(4)% in (b)(4) minutes, all submitted batches would require S2 testing and 21% of them would require S3 testing. Considering the median (range) T_{max} for the proposed product is approximately 4 (1, 8) hours and dissolution may not be the rate limiting step (BCS IV) in oral absorption, the proposed dissolution acceptance criterion of Q=(b)(4)% in 45 minutes is deemed acceptable.

Bridging:

There is no significant change to the formulation, drug substance, manufacturing site nor process between the clinical batches, registration (stability) batches and TBM products. No further bridging information/data are warranted to support this NDA.

Submitted documents assessed under NDA review

Document number	Date Received
SDN-1 Original submission	02/15/2022
SDN-26 (Response to Biopharmaceutics Information Request)	06/24/2022
SDN-30 (Response to Biopharmaceutics Information Request)	07/08/2022
SDN-32 (Response to Biopharmaceutics Information Request)	07/20/2022
SDN-33 (Response to Biopharmaceutics Information Request)	07/29/2022
SDN-36 (Response to Biopharmaceutics Information Request)	08/11/2022

RECOMMENDATION

From a Biopharmaceutics perspective, NDA 215814 for REZLIDHI® (Olutasidenib) Capsule, 150 mg, is recommended for **Approval**. The following dissolution method and acceptance criterion are deemed acceptable as QC test for the proposed drug product.

Acceptable/approved dissolution method and acceptance criterion:

USP Apparatus	USP apparatus 2 (paddle) with JP cage sinkers
Rotation Speed	65 rpm
Temperature	37 ± 0.5°C
Volume	500 mL
Dissolution medium	McIlvaine Buffer, pH 2.2 with 1.25% SDS
Acceptance criterion	Q= (b) (4) % in 45 minutes

BIOPHARMACEUTICS REVIEW

1. Drug Substance (DS) solubility and permeability

The Applicant submitted solubility profile data of DS in aqueous media of pH 2 to pH 10.

Table 1. Aqueous solubility for olutasidenib (FT-2102) drug substance
(*M 3.2.P.2 (0032) Drug product/Dissolution Development Report,* Table 7, Page 44)

Sample	Final pH	[FT-2102] (µg/mL)
50 mM Phosphate pH 2	1.93	0.44
50 mM Citrate pH 3	2.89	0.54
50 mM Citrate pH 4	4.12	0.38
50 mM Citrate pH 5	5.04	0.33
50 mM Citrate pH 6	5.99	0.29
50 mM Phosphate pH 7	6.96	0.27
50 mM Phosphate pH 8	8.21	0.32
50 mM Borate pH 9	9.19	0.34
50 mM Borate pH 10	10.14	0.31
Water	8.93	0.44
1% Poloxamer 188	8.61	1.10
1% Tween 80	8.78	47.70
1% SDS	9.11	807.40
(b) (4)		
0.1 N HCl	1.07	0.696
0.1 N HCl w/ 50 mM NaCl	1.08	0.930
0.1 N HCl w/ 100 mM NaCl	1.08	1.261
0.1 N HCl w/ 200 mM NaCl	1.07	1.144
200 mM Phosphate Buffer	1.99	0.756
200 mM Phosphate Buffer	7.91	0.202
McIlvaine Buffer	2.20	2.777
McIlvaine Buffer	5.03	0.652
McIlvaine Buffer	7.98	0.328

Olutasidenib showed low aqueous solubility, high *in vitro* permeability (Caco-2 cell), but low *in vivo* permeability (Mass Balance Study 2102-HVS-104).

Reviewer's Assessment:
The submitted data indicate that olutasidenib is a low soluble DS (BCS IV) as per the BCS criteria.

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(b) (4)

3. Evaluation of discriminating ability

3.1 API particle size

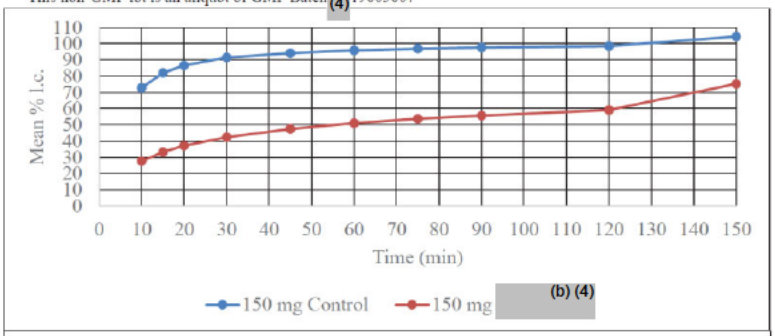
According to the Applicant, DS particle size is (b) (4) (b) (4). The Applicant evaluated the discriminating ability of the proposed dissolution method using Olutasidenib Capsules manufactured (b) (4) (b) (4)

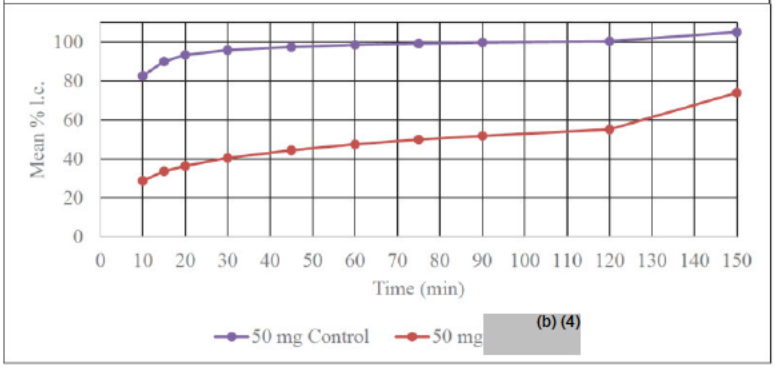
Figure 2. Comparison of dissolution profiles of Olutasidenib Capsules manufactured (b) (4)

(*M 3.2.P.2 (0032) Drug product/Dissolution Development Report,* Figure 2/3, Page 54)

Capsule Strength	Lot Number Drug Product	Drug Substance	Description	Particle Size (µm)		
				D_{10}	D_{50}	D_{90}
150 mg	18/779-27	Lot 00295-62-1[1]	(b) (4)			
	M10804 (bulk) M10840 (FP)	Lot (b) (4) 18103336				
50 mg	192298-88	Lot 00295-62-1				
	M10803 (bulk) M10838(FP)	Lot (b) (4) 18103336				

[1]This non-GMP lot is an aliquot of GMP Batch (b) (4) 19063067





Reviewer's Assessment:

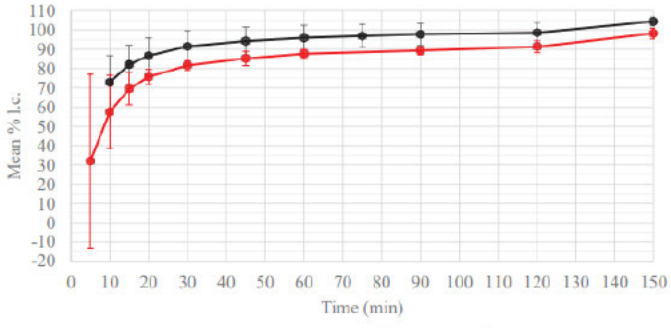
A DS specification of D_{90}< (b) (4) µm is proposed for the (b) (4) DS. The submitted data showed incomplete dissolution for Olutasidenib Capsules manufactured (b) (4) (b) (4), indicating that the proposed method is discriminating towards API particle size ((b) (4)).

3.2 Critical formulation variables

The Applicant evaluated the discriminating ability of the proposed dissolution method towards level (b) (4)% (target) vs. (b) (4)%) of (b) (4) in the formulation.

Figure 3. Comparison of dissolution profiles of Olutasidenib Capsules manufactured with (b) (4)% (target) and (b) (4)% (b) (4)

(*M 3.2.P.2 (0032) Drug product/Dissolution Development Report,* Figure 4, Page 55)



Mean Data	Minutes									
	10	15	20	30	45	60	75	90	120	150
Dissolution Profile with (b) (4)										
Mean	73	82	87	92	94	96	97	98	99	104
Max.	(b) (4)									
Min.										
% RSD	13.9	10.2	9.2	8.1	7.2	6.5	6.0	5.6	5.2	2.3
Dissolution Profile with (b) (4)										
Mean	58	70	76	82	85	88	-	89	91	98
Max.	(b) (4)									
Min.										
% RSD	19.1	8.3	3.9	2.4	3.7	2.2	-	2.2	3.1	2.7

Reviewer's Assessment:

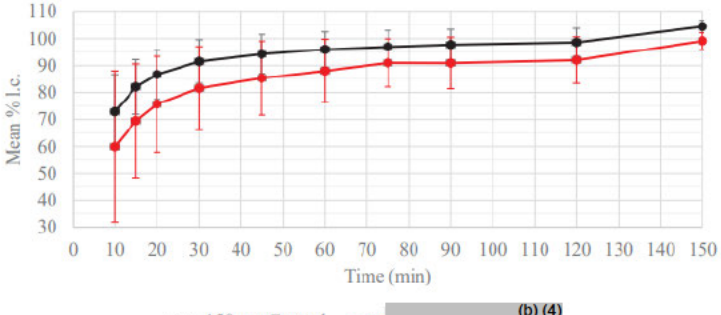
The submitted data indicate that an increased level of (b) (4) may slow the dissolution, but the proposed method may not have adequate discriminating ability to reject the aberrant batch used in the study.

3.3 Critical process parameters

The Applicant evaluated the discriminating ability of the proposed dissolution method towards (b) (4) using Olutasidenib Capsules manufactured using a (b) (4) (b) (4)), compared to the control batch manufactured with (b) (4) (b) (4)

Figure 4. Comparison of dissolution profiles of Olutasidenib Capsules manufactured with target and deviant [redacted] conditions

(*M 3.2.P.2 (0032) Drug product/Dissolution Development Report,* Figure 5, Page 57)



Mean Data	Minutes									
	10	15	20	30	45	60	75	90	120	150
Dissolution Profile – Control [redacted]										
Mean	73	82	87	92	94	96	97	98	99	104
Max.	[redacted]									
Min.										
% RSD	13.9	10.2	9.2	8.1	7.2	6.5	6.0	5.6	5.2	2.3
Dissolution Profile – [redacted]										
Mean	60	70	76	82	85	88	91	91	92	99
Max.	[redacted]									
Min.										
% RSD	28.1	21.1	17.7	15.5	13.7	11.7	8.9	9.5	8.6	3.1

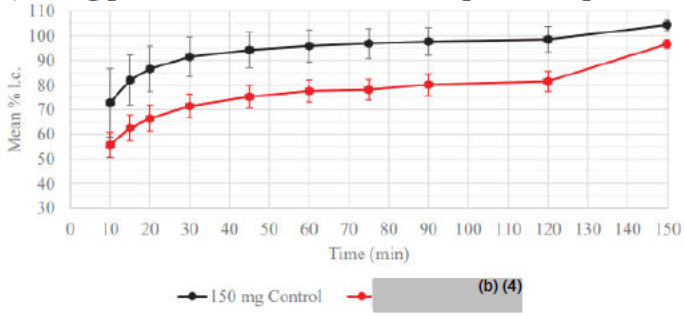
Reviewer's Assessment:

The submitted data indicate that a [redacted] and [redacted] may slow dissolution, but the proposed method may not have adequate discriminating ability to reject the aberrant batch used in the study.

In addition, the Applicant evaluated the discriminating ability of the proposed dissolution method towards the type of manufacturing process using drug product manufactured using [redacted] (proposed) vs [redacted].

Figure 5. Comparison of dissolution profiles of Olutasidenib Capsules manufactured [redacted]

(*M 3.2.P.2 (0032) Drug product/Dissolution Development Report,* Figure 6, Page 58)



Reviewer's Assessment:

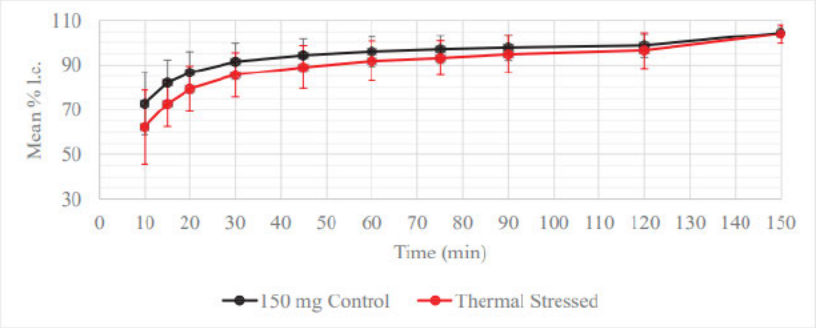
The submitted data indicate that the proposed method is discriminating towards the type of manufacturing process ([redacted] vs [redacted]), but the submitted study may

not be considered appropriate for the evaluation of discriminating ability of the proposed method towards meaningful CPPs due to the change of entire process.

3.4 Thermal stress conditions

The Applicant evaluated the discriminating ability of the proposed dissolution method towards thermal stress conditions using the drug product stored under stress conditions (60 °C for 10 days), compared to unstressed drug product stored at room temperature.

Figure 6. Comparison of dissolution profiles of Olutasidenib Capsules stored under thermal stressed and unstressed conditions
(*M 3.2.P.2 (0032) Drug product/Dissolution Development Report,* Figure 7, Page 59)



Reviewer's Assessment:
A slightly slower dissolution was observed from the drug product stored under heat stress conditions (60 °C, 10 days), compared to unstressed drug product stored at RT.

4. Evaluation of dissolution acceptance criterion

According to the Applicant, the currently proposed dissolution method (NBR-05438) [USP 2 (paddle) with JP cage sinkers, 65 rpm, 500 ml of pH 2.2 McIlvaine's Buffer with 1.25% SDS] was developed and validated after the registration batches passed the 24-month stability pull time. Two previous dissolution methods (b) (4) (b) (4) (b) (4) were used for the stability studies for the registration/clinical/stability batches (M10779, M10840 and M10841) and clinical batches (15H170, M10435 and M10570). The stability data (*M 3.2.P.8.3 (0001)*) using previous dissolution methods showed no significant trend in dissolution through the stability studies.

The Applicant proposed an acceptance criterion of NLT (b) (4)% in 45 minutes with the currently proposed dissolution method (NBR-05438). In the IR response dated 07/20/2022 (SDN32), the Applicant submitted dissolution profile data (n=12) for clinical batches (M10570, M10966 and M11672) and registration//clinical/stability batches (M10779, M10840, M10841) using the proposed dissolution method (NBR-05438). The age and storage conditions for each batch at the time of dissolution testing were also provided.

Table 6. Dissolution profile data for clinical batch M10570 (Mfg. Date: 06/13/2018)
(*M 1.11.1 (0032) Quality Information Amendment,* Table 7, Page 7)

Vessel	USP Stage	Minutes									
		10	15	20	30	45	60	75	90	120	150
1		(b) (4)									
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
Mean		65	71	76	80	83	85	86	87	88	101
Max.		(b) (4)									
Min.											
%RSD		8.6	7.3	7.6	6.9	6.6	5.9	5.7	5.1	5.0	2.6

Table 7. Dissolution profile data for clinical batch M10966 (Mfg. Date: 10/18/2019)
(*M 1.11.1 (0032) Quality Information Amendment,* Table 8, Page 8)

Vessel	USP Stage	Minutes									
		10	15	20	30	45	60	75	90	120	150
1		(b) (4)									
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
Mean		73	79	82	86	89	89	91	91	93	101
Max.		(b) (4)									
Min.											
%RSD		10.3	9.3	6.8	6.2	5.8	5.9	5.5	5.4	5.1	3.9

Table 8. Dissolution profile data for clinical batch M11672 (Mfg. Date: 08/11/2021)
(*M 1.11.1 (0032) Quality Information Amendment,* Table 9, Page 9)

Vessel	USP Stage	Minutes									
		10	15	20	30	45	60	75	90	120	150
1		(b) (4)									
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
Mean		63	76	83	89	93	95	97	98	99	103
Max.		(b) (4)									
Min.											
%RSD		26.8	14.6	10.9	9.0	7.3	6.2	4.4	3.6	3.5	4.0

Table 9. Dissolution profile data for registration batch M10779 (Mfg. Date: 12/12/2018)
(*M 1.11.1 (0032) Quality Information Amendment,* Table 10, Page 10)

Vessel	USP Stage	Minutes									
		10	15	20	30	45	60	75	90	120	150
1		(b) (4)									
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
Mean		64	75	79	83	86	88	90	91	92	102
Max.		(b) (4)									
Min.											
%RSD		18.2	18.3	16.5	14.0	12.3	11.1	9.7	9.0	8.3	4.0

Table 10. Dissolution profile data for registration batch M10840 (Mfg. Date: 01/08/2019)
(*M 1.11.1 (0032) Quality Information Amendment,* Table 11, Page 11)

Vessel	USP Stage	Minutes									
		10	15	20	30	45	60	75	90	120	150
1		(b) (4)									
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
Mean		68	80	85	89	92	94	96	96	98	103
Max.		(b) (4)									
Min.											
%RSD		14.6	12.3	10.9	9.7	8.4	7.1	6.2	5.8	5.2	3.7

Table 11. Dissolution profile data for registration batch M10841 (Mfg. Date: 01/15/2019)
(*M 1.11.1 (0032) Quality Information Amendment,* Table 12, Page 12)

Vessel	USP Stage	Minutes									
		10	15	20	30	45	60	75	90	120	150
1		(b) (4)									
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
Mean		72	82	87	92	95	97	99	100	102	107
Max.		(b) (4)									
Min.											
%RSD		10.6	7.9	8.0	7.8	7.8	7.5	6.9	6.8	6.5	3.8

Reviewer's Assessment:

The Applicant proposed a shelf life of 36M and the submitted registration batches (M10779, M10840 and M10841) (b) (4) and clinical batch M10570 (b) (4) have passed 36M shelf life at the time of dissolution testing. The submitted dissolution profile data from clinical batches M10966 (36M expiry date: 09/22) and M11672 (36M expiry date: 07/24) showed high variability and may support an acceptance criterion of Q= (b) (4)% in (b) (4) minutes (S2 testing is required for both 30- and 40-minute timepoints). Therefore, a dissolution criterion of Q= (b) (4)% in (b) (4) minutes was recommended via Biopharmaceutics IR dated 07/28/2022. As per the IR response dated 07/29/2022 (SDN33), the Applicant stated that a higher probability that S2 testing would be required on most batches if Q= (b) (4)% in (b) (4) minutes is implemented, probably due to the (b) (4) (b) (4). To further evaluate the Applicant's response and proposed acceptance criterion of Q= (b) (4)% in 45 minutes, the Applicant was requested to provide all available complete dissolution profile data for the clinical, registration and stability batches of less than 36M-old using the proposed dissolution method, as well as dissolution profile data for clinical and registration batches that passed the 36M shelf life using the proposed dissolution method with (b) (4) (e.g., (b) (4)) in the dissolution medium. In the IR response dated 08/11/22 (SDN36), the Applicant submitted complete dissolution profile data for the available bathes as shown below using the currently proposed dissolution method.

Table 12. Listing of submitted batches using the proposed dissolution method
(M 1.11.1 (0036) Quality Information Amendment, Table 1, Page 2)

Stability Study/Transaction	Purpose	Manufacture Date	Age at Time of Testing	Storage Condition	Bulk Lot	Package Lot
TR 46367-2	CTM	13-Jan-18	45-months	Controlled RT	M10565	M10570
SSFO-22	Registration	12-Dec-18	36-months	25C/60% RH	M10769	M10779
SSFO-25	Registration	8-Jan-19	35-months	25C/60% RH	M10804	M10840
SSFO-27	Registration	14-Jan-19	35-months	25C/60% RH	M10806	M10841
TR 46367-3	CTM	8-Oct-19	29-months	Controlled RT	M10965	M10966
SSFO-32	Development	8-Oct-19	12-months	25C/60% RH	18/779-37	18/779-37
SSFO-34	CTM	11-Aug-21	4-months	25C/60% RH	M11659	M11672
SSFO-35	CTM	6-Oct-21	6-months	25C/60% RH	M11772	M11756
SSFO-35	CTM	6-Oct-21	6-months	40C/75% RH	M11772	M11756
SSFO-36	Pre-PV	3-Nov-21	Initial	25C/60% RH	T13407	211540-032
SSFO-36	Pre-PV	3-Nov-21	3-months	25C/60% RH	T13407	211540-032
SSFO-36	Pre-PV	3-Nov-21	6-months	25C/60% RH	T13407	211540-032
SSFO-36	Pre-PV	3-Nov-21	3-months	40C/75% RH	T13407	211540-032
SSFO-36	Pre-PV	3-Nov-21	6-months	40C/75% RH	T13407	211540-032
SSFO-39	CTM	30-Jun-22	Initial	25C/60% RH	M11999	M12006

The submitted dissolution data (M.3.2.P.5.2 (0036)) showed a high capsule-to-capsule variability with RSD over 5% for all submitted batches at 60-minute timepoint. If the dissolution acceptance criterion is tightened to Q= (b) (4)% in (b) (4) minutes, all submitted batches would require S2 testing and 21% of the batches would require S3 testing. For 45-minute timepoint, the incidence of batches requiring S2 testing is still greater than 80%. In addition, the Applicant submitted the pictures of capsule (b) (4)

(b) (4) observed during the dissolution testing. However, the dissolution data from the expired clinical/registration batches indicated that the use of (b) (4) in dissolution medium showed no improvement in intra-batch variability.

(b) (4)

Based on the totality of provided dissolution data (in IR responses), and considering the median (range) T_{max} for the proposed product is approximately 4 (1, 8) hours and dissolution may not be the rate limiting step (BCS IV) in oral absorption, the proposed dissolution acceptance criterion of Q=(b) (4)% in 45 minutes is deemed acceptable.

5. Bridging

According to the Applicant, the formulation development was initiated at (b) (4) (b) (4) and later transferred to Metrics Contract Services (Metrics) for process development and manufacture. (b) (4) performed lab-scale development studies with a fit-for-purpose, phase-appropriate formulation. Metrics modified the formulation slightly (b) (4) According to the IR response dated 07/08/2022 (SDN30), the Applicant confirmed that these development batches were not used in any clinical studies.

Table 13. Summary of formulation development for Olutasidenib Capsules
(*M 3.2.P.2 (0032) Drug product/Dissolution Development Report*, Table 7, Page 10)

(b) (4)

According to the Applicant, the clinical batches used in the pivotal study (2102-HEM-101), registration/stability batches and the proposed TBM product have the same formulation (M.2.7.1 *Summary of Biopharmaceutic Studies and Associated Analytical Methods*).

Table 14. Formulation of clinical, registration and TBM products
(*M 3.2.P.2 (0032) Drug product/Dissolution Development Report,* Table 1, Page 4)

Component	Nominal mg/Capsule	Wt %/ Capsule	Function	Quality Standard
(b) (4) olutasidenib	150.0 mg	(b) (4)	Active ingredient	In-house
Microcrystalline Cellulose NF (b) (4)	(b) (4)		(b) (4)	NF/Ph. Eur.
Croscarmellose Sodium NF				NF/Ph. Eur.
Magnesium Stearate NF				NF/Ph. Eur.
Hard gelatin, capsule shell, size 00, white opaque[2]				(b) (4)
Fill weight (b) (4) **per capsule**		100%		

Ph. Eur. = European Pharmacopeia; NF = National Formulary; Wt = weight.
[1] (b) (4)
[2] commercial capsules will have black ink imprint

Table 15. Clinical and registration batches used in pivotal Study 2102-HEM-101
(*Module 1.11.1 (0021) dated 06/02/22,* Table 1, Page 1)

Drug Product Lot No.	Date of Manufacture	API Manufacturer, Lot #	Phase I	Used in pivotal Phase II (Cohort 1)	Phase II[a]
15H170	15 Sept 2015	(b) (4) BF0609	X	X	X
M10435	14 Dec 2017	(b) (4) 3H0753	X	X	X
M10570	13 June 2018	(b) (4) 18043747	X	X	X
M10779	12 Dec 2018	18103335	X	X	X
M10840	8 Jan 2019	18103336	X	X	X
M10841	14 Jan 2019	18103337	X	X	X
M10965	08 Oct 2019	19083140	X		X
M11672	11 Aug 2021	20072893	X	X	X

X denotes that this batch has been used in the specified Phase of Study 2102-HEM-101
[a] Includes Cohorts 2-8 in Phase II portion of Study 2102-HEM-101

According to the Applicant (*M. 3.2.P.5.4 Batch Analysis*), the clinical batches 15H170, M10435 and M10570 were manufactured at Metrics using DS batches (b) (4) BF0609, (b) (4) BH0753 and (b) (4) 18043747, respectively. The registration batches M10779, M10840 and M10841 were manufactured at Metrics using DS batches (b) (4) 18103335, (b) (4) 18103336 and (b) (4) 18103337, respectively. According to the IR response dated 07/08/2022 (SDN30), the (b) (4) DS batches BF0609 and BH0753 ((b) (4)) were (b) (4)

Table 16. DS and formulation for clinical and registration batches used in pivotal study (*M 1.11.1 (0030) Quality Information Amendment,* Table 2, Page 1)

Batch use	DP Lot number	DS Lot number	DS Lot number (Final DS Lot number)	Formulation Composition		
				Component	mg/capsule	%w/w
Clinical	15H170	BF0609	NA[1]	FT-2102 (b) (4)	150.0	(b) (4)
	M10435	BH0753	NA[1]	Microcrystalline Cellulose (b) (4)	(b) (4)	
	M10570	(b) (4) 8023509	(b) (4) 8043747	Croscarmellose Sodium		
	M10965	19073069	19083140	Magnesium Stearate, (b) (4)		
	M11672	20032560	20072893	Hard gelatin Capsule shell, size 00 white/white opaque		
Registration	M10779	18054008	18103335	Fill weight (b) (4) per capsule		100
	M10840	18054007	18103336			
	M10841	18054006	18103337			
Proposed Commercial	TBD	20046569	20086894			
	TBD	20046570	20086895			
	TBD	20046571	20086896			

(b) (4) was performed as part of drug product manufacturing at (b) (4)

In the IR response dated 07/20/2022 (SDN32), the Applicant submitted the dissolution comparison between the clinical (M10570, M10966, M11672) and registration (M10779, M10840, M10841) batches using the proposed dissolution method (see Section 4 above: Table 6-11). Similar dissolution profiles between the unexpired clinical batches (M109666 and M11672) and registration batches were observed.

Table 17. Dissolution profile comparison between the clinical and registration batches (*M 1.11.1 (0032) Quality Information Amendment,* Table 12, Page 12)

Clinical Lot Number	Manufacture Date	36M Expiration Date	f1 (M10779)	f2 (M10779)	f1 (M10840)	f2 (M10840)	f1 (M10841)	f2 (M10841)
M10570	13-Jun-2018	May-21	3.7	74	9.6	53	12.5	47
M10966	18-Oct-2019	Sep-22	5.7	65	3.6	73	4.9	66
M11672	11-Aug-2021	Jul-24	5.6	64	2.0	80	4.2	69

In addition, the submitted dissolution profile data for the drug product with and without black ink (b) (4) on capsule shell using previous dissolution method showed no impact of ink (b) (4) on capsule shell on dissolution (USP 2 (paddle) at 75 rpm) (*M 3.2.P.2 (0032) Drug product/Dissolution Development Report,* Table 15, Page 19), indicating there is a low risk that the ink (b) (4) may impact the dissolution and *in vivo* performance.

Reviewer's Assessment:

The submitted data and information indicate that there is no significant change to the formulation, drug substance, manufacturing site nor process between the clinical batches, registration (stability) batches and proposed TBM products. No further bridging data and information are warranted to support this NDA.

Kevin Wei

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