CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216340Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA OPQ Review and Evaluation

NDA 216340
Review # 01

OPQ RECOMMENDATION: APPROVAL

Drug Substance Retest Period: The proposed initial retest period is [redacted]. The proposed storage conditions are [redacted]
FDA Assessment: Retest date of [redacted] may be granted when stored at the proposed storage conditions.

Drug Product Expiration Dating Period: The proposed initial expiration dating period is [redacted]. The proposed storage conditions are "Store at 20°C to 25°C (68°F to 77°F). Excursions permitted from 15°C to 30°C (59°F to 86°F)''
FDA Assessment: An expiration dating period of 27 months may be granted when stored at the proposed storage conditions.

Drug Name/Dosage Form	Krazati (adagrasib) / Tablet
Strength	200 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Indication	Treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with KRAS G12C mutation as determined by an FDA approved test, and who have received at least one prior systemic therapy
Applicant	Mirati Therapeutics, Inc
US agent, if applicable	Not Applicable

[FDA will complete these sections.]

Submit Date(s)	**December 14, 2021**
Received Date(s)	**December 14, 2021**
PDUFA Goal Date	**December 14, 2022**
Division/Office	**Division of Oncology 2/Office of Oncologic Diseases**
Review Completion Date	**August 12, 2022**
Established Name	**Adagrasib**
(Proposed) Trade Name	**Krazati**
Pharmacologic Class	**Inhibitor of the RAS GTPase family**

FDA assessment is indicated in colored fonts

Recommendation on Regulatory Action	**Approval**

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA submission	12/14/2021	All
Quality amendment	5/3/2022	Biopharm, DP
Quality amendment	5/13/2022	Biopharm
Quality Amendment	6/8/2022	DMEPA, DP
Quality Amendment	6/29/2022	DS
Quality Amendment	7/8/2022	OPMA
Quality Amendment	7/28/2022	Biopharm
Quality Amendment	8/5/2022	DP

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Rajan Pragani	Haripada Sarker
Drug Product	Olen Stephens	Xing Wang
Manufacturing	Diane Goll	Zhaoyang Meng
Biopharmaceutics	Kevin Wei	Anitha Govada
Regulatory Business Process Manager	Rabiya Haider	-
Application Technical Lead	Xing Wang	-
ORA Lead	N/A	-
Environmental	Olen Stephens	Xing Wang

RELATED/SUPPORTING DOCUMENTS

DMFs:

[Applicant will complete]				[FDA will complete]	
DMF #	**Type**	**Holder**	**Item Referenced**	**Status**	**Comments**
(b) (4)	III		(b) (4)	Active	Supports several approved A/NDAs
	III			Active	Supports several approved A/NDAs
	III			Active	Supports several approved A/NDAs
	III			Active	Supports several approved A/NDAs
	III			Active	Supports several approved A/NDAs
	III			Active	Supports several approved A/NDAs
	III			Active	Supports several approved A/NDAs
	III			Active	Supports several approved A/NDAs

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	138735	Indication: Treatment of patients with advanced solid tumors with *KRAS* G12C mutation
IND	146808	Indication: Treatment of patients with advanced solid tumors with *KRAS* G12C mutation
IND	151272	Indication: Treatment of patients with advanced non-small cell lung cancer (NSCLC) with *KRAS* G12C mutation

IND	152345	(b) (4)
IND	152385	Indication: Treatment of patients with advanced non-small cell lung cancer (NSCLC) with *KRAS* G12C mutation
IND	154921	Indication: Treatment of patients with advanced solid tumors with *KRAS* G12C mutation

CONSULTS

[FDA will complete this section.]

None

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EVALUATION OF THE QUALITY INFORMATION

1. EXECUTIVE SUMMARY

[FDA ATL will complete this section.]

a. Summary of Rationale for Recommendation:

The applicant provided sufficient information to assure the identity, strength, purity, and quality of the proposed drug product. No further in vitro bridging data and information is warranted to support this NDA, and the additional in vivo bridging data will be assessed by Clinical Pharmacology (pending). Another key review issue (cGMP status of one packaging facility) has been adequately resolved. The labels and labeling include adequate quality information as required. All associated manufacturing, testing, packaging facilities were deemed acceptable. Based on the OPQ review team's evaluation of the information provided in the submission, OPQ recommends APPROVAL of NDA 216340 for Krazati (adagrasib) Tablets, 200 mg, for oral use.

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

Recommendation by Subdiscipline:

Drug Substance	-	Adequate
Drug Product	-	Adequate
Quality Labeling	-	Adequate
Manufacturing	-	Adequate
Biopharmaceutics	-	Adequate
Microbiology	-	Adequate

Life Cycle Considerations:

[FDA ATL to include any life-cycle considerations here]

None

2. APPLICATION BACKGROUND

Include information such as IND references, BTD/Fastrack/Orphan designations, etc.

Date	Summary of Events
29 October 2018	IND 138735 submitted
28 November 2018	IND 138735 Study May Proceed letter received
23 March 2020	Request for Fast Track Designation submitted
20 May 2020	Fast Track Designation granted
30 April 2021	Request for Breakthrough Therapy Designation submitted.
24 June 2021	Breakthrough Therapy Designation granted
27 August 2021	Request for participation in RTOR pilot submitted
28 October 2021	Request for participation in RTOR pilot granted

3. SUMMARY OF CMC SPECIFIC PRESUBMISSION AGREEMENTS

The Applicant's Position:

1. A Type B CMC End of Phase 1 teleconference was held 02 September, 2020. The FDA agreed or commented on CMC development and registration plans to support the overall MRTX49 registration program. Meeting agreements included:

   - The FDA requested drug substance stability data through 12 months storage at the long-term condition and 6 months at the accelerated condition when the NDA is submitted for the three (3) primary stability batches produced at (b) (4)
     - At the meeting discussion, the FDA noted they are comfortable with stability data through 9 months storage at the long-term condition and 6 months storage at the accelerated condition, for batches produced at the facility considered the primary one ((b) (4)), at the time the NDA is submitted and a retest date for the drug substance will be assigned based on the data available at the time of review.
   - The FDA agreed to accept the stability package in Table 32 of the briefing document which specified that six months of stability data for the three primary batches of drug product would be available at the time of the NDA submission.

2. A Type C CMC Guidance teleconference was held August 30, 2021 in order to discuss registration plans and address remaining CMC questions. Meeting agreements included:

- The FDA agreed that the proposed formulation bridging strategy appears acceptable and will assess the adequacy of the bioequivalence study results at the time of NDA review.
- The FDA agreed the proposal of submitting MRTX849 tablet as the sole commercial dosage form in the NDA submission with the proposed bridging strategy for the MRTX849 intended commercial tablet formulation to the capsule formulation used in the Phase 1 and 2 studies appears reasonable; however the submission must contain sufficient data to evaluate the dosage form used in the conducted clinical trials and to support the proposed commercial dosage form.
- The FDA agreed with the proposed drug substance (b) (4).
- The FDA noted that the proposed strategy for (b) (4) of the drug substance generally appears reasonable (b) (4)
- The FDA agreed that the proposed comparability strategy for the drug substance process changes between the registration stability batches and commercial batches generally appears reasonable; however, drug substance (DS) process changes may lead to the production of DS with different physical properties such as particle size distribution (PSD), densities, and flowability, etc., which could impact downstream drug product (DP) manufacturing and quality.
- The FDA agreed that drug substance manufactured (b) (4) appear comparable, and that stability data generated (b) (4) (used for registration stability batches) is expected to represent the stability of drug substance produced (b) (4).

The FDA's Assessment: ***Consistent with FDA's records***

The applicant's summary of the IND meetings and agreements is acceptable. The most significant remaining review issues for this NDA regard the (b) (4) drug substance, the bridging of the drug substance manufacturing sites/processes, and the bridging of the developmental data from early capsule formulations to the proposed tablet formulation.

4. ENVIRONMENTAL ASSESSMENT

The Applicant's Position:

In keeping with the Guidance for Industry "Environmental Assessment of Human Drug and Biologics Applications" July 1998, Mirati Therapeutics claims categorical exclusion and requests a waiver from the requirement to submit an environmental analysis in NDA 216340 for MRTX849 according to 21 CFR 25.31(b). For the proposed indication,

the amount of drug substance to be manufactured in association with anticipated commercial demand results in an estimated concentration of active moiety at the point of entry into the aquatic environment (EIC, Expected Introductory Concentration) of (b) (4) part per billion (ppb), below the 1 (ppb) threshold. Additionally, to the applicant's knowledge the drug is not a substance of special concern and no extraordinary circumstances exist for MRTX849 that would require submission of an environmental assessment (21 CFR 25.15(d)).

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

Mirati Therapeutics Inc. claims a categorical exclusion and requests a waiver from the requirement to submit an environmental analysis for the lorlatinib drug substance in NDA 216-340 according to 21 CFR 25.31(b). Mirati Therapeutics Inc. provided an estimated concentration of active moiety at the point of entry into the aquatic environment during marketing ((b) (4) ppb), which falls below the 1 part per billion (ppb) cutoff stipulated in 21 CFR 25.31. Mirati Therapeutics Inc. also certifies that, to the applicant's knowledge, no extraordinary circumstances exist with regard to MRTX849 (21 CFR 25.15(d)). The chemical structure of MRTX849 does not resemble pharmacophores for receptors of interest (estrogenic, androgenic, or thyroid hormone pathway activity). KRAS G12C inhibition has not been reported to be associated with endocrine disruption in either nonclinical or clinical studies.

5. FACILITIES

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

(b) (4)

99 Pages have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

(b) (4)

8. BIOPHARMACEUTICS

a. BCS Classification

In accordance with the criteria given in ICH M9 guideline, the drug substance is classified as a BCS Class II compound at the highest proposed dose of 600 mg per intake based on in vitro permeability and solubility data. MRTX849 drug substance solubility is pH-dependent with aqueous solubility at 37°C ranging from > 262 mg/mL at pH 1.2 to < 0.010 mg/mL at pH 6.8. As a result, the drug substance is classified as low solubility.

MRTX849 is assessed to have high permeability and be passively transported using a validated Caco-2 cell in-vitro method (efflux ratio of 1.28). The drug's permeability was shown to be higher than that of the co-dosed high-permeability internal standard, minoxidil, for which the human fraction absorbed is > 85%. In addition, MRTX849 demonstrates chemical stability in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) at 37°C.

Applicant to fill:	FDA assessment (FDA to fill): Based on the highest proposed single therapeutic dose of 600 mg, a minimum solubility of 2.4 mg/ml of DS is needed to be considered highly soluble as per BCS criteria. MRTX849 exhibits pH-dependent solubility (low solubility of less than 0.5 mg/mL at higher pH conditions of 4.5 and 6.8). Therefore the DS is considered to have low solubility (solubility data (*3.2.S.1.3 (0002)*).
BCS Classification: BCS II	Acceptable

DS has low solubility and could belong to either BCS class II or IV.

b. Dissolution Test

USP Apparatus	Paddle Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criterion
Paddle	75 rpm	900 mL	37°C	pH 6.8 phosphate buffer with 0.3% sodium lauryl sulfate (SLS)	Q = (b) (4)% at (b) (4) minutes

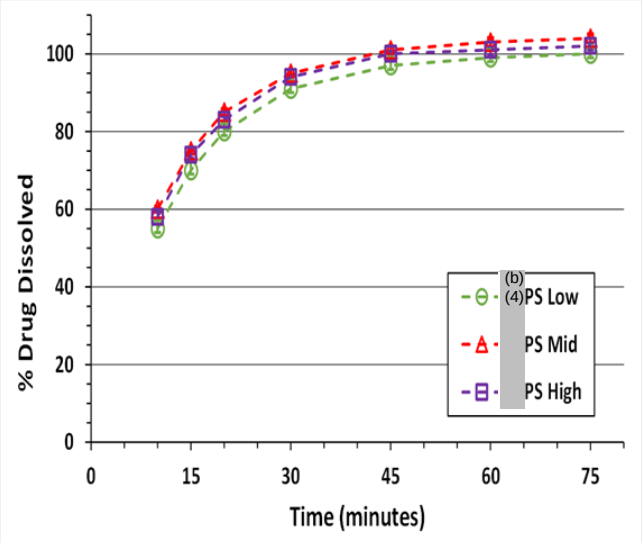
Biopharmaceutics Figure 1: Dissolution Profiles as a function of:

(b) (4)

(b) (4)

[redacted]

d. Impact of drug substance attribute on drug product dissolution measured with proposed test (n=12, ± SD): particle size



Individual vessel dissolution results for test method development are provided in Excel format in Section 3.2.P.5.4.

The average dissolution profiles of drug product batches made with drug substance of different particle sizes, ranging from d_{90} of (b) (4) µm to (b) (4) µm, are similar to each other. Thus, the proposed dissolution method is not discriminating towards the drug substance particle size, which is controlled by manufacturing process described in Section 3.2.S.2.6 and by testing acceptance criterion described in Section 3.2.S.4.1.

FDA Comment: The proposed dissolution method is not discriminating towards API particle size within the tested range (d_{90} of (b) (4) µm to (b) (4) µm) and rapid dissolution were observed for all test Tablets. The proposed specification for API particle size is set as D_{90} (b) (4) µM, and thus the test Tablet batches manufactured with API particle size of D_{90}= (b) (4) and (b) (4) µM (smaller-than-target) show similar and rapid dissolution profiles.

e. Impact of drug substance attribute on drug product dissolution measured with proposed test (n=12, ± SD): (b) (4)

(b) (4)

FDA Comment: The proposed dissolution method is not discriminating towards (b) (4). The Applicant submitted a relative bioavailability (BA) Study 849-011

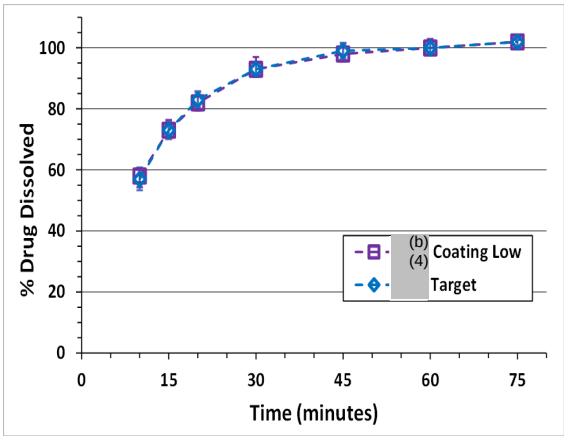
(Part 1-2) data to further demonstrate that the DS (b) (4) has no impact on oral bioavailability (refer to the internal discussion with Clinical Pharmacology reviewers under Type B meeting, dated 05/23/2022).

f. Impact of formula composition on drug product dissolution measured with proposed test (n=6, ± SD): (b) (4)

(b) (4)

FDA Comment: The proposed dissolution method has demonstrated discriminating ability towards a change in the levels of (b) (4) within the tested range and the submitted data indicates that test batch (b) (4) (relative to target value (%): (b) (4)) can be rejected when a dissolution acceptance criterion of Q= (b) (4)% in 30 minutes is implemented.

g. Impact of in-process control on drug product dissolution measured with proposed test (n=6 or 12, ± SD): coating weight gain

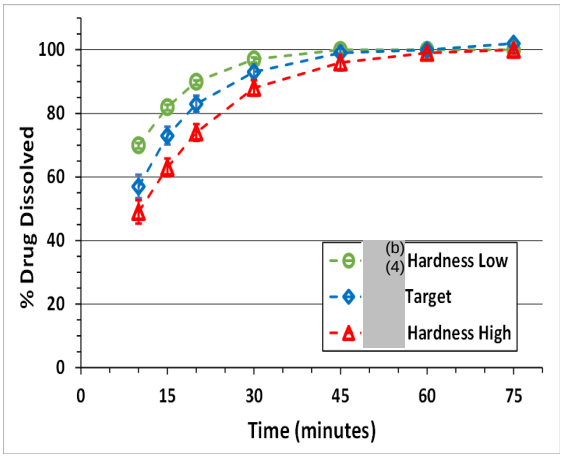


Individual vessel dissolution results for test method development are provided in Excel format in Section 3.2.P.5.4.

The average dissolution profiles of tablets manufactured with coating weight gain ranging from (b) (4) (low) to (b) (4) (target) are similar, which is consistent with the use of a cosmetic film-coat for the drug product. Thus, it can be concluded that the proposed test is not discriminating towards coating weight gain, which is controlled in the manufacturing process per Section 3.2.P.3.3 and Section 3.2.P.3.4.

FDA Comment: The proposed dissolution method is not discriminating towards coating weight gain within the tested range ((b) (4)).

h. Impact of in-process control on drug product dissolution measured with proposed test (n=6 or 12, ± SD): table hardness



Individual vessel dissolution results for test method development are provided in Excel format in Section 3.2.P.5.4.

The average dissolution profiles are different for tablet batches produced with low and high tablet hardness relative to the target drug product. Tablet dissolution rate is sensitive to variation in tablet hardness outside of established in-process control. Thus, it can be concluded that the proposed test is discriminating towards tablet hardness, which is controlled in the manufacturing process per Section 3.2.P.3.3 and Section 3.2.P.3.4.

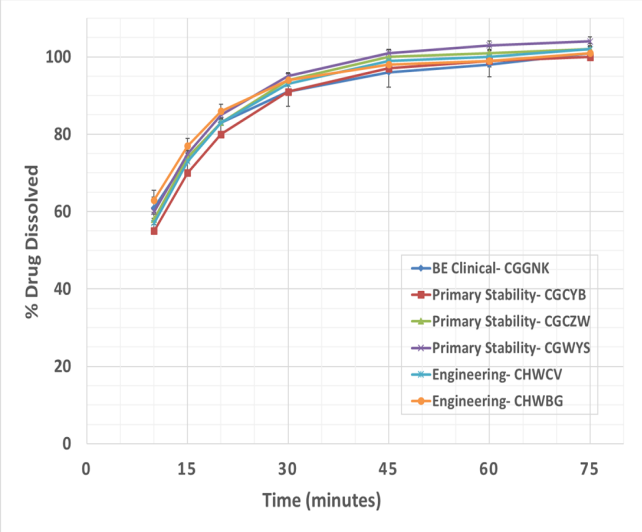
FDA Comment: The proposed dissolution method is discriminating towards the tablet hardness. The test product (b) (4) manufactured with higher hardness ((b) (4) kp), compared

to the target value ((b) (4)kp), may be rejected when a dissolution acceptance criterion of Q=(b) (4)% in 30 minutes is implemented.

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

Applicant to indicate whether complete dissolution profile data are available for all stability timepoints. Applicant to insert multipoint dissolution profile in a graphical format from clinical/PK and primary registration batches figure(s) here:

Dissolution profiles of drug product batches used in BE Study 849-015, primary stability studies and commercial scale manufacturing (engineering) and tested using proposed dissolution test (n=12, ± SD)



Individual vessel dissolution results for batches used in similarity (f2) comparisons are provided in Excel file format in Section 3.2.P.5.4.

Dissolution profile data is provided for all timepoints for primary stability studies in Section 3.2.P.8.3 with individual vessel data provided in Excel file format in Section 3.2.P.5.4.

Acceptance criterion of Q = (b) (4)% at (b) (4) minutes is proposed based on tablet batch release and primary stability study results along with discriminative capabilities of the method. Acceptance criterion for a single timepoint is proposed based on the design of the tablet for immediate release.

As required by ICH Q6A, an evaluation for tablet dissolution has been added to the specification as part of the overall drug product control strategy and is conducted per USP <711> using Apparatus 2, with a paddle speed of 75 rpm. Based on demonstrated discriminative capabilities, 900 mL of pH 6.8 phosphate buffer with 0.3% w/w SLS is the selected dissolution medium.

All batches of MRTX849 tablets tested with the proposed dissolution method have met the proposed specification at release and on accelerated and long-term primary stability. No significant change or trends have been observed up to 6 months at 25°C/60%RH and 40°C/75%RH.

Dissolution similarity factor (f2) was determined for batches used in primary stability studies and commercial scale batches relative to batch CGGNK used in BE Study 849-015. The f2 results (> 50) demonstrate similar

	dissolution profiles and are provided in Module 2.1.7 and Section 3.2.P.2.3.
FDA Comment: Based on the dissolution profile data from the BE clinical and stability batches and considering the dissolution data to support the discriminating ability of the proposed method, the proposed acceptance criterion of Q=(b)(4)% in (b)(4) minutes is too (b)(4), and hence is not acceptable. The Applicant was recommended to (b)(4) the dissolution acceptance criterion to Q=(b)(4)% in 30 minutes (Biopharmaceutics IR dated 05/11/22). In the IR response dated 05/13/22 (SDN 26)), the Applicant accepted FDA's recommendations and revised the drug product release and stability specifications in *M 3.2.P.5.1* and *M 3.2.P.8.1/3* accordingly. The Applicant's response and revised acceptance criterion to Q=(b)(4)% in 30 minutes are deemed acceptable.	

	Applicant to fill:	FDA assessment:
The dissolution method is discriminating for:		
i) Particle size distribution (PSD)	Not discrimitating	Agree
Link[1]: Tablet Dissolution Method Development Report		Page#: 22-23
ii) (b)(4)	Not discrimitating	Agree
Link[1]: Tablet Dissolution Method Development Report		Page#: 23-25
iii) Formulation variation (b)(4)	Not discrimitating	Agree
Link[1]: Tablet Dissolution Method Development Report		Page#: 25-26
iv) Formulation variation in (b)(4)	Discriminating	Agree
Link[1]: Tablet Dissolution Method Development Report		Page#: 25-26
v) Manufacturing process variation in coating weight gain	Not discrimitating	Agree
Link[1]: Tablet Dissolution Method Development Report		Page#: 27-28
vi) Manufacturing process variation in tablet hardness	Discriminating	Agree
Link[1]: Tablet Dissolution Method Development Report		Page#: 27-28

[1] **The applicant to provide link to the appropriate section in the submission. FDA reviewer may update the link as needed.**

c. Bridging Throughout Drug Product Development (Formulation, Process, or Site Change)

Figure 4: Schematic Representation of Drug Product Development

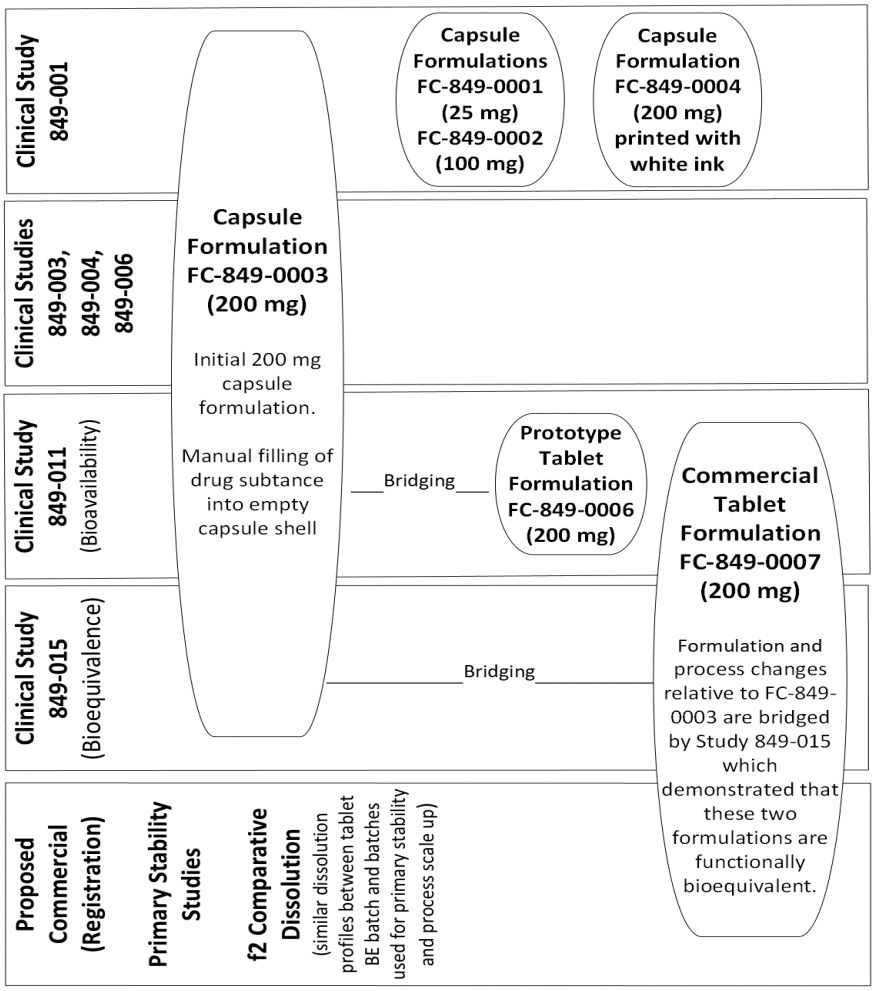


Table 36: Summary of MRTX Formulations, Changes Made and Rationale (Chronological Order)

Formulation	Dosage Form (mg Strength)	Used in Clinical Study[a]	Changes, Rationale and Bioequivalence Relative to Reference Product (Formulation FC-849-0003)
FC-849-0001	Capsule (25)	849-001	No change. Initial clinical formulation manufactured by filling drug substance into empty capsule shell.
FC-849-0002	Capsule (100)	849-001	No change. Initial clinical formulation manufactured by filling drug substance into empty capsule shell.

Formulation	Dosage Form (mg Strength)	Used in Clinical Study[a]	Changes, Rationale and Bioequivalence Relative to Reference Product (Formulation FC-849-0003)
FC-849-0003 (Clinical, Reference Product)	Capsule (200)	849-001, 849-003, 849-004, 849-006, 849-011, 849-015	No change. Initial clinical formulation manufactured by filling drug substance into empty capsule shell.
FC-849-0004 (Clinical)	Capsule (200)	849-001	Capsule shells are printed with white ink with no other changes to formulation or process. Change assessed not to impact product CQA (refer to batch analysis data in Section 3.2.P.5.4).
FC-849-0006 (Clinical)	Tablet (200)	849-011	Initial tablet formulation developed to enable manufacturing at pilot scale (b) (4) Bioequivalent to formulation 849-0003 (capsule) per Clinical Study 849-011 Part 1 [refer to Module 2.7.1].
FC-849-0007 (Clinical & Proposed Commercial)	Tablet (200)	849-011, 849-015	(b) (4) Changes assessed not to impact product CQA (refer to batch analysis data in Section 3.2.P.5.4 and stability data in Section 3.2.P.8.3). Functionally bioequivalent to formulation 849-0003 capsule per Clinical Study 849-015 [refer to Module 2.7.1].

[a] Reference clinical studies are the clinical studies in support of this NDA

Link:
Section 3.2.S.3.1
Section 3.2.P.2.2
Section 3.2.P.2.3
Section 3.2.P.5.4
Section 3.2.P.8.1
Module 2.7.1
Tablet Dissolution Method Development Report

The bridging of the reference capsule formulation (FC-849-0003) used in pivotal Clinical Study 849-001 and the proposed commercial tablet formulation (FC-849-0007) is summarized in Figure 4. A summary of formulation changes and rationale is provided in Table 36.

To confirm that the formulation changes summarized in Table 36 and drug substance (b) (4) did not impact oral bioavailability, formulations FC-849-0003 (capsule, 200 mg), FC-849-0006 (tablet, 200 mg) and FC-849-0007 (commercial tablet, 200 mg) were evaluated in healthy subjects.

In Clinical Study 849-011 Part 1, formulation FC-849-0003 capsules made with drug substance consisting of (b) (4) (designated as the reference product) or (b) (4) (designated as the test product) were shown to be bioequivalent, demonstrating that drug substance (b) (4) did not impact oral bioavailability. Additionally, formulation FC-849-0006 tablets (bulk batch CFWGK) was also confirmed to be bioequivalent to formulation FC-849-0003 (capsule, 200 mg, reference product), demonstrating that change in dosage form from capsule to tablet did not affect oral bioavailability.

In Clinical Study 849-015, the proposed commercial formulation FC-849-0007 tablets (bulk batch CGGNK) were confirmed to be functionally bioequivalent to reference formulation FC-849-0003 (capsule, 200 mg). Results from clinical studies 849-011 and 849-015 to support the bioequivalence of the capsule and tablet formulations are presented in Module 2.7.1.

As shown in the tablet dissolution method development report provided in Module 3 Section 3.2.P.2, similar dissolution profiles were observed between bulk tablet batches CFWGK and CGGNK (used in BA/BE studies 849-011 and 849-015) when tested using the proposed commercial test method. In addition, the average dissolution profiles of bulk tablet batches (CFWGK, CGGNK and CFKFG), manufactured with drug substance batches consisting of (b) (4) content ranging from (b) (4), are similar. The similar tablet dissolution profile results are consistent with results summarized above for Clinical Study 849-011 Part 1 and data presented in Module 3, Section 3.2.S.3.1 demonstrating that drug substance (b) (4) similar equilibrium solubility and dissolution profiles in biorelevant media.

The formulation (qualitative and quantitative composition) of the tablets utilized in the BE Study 849-015, primary stability batches (registration), and commercial batches are identical. While the BE clinical batch and primary stability batches have been produced at smaller scales, (b) (4), respectively, the proposed commercial batches will be produced at a larger scale ((b) (4) kg) with similar manufacturing process. In addition, the manufacturing equipment used for BE clinical batch, primary stability batches and commercial batches have the same operating principles and design (see Section 3.2.P.2.3).

To bridge process parameters and equipment size utilized from development to commercial batch size, comparative multi-point dissolution data profiles (n=12) were generated using the proposed commercial method to assess the in vitro dissolution equivalence of the MRTX849 immediate release film-coated tablets used in BE study 849-015, primary stability batches (registration) and commercial scale batches. Dissolution profiles of primary stability batches (CGWYS, CGCZW and CGCYB) and commercial scale batches (CHWCV and CHWBG) are similar (f_2 >50) to the tablet BE bulk tablet batch CGGNK.

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

According to the Applicant, the pivotal phase 1/2 study 849-001 (efficacy and safety) and phase 1 studies, 849-004 (renal impairment), 849-005 (mass balance) and 849-006 (DDI), were conducted using drug-in-capsule formulation FC-849-0001 (25 mg), 0002 (100 mg), 0003 (200 mg), and 0004 (200 mg), that were manufactured by filling (b) (4) into empty capsule shell (no excipients). Capsules FC-849-0001, 0002 and 0003 are clinical product in different strengths and Capsules FC-849-0004 (200 mg) and FC-849-0003 only differ in ink on the capsule shell.

Subsequently, the Applicant developed two Tablet formulations, FC-849-0006 (prototype) and FC-849-0007, that were both manufactured at (b) (4) using similar manufacturing process. Tablet FC-849-0007 were used in the ongoing clinical studies (e.g., Study 849-012), for the registration batches and proposed for the TBM product.

Tablets FC-849-0007 and FC-849-0006 differ in the following perspectives:

1) Tablet FC-849-0007 contains (b) (4), while Tablet FC-849-0006 contains (b) (4) (the impact of (b) (4) on BA was evaluated in BA study 849-011, Part 1_2).

2) Tablet FC-849-0007 contains (b) (4) along with proportional (b) (4), compared to Tablet FC-849-0006. It's noted that the change in the (b) (4) exceeds Level 2 criteria (b) (4) as per the SUPAC-IR Guidance, and hence Level 3 supporting documentation (in vivo bioequivalence) would be requested if this change is reported as an NDA supplement.

In vivo bridging:

The Applicant conducted relative bioavailability (BA) Study 849-011 (part 1 and 2) and bioequivalent (BE) Study 849-015 to bridge the clinical Capsule FC-849-0003 and TBM Tablet FC-849-0007.

In the part 1 of the BA Study 849-011, the Applicant conducted the relative BA studies under fasted condition between 1) Capsules FC-849-0003 (b) (4) and prototype Tablets FC-849-0006 (b) (4), and 2) Capsules FC-849-0003 (b) (4) and Capsules that contain (b) (4).

In the part 2 of the BA Study 849-011, the Applicant conducted the relative BA study between the clinical Capsules FC-849-0003 (b) (4) and TMB Tablet FC-849-0007 (b) (4).

In addition, the Applicant also conducted BE Study 849-015 between the clinical Capsules FC-849-0003 (b) (4) and TMB Tablets FC-849-0007 (b) (4). The summary of Capsule and Tablet batches used in the BA/BE studies (849-011 and 849-015) and the statistical analysis of the pharmacokinetic (PK) data and information are shown as below:

Capsules and Tablets batches used in the BA 849-011 and BE 849-015

(2.7.1 (0002), *Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 4 and 5, Page 13*)

Formulation Number	DP Batch Number	Clinical Studies 849-011 and 849-015 Disposition	DP Site	DP Date of Manufacturing	DS Batch Number	DS Site
FC-849-0003	1245870401 (packaged)	849-011 Part 1 and Part 2	(b) (4)	April 2020	CPo124587-03-06-01-75-01	(b) (4)
FC-849-0003	1264160101 (packaged)	849-011 Part 1		July 2020	CPo126416-01-01-01-29-01	
FC-849-0003	1245870402 (packaged)	849-015		May 2020	CPo124587-03-06-01-75-01	

(b) (4)

Formulation Number	DP Batch Number	Clinical Studies 849-011 and 849-015 Disposition	DP Site	DP Date of Manufacturing	DS Batch Number	DS Site
FC-849-0006	CFWGK (bulk), CFWGN (packaged)	849-011 Part 1	(b) (4)	May 2020	CPo124587-03-06-01-75-01	(b) (4)
FC-849-0007	CGGNK (bulk), CGGVK (packaged)	849-011 Part 2; 849-015		Sep 2020	CPo126416-01-01-01-29-01	

(b) (4)

BA 849-011: Part 1 1. Statistical analysis of the primary PK endpoints to assess the relative BA of (b) (4) Capsules (Reference) and Tablets (Test 1) (Fasted)

(5.3.1.1 (002) (849-011) Synopsis, Table 4, Page 10)

Parameter	Treatment	n	GLSM	Comparison	Ratio GLSM (%)	90% CI For the Ratio (%) Lower	90% CI For the Ratio (%) Upper	Within-subject CV (%)
AUC_{∞} (h*ng/mL)	R	23	12927.42					
	T1	23	12315.56	T1 vs R	95.27	84.93	106.86	22.9
AUC_{last} (h*ng/mL)	R	23	12886.28					
	T1	23	12272.80	T1 vs R	95.24	84.87	106.87	23.0
C_{max} (ng/mL)	R	23	514.13					
	T1	23	495.02	T1 vs R	96.28	86.59	107.06	21.1

AUC_{∞} = area under the plasma concentration-time curve from time zero to infinity; AUC_{last} = area under the plasma concentration-time curve from time zero to time of last measurable concentration; CI = confidence interval; C_{max} = maximum (peak) plasma drug concentration; GLSM = geometric least squares mean; ln = natural logarithm; n = number of subjects with valid observations;
R: 600 mg MRTX849 (b) (4)
T1: 600 mg MRTX84

BA 849-011: Part 1 2. Statistical analysis of the primary PK endpoints to assess the relative BA of (b) (4) Capsules (Reference) and (b) (4) Capsules (Test 2) (fasted)

(5.3.1.1 (002) (849-011) Synopsis, Table 5, Page 10)

Parameter	Treatment	n	GLSM	Comparison	Ratio GLSM (%)	90% CI For the Ratio (%) Lower	Upper	Within-subject CV (%)
AUC_{∞} (h*ng/mL)	R	22	12960.27					
	T2	22	12727.46	T2 vs R	98.20	86.66	111.28	24.5
AUC_{last} (h*ng/mL)	R	22	12918.32					
	T2	22	12676.64	T2 vs R	98.13	86.53	111.28	24.6
C_{max} (ng/mL)	R	22	513.91					
	T2	22	532.92	T2 vs R	103.70	92.47	116.29	22.4

AUC_{∞} = area under the plasma concentration-time curve from time zero to infinity; AUC_{last} = area under the plasma concentration-time curve from time zero to time of last measurable concentration; CI = confidence interval; C_{max} = maximum (peak) plasma drug concentration; GLSM = geometric least squares mean; ln = natural logarithm; n = number of subjects with valid observations;
R: 600 mg MRTX849 (b) (4)
T2: 600 mg MRTX84

BA 849-011: Part 2. Statistical analysis using average BE analysis to assess bioequivalence of (b) (4) Capsules (Reference) and (b) (4) Tablets (Test)

(5.3.1.1 (002) (849-011) Synopsis, Table 6, Page 11)

Parameter	Treatment	n	GLSM	Ratio (%) GLSM (T vs R)	90% CI For the Ratio (%) Lower	Upper	Within-subject CV (%)
AUC_{∞} (h*ng/mL)	R	35	14154.12				
	T	35	12582.72	88.90	79.98	98.81	26.6
AUC_{last} (h*ng/mL)	R	35	14102.37				
	T	35	12526.36	88.82	79.87	98.78	26.7
C_{max} (ng/mL)	R	35	558.67				
	T	35	483.07	86.47	77.53	96.43	27.4

AUC_{∞} = area under the plasma concentration-time curve from time zero to infinity; AUC_{last} = area under the plasma concentration-time curve from time zero to time of last measurable concentration; CI = confidence interval; C_{max} = maximum (peak) plasma drug concentration; GLSM = geometric least squares mean; ln = natural logarithm; n = number of subjects with valid observations;
R: 600mg MRTX849 (b) (4)
T: 600mg MRTX849

BE 849-015: Statistical analysis using average BE analysis to assess bioequivalence of (b) (4) Capsules (Reference) and (b) (4) Tablets (Test)

(5.3.1.1 (002) (849-011) Synopsis, Table 3, Page 9)

Parameter	Treatment	n	GLSM	GLSM Ratio (%) (T vs R)	90% CI for the Ratio (%) Lower	Upper	Within-subject CV%
AUC_{last} (h*ng/mL)	R (Reference)	51	14701.14				33.2
	T (Test)	51	13068.11	88.89	81.17	97.35	34.7
AUC_{∞} (h*ng/mL)	R (Reference)	51	14877.26				33.0
	T (Test)	51	13201.78	88.74	81.08	97.12	34.4
C_{max} (ng/mL)	R (Reference)	56	589.92				31.6
	T (Test)	56	501.96	85.09	76.71	94.38	48.4

AUC_{∞} = area under the plasma concentration-time curve from time zero to infinity; AUC_{last} = area under the plasma concentration-time curve from time zero to time of last measurable concentration; CI = confidence interval; C_{max} = maximum (peak) plasma drug concentration; GLSM = geometric least squares mean; n = number of subjects with valid observations
R: MRTX849 600 mg (3 × 200-mg) (b) (4)
T: MRTX849 600 mg (3 × 200-mg)

The study results from BA 849-011/Part 1 showed that the bridging for clinical Capsule FC-849-0003 (b) (4)) to prototype Tablet FC-849-0006 ((b) (4)) and (b) (4) Capsule met the BE criteria (80%-125%). However, two bioequivalence studies, BA 849-011/Part 2 and BE 849-015, failed to bridge clinical

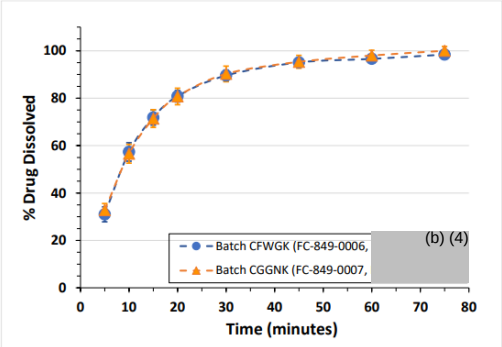
Capsule FC-849-0003 (b) (4)) and TMB Tablet FC-849-0007 ((b) (4)) (e.g., BA 849-011/part 2 failed on AUC and Cmax; BE 849-015 failed on Cmax).

According to the T-con meeting with Applicant (Type B, IND 138735) dated 05/23/2022, the Applicant proposed to submit additional PK data and information for Tablet FC-849-0007 from the ongoing Phase 3 Study 849-012 (600 mg BID arm) to support the in vivo bridging between the Capsules FC-849-0003 and Tablet FC-849-0007. The study results are expected to be reported to FDA in September 2022 and will be reviewed by the Clinical Pharmacology reviewer (pending)

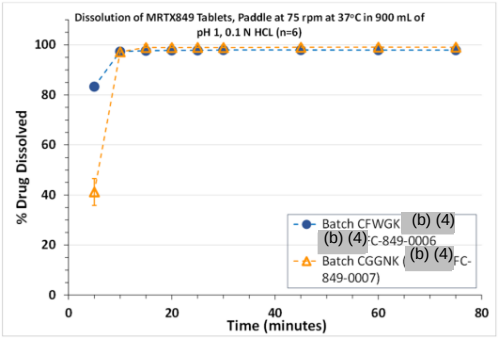
In vitro bridging:

Under IND 138735 (0292(297), dated 03/25/22), the Applicant submitted comparative dissolution profiles between batch CFWGK of prototype Tablet formulation FC-849-0006 and batch CGGNK of TBM Tablet formulation FC-849-0007 using USP apparatus 2 (Paddle) at 75 rpm in 900 mL of pH 6.8, 50 mM phosphate buffer with 0.3% w/w SLS (the proposed dissolution media) and in pH 1, 2 and 6.5 media.

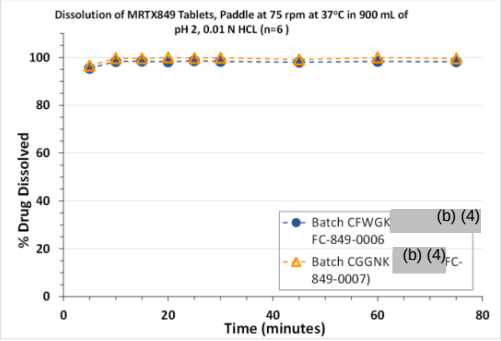
Dissolution profiles in pH 6.8 phosphate buffer with 0.3% w/w SLS



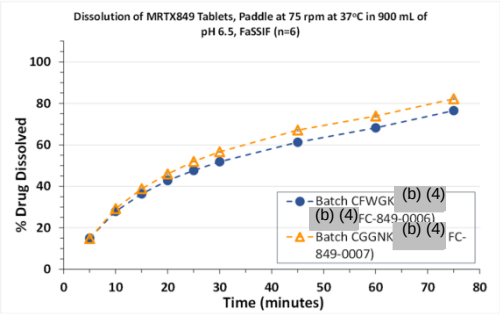
Dissolution profiles in 0.1N HCl (pH 1)



Dissolution profiles in 0.01N HCl (pH 2)



Dissolution profiles in FaSSIF (pH 6.5)



Similar dissolution profiles from prototype Tablet FC-849-0006 and TBM Tablet FC-849-0007 were observed using the proposed dissolution method and in pH 1, 2 and 6.5 media. However, the proposed formulation changes between the prototype and TBM Tablet formulations are identified as a Level 3 change, therefore the in vitro dissolution data is not sufficient to support a scientific bridge and in vivo bridging data is needed. Considering two in vivo BA and BE studies have failed to bridge the clinical Capsules FC-849-0003 and TMB Tablet FC-849-0007 (b) (4) and the in vivo clinical bridging results will take precedence over the in vitro dissolution results, in vivo bioequivalence data will be warranted.

In addition, similar dissolution profiles were observed between the primary stability batches (CGWYS, CGCZW and CGCYB) and commercial scale batches (CHWCV and CHWBG) (see section i above) and the study result supports the bridge between the registration and TBM products with respect to the minor changes in debossing.

From a Biopharmaceutics perspective, no further (in vitro) bridging data and information is warranted to support this NDA and the additional in vivo bridging data will be reviewed by the Clinical Pharmacology reviewer (pending).

d. Biowaiver Request

The Applicant's Position:

The NDA does not contain a biowaiver request.

Link: Page#:

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

Not Applicable. this is a single strength product (200 mg) that was used in the clinical studies.

e. Data to Support IVIVC and/or PBBM Modeling, If Applicable.

Not applicable. This NDA does not contain either IVIVC or PBBM modeling.

Link: Page#:

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

Not Applicable. No IVIVC or PBBM modeling was submitted in the current Application

9. LABELING

USPI

Highlights: ***Adequate***

Nonproprietary name 'adagrasib' is listed with a company code 'MRTX849™' for the proprietary name.

Section 2 (if relevant): ***Adequate***

No extemporaneous solution is allowed by the label and no dosage preparation is necessary.

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

200 mg tablets: immediate release, oval shaped, white to off-white, film coated tablets with "200" on one side and stylized "M" on the opposite side.

Section 11 Description: ***Adequate***

If the following excipients used in the drug product, include warning/declaration in the USPI:

- FD&C Yellow No.5 or No.6, as a color additive (21 CFR 201.20) is not used.
- Phenylalanine, as a component of aspartame (21 CFR 201.21) is not used.
- Sulfites (21 CFR 201.22) is not used.

The proprietary name 'MRTX849' will need to be replaced. The pharmacological class is listed for the nonclinical reviewer to confirm. The molecular formula and weight are provided. The IUPAC name is listed with the structure. The drug substance is described as a crystalline solid with solubility in aqueous media decreasing over the range pH 1.2 to 7.4 from >262 mg/mL to <0.010 mg/mL. The inactive ingredients are listed and the strength of the tablet complies with the salt nomenclature guidance (the active ingredient is not a salt).

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

The two container configurations (120-count and 180-count bottles are listed with a description of the container closure. The storage condition is standard USP controlled room temperature.

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

Provided.

Carton/Container Label ***Adequate***

The labels and carton containers accurately depict the strength of the tablets and container count. The manufacturer information is included with (b) (4). The storage conditions is standard USP controlled room temperature. Route of administration is listed. Lot number and expiration date space is designated.

The labels include (b) (4) DMEPA was consulted and they stated their current practice allows the inclusion of (b) (4).

(b) (4)

1 Page of Draft Labeling has been Withheld in Full as B4(CCI/TS) Immediately Following this Page

FINAL RISK ASSESSMENTS

[FDA will complete this section.]

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	Minimal changes observed	Low	Analytical method development coincided with accelerated clinical development. Mass balance and initial assay results seem to be outliers. Monitor analytical method changes and future batch/stability data for evidence of trending data or method instability. Individual impurity limits for (b) (4) and (b) (4) were negotiated based on (b) (4) . The applicant agreed to revise (lower) these limits with additional batch and stability data.
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low		Low	No epimerization observed
Content Uniformity	• Formulation • Container closure • Raw material • Process Parameters • Scale/equipment • Site	Low		Low	
(b) (4)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	Low		Low	
Microbial Limits	• Formulation	Low		Low	

	• Raw materials • Process parameters • Scale/equipment • Site				
Dissolution – BCS Class II & IV	• Formulation • Container Closure • Raw materials • Process parameters • Scale/equipment • Site	Low		Low	

RECOMMENDATION PAGE

[FDA will complete this section.]

Drug Substance: Approval

Primary Reviewer: Rajan Pragani — Date: August 2, 2022
Secondary Reviewer: Haripada Sarker — Date: August 5, 2022

Drug Product: Approval

Primary Reviewer: Olen Stephens — Date: August 8, 2022
Secondary Reviewer: Xing Wang — Date: August 12, 2022

Manufacturing: Approval

Primary Reviewer: Diane Goll — Date: August 3, 2022
Secondary Reviewer: Zhaoyang Meng — Date: August 3, 2022

Biopharmaceutics: Approval

Primary Reviewer: Kevin Wei — Date: July 13, 2022
Secondary Reviewer Anitha Govada — Date: July 13, 2022

Application Technical Lead: Approval

Xing Wang — Date: August 12, 2022

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/

XING WANG
08/15/2022 08:56:12 AM

RAJAN PRAGANI
08/15/2022 09:14:49 AM

HARIPADA SARKER
08/15/2022 09:55:22 AM
Adequate from DS perspective.

OLEN M STEPHENS
08/15/2022 10:00:47 AM

DIANE W GOLL
08/15/2022 12:46:25 PM

ZHAOYANG MENG
08/15/2022 12:56:05 PM

LINYI WEI
08/15/2022 01:04:43 PM

ANITHA P GOVADA
08/15/2022 01:19:05 PM