CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218213Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA OPQ Review and Evaluation

NDA 218213
Review # 01

OPQ RECOMMENDATION: APPROVAL

Drug Substance Retest Period: The repotrectinib storage condition is [redacted] with a [redacted]-month retest period.
FDA Assessment: Retest date of [redacted] months may be granted when stored at the proposed storage conditions

Drug Product Expiration Dating Period: The storage condition for repotrectinib capsules, 40 mg, is "Store at 20° to 25°C (68° to 77°F); excursions permitted between 15°–30°C (59°–86°F)" with a 36-month shelf life.
FDA Assessment: An expiration dating period of 36 months may be granted when stored at the proposed storage conditions.

[Applicant will complete this section.]

Drug Name/Dosage Form	Repotrectinib/Capsule
Strength	40 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Indication	Treatment of adult patient with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC)
Applicant	Bristol Myers Squibb
US agent, if applicable	N/A

[FDA will complete these sections.]

Submit Date(s)	March 27, 2023
Received Date(s)	March 27, 2023
PDUFA Goal Date	November 27, 2023
Division/Office	Division of Oncology 2/Office of Oncologic Diseases
Review Completion Date	October 3, 2023
Established Name	Repotrectinib
(Proposed) Trade Name	Augtyro
Pharmacologic Class	Adenosine triphosphate (ATP)-competitive small molecule inhibitor of ROS1, TRK, and ALK.

FDA assessment is indicated in colored fonts

Recommendation on Regulatory Action	Approval

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
#0002	*03/27/2023*	*API, DP, OPMA, and Biopharm*
#0015	*06/05/2023*	*DP, Biopharm*
#0021	*06/22/2023*	*OPMA*
#0022	*06/22/2023*	*Biopharm*
#0023	*06/22/2023*	*DP*
#0026	*07/03/2023*	*Biopharm*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Kabir Shahjahan	Haripada Sarker
Drug Product	Xiao Hong Chen	Xing Wang
Manufacturing	Yifan Wang	Zhaoyang Meng
Biopharmaceutics	Gerlie Gieser	Anitha Govada
Regulatory Business Process Manager	Janell Artis	
Application Technical Lead	Xiao Hong Chen	
ORA Lead		
Environmental	Xiao Hong Chen	Xing Wang

ORBIS Partner Agency Quality Review Team (To be redacted for FOIA)

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

APPEARS THIS WAY ON ORIGINAL

RELATED/SUPPORTING DOCUMENTS

DMFs:

[Applicant will complete]				[FDA will complete]	
DMF #	**Type**	**Holder**	**Item Referenced**	**Status**	**Comments**

(b) (4)	III	(b) (4)	Adequate	
	III		Adequate	
	III		Adequate	
	III		Adequate	
	III		Adequate	
	III		Adequate	

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

[Applicant will complete this section.]

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	130465	Treatment of advanced solid tumors harboring ALK, ROS1 or NTRK1-3 rearrangements

CONSULTS

[FDA will complete this section.]

Not applicable.

TABLE OF CONTENTS

Evaluation of the Quality Information

[Applicant to provide link to the data in m3 sections as appropriate]

DIFFERENCES IN M3 MODULE IN SUBMISSIONS TO DIFFERENT AGENCIES

[To the Applicant: Insert text here.] Report any differences in formulation, manufacturing, container closure system, presentation, etc. ***Do not include labeling differences***.

#	FDA (US)	Country 1	Country 2	Country 3	Country 4

APPEARS THIS WAY ON ORIGINAL

1. EXECUTIVE SUMMARY

NDA 218213 was submitted under 505(b)(1) for the Repotrectinib Capsules to treat adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC). Repotrectinib is a tyrosine kinase inhibitor (TKI). It received Fast Track, Breakthrough Therapy and Orphan Drug Designations. The NDA review will be participated in the ORBIS program with the following partner Agencies: HAS Singapore and Brazil.

Repotrectinib drug substance is manufactured at (b) (4) The commercial manufacturing process for the synthesis of repotrectinib drug substance (b) (4) (b) (4) (b) (4) Repotrectinib is referred to as BMS-986472 or TPX-0005 (designated as BMS-986472-01). Appropriate controls for release and stability testing have been established to ensure the quality of the drug substance batches manufactured under cGMP process. Based on available (b) (4) month long-term stability data the applicant's proposed (b) (4) month retest period when store at (b) (4) C is found acceptable.

Repotrectinib capsule, 40 mg is manufactured at (b) (4). Repotrectinib capsules are prepared by (b) (4) The commercial drug product is packaged in HDPE bottles (b) (4)

(b) (4) The proposed drug product regulatory specifications consisting of common tests for solid oral dosage forms are per ICH Q6A guidelines, and ensure the identity, quality, purity and strength of the drug product batches manufactured using the commercial manufacturing process when tested. Based on the available 24-month long-term stability data the applicant's proposed 36-months shelf life for the drug product when stored at 20°C to 25°C (68° to 77°F) with excursions permitted between 15°-30°C (59°-86°F) is found acceptable.

Repotrectinib exhibits the characteristics of a *BCS IV* (low solubility/low permeability) drug substance. The proposed dissolution specification has been tightened to Q= (b) (4)% at 20 minutes based on FDA's recommendation. All clinical studies used the proposed to-be-marketed formulation. The drug product lots produced at commercial scale by the proposed commercial drug product manufacturer (b) (4) using the proposed commercial (b) (4) capsules formulation and process and input API (b) (4) were used in the pivotal clinical trial, TRIDENT-1. The bridging between the clinical batches and the proposed commercial drug product batches has been found acceptable with the applicant's commitment to provide confirmatory dissolution profile data of three process performance qualification (PPQ) batches that possess the final commercial image of the repotrectinib 40 mg capsules

All drug substance and drug product manufacturing and controls facilities are found acceptable.

Life Cycle Considerations:
NA

2. APPLICATION BACKGROUND

[Applicant will complete this section.] Include information such as IND references, BTD/Fastrack/Orphan designations, etc.

A summary of key interactions during repotrectinib development program is presented in Table 1.

Table 1: Summary of Key Regulatory Interactions for Repotrectinib Development

Date	Content
30 Sep 2016	**Submission of IND and protocol TPX-0005-01 (TRIDENT-1)** – *A Phase 1/2, Open-Label, Multi-Center, First-in-Human Study of the Safety, Tolerability, Pharmacokinetics and Anti-Tumor Activity of TPX-0005 in Patients with Advanced Solid Tumors Harboring ALK, ROS1, or NTRK1-3 Rearrangements*

Date	Content
22 Jun 2017	**Granted: Orphan Drug Designation # 17-5735 (NSCLC with adenocarcinoma histology)**
07 Dec 2018	**Type B EOP1 Meeting (Clinical)** Outcome: Discussed and obtained feedback on the TRIDENT-1 study design, target ORR for approvability, clinical pharmacology plan, companion diagnostic, and nonclinical program
22 Jul 2019	**Type C Meeting (Clinical Pharmacology)** Preliminary Comments only[a]: Agreement with FDA on RP2D
27 Nov 2019	**Type B EOP1 Meeting (CMC)** Preliminary Comments only[a]: Agreement with FDA on regulatory starting materials, proposed impurity control strategy, proposed specifications for (b) (4) and repotrectinib DS and DP, and a categorical exclusion; feedback on the proposed control strategy for (b) (4) and its by-products (b) (4), dissolution method, and provision of 12 months stability data
19 Aug 2020	**Type C Meeting, Written Responses Only (Clinical)** Written Responses: Agreement with FDA that efficacy data from the Phase 1 and Phase 2 portions of the TRIDENT-1 study can be pooled for the primary analysis of efficacy to support registration in the targeted patient populations with *ROS1*+ advanced NSCLC (both TKI-naïve and TKI-pretreated)
07 Dec 2020	**Granted: Breakthrough Therapy Designation (*ROS1*+ NSCLC TKI-Naïve, EXP-1)**
12 Apr 2021	**Type B Initial Comprehensive Multidisciplinary Breakthrough Therapy Meeting (*ROS1*+ NSCLC TKI-Naïve, EXP-1)** Outcome: Feedback on the nonclinical safety data package, proposed efficacy population, TRIDENT-1 statistical analysis plan, proposed integrated safety data plan, QT assessment plan, (b) (4) strength capsule formulation, clinical pharmacology plan, stability data, companion diagnostic and pre-NDA meeting
15 Dec 2021	**Agreement reached with FDA on initial Pediatric Study Plan (iPSP)** Proposed General Plan: At the time of submission of the initial NDA, the Sponsor plans to (b) (4) the Sponsor plans to submit a deferral request for the report for the molecularly targeted pediatric investigation (Study TPX-0005-07 [CARE])
09 May 2022	**Granted: Breakthrough Therapy Designation (*ROS1*+ NSCLC Previously Treated with One ROS1 TKI and No Prior Chemotherapy, EXP-4)**
27 Jun 2022	**Type B pre-NDA Meeting (Clinical)** Outcome: Discussion and agreements regarding the clinical efficacy, safety and pharmacology plans for an NDA submission
28 Jun 2022	**Type B pre-NDA Meeting (CMC)** Preliminary Comments only[a]: Feedback regarding the (b) (4) capsule formulation, (b) (4) proposed registration strategy for the (b) (4) 40 mg dosage strengths, registration stability plan, stability studies and dissolution method for the 40 mg (b) (4) formulations
21 Dec 2022	(b) (4) .
16 Feb 2023	**Type B Meeting (CMC and CDx)** Preliminary Comments only[a] : Agreement reached with FDA that the 40 mg capsule formulation (b) (4)) can be submitted in the planned NDA, it may be acceptable for a supplemental PMA filing for a CDx to be a post marketing commitment and that MAPP

Date	Content
	5015.13 "Quality Assessment for Products in Expedited Programs" may apply to the repotrectinib NDA review

[a] Meeting canceled at the Applicant's request since no further discussion was needed.

3. SUMMARY OF CMC SPECIFIC PRESUBMISSION AGREEMENTS

The Applicant's Position:

[To the Applicant: Insert text here.] Include CMC meeting dates and any Pre-NDA agreements

Key CMC interactions are summarized below in Table 2.

Table 2: Summary of Key CMC Interactions for Repotrectinib Development

Type of Meeting/Correspondence		Content
Type B EOP1 Meeting (CMC)	27 Nov 2019	Preliminary Comments only[a]: FDA agreed with the regulatory starting materials, proposed impurity control strategy, proposed specifications for (b) (4) and repotrectinib DS and DP, and a categorical exclusion; feedback on the proposed control strategy for (b) (4) and its by-products (b) (4) dissolution method, provision of 12 months stability data,
Type B Initial Comprehensive Multidisciplinary Breakthrough Therapy Meeting	12 Apr 2021	FDA agreed to use the 40 mg formulation used in the TRIDENT-1 study as the to-be-marketed formulation in the initial NDA.
Request for Comments and Advice	24 Mar 2022	FDA agreed with the proposed dissolution method in the initial NDA to support testing of the to-be-marketed formulation.
Type B pre-NDA Meeting (CMC)	28 Jun 2022	Preliminary Comments only[a]: FDA provided feedback regarding the (b) (4) capsule formulation, (b) (4) proposed registration strategy for the (b) (4) 40 mg dosage strengths, registration stability plan, stability studies and dissolution method for the 40 mg (b) (4) formulations

Type of Meeting/Correspondence		Content
Type B pre-NDA Meeting (CMC and CDx)	21 Feb 2023	Preliminary Comments only[a]: FDA agreed with the 40 mg capsule formulation ([redacted (b) (4)]) in the planned NDA, registrational stability batch scale, and [redacted (b) (4)] impurity control strategy. FDA also agreed that MAPP 5015.13 "Quality Assessment for product in Expedited Programs" may apply to the repotrectinib NDA review

[a]Meeting canceled at the Applicant's request since no further discussion was needed.

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

4. ENVIRONMENTAL ASSESSMENT

The Applicant's Position:

Repotrectinib (BMS-986472/TPX-0005) is a potent small-molecule inhibitor of receptor tyrosine kinase encoded by the ROS1 gene (ROS1), anaplastic lymphoma (ALK) and tropomyosin receptor kinases (TPK) family and it also inhibits resistant mutations, such as gatekeeper and solvent front mutations (SFMs). Pursuant to 21 CFR 25.31(b), Bristol Myers Squibb Company hereby requests a categorical exclusion from the requirement of an Environmental Assessment (EA) for the proposed action since the estimated concentration of repotrectinib at the point of entry into the aquatic environment is estimated to be below 1 part per billion. Detailed calculations are provided in the Confidential Appendix 1 of Module 1.12.14 Environmental Assessment. To Bristol Myers Squibb Company's knowledge, no extraordinary circumstances exist that would warrant the preparation of an EA per 21 CFR 25.15(d). Additionally, it is not derived from any wild-sourced plant and/or animal material 21 CFR 25.21(b).

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

The applicant's request for a categorical exclusion from the requirement of an Environmental Assessment (EA) for the proposed action is deemed acceptable based on the concentration of repotrectinib at the point of entry into the aquatic environment being estimated to be below 1 part per billion.

5. FACILITIES

[Applicant will complete this section.]
Drug substance manufacturing, packaging and testing facilities are listed below:

The FDA's Assessment: ***Not Applicable***
No comparability protocol was proposed.

8. BIOPHARMACEUTICS

a. BCS Classification

Applicant to fill:
BCS Classification: (b) (4)

FDA assessment (FDA to fill):
Not acceptable

Information to support the BCS Class I designation request, if applicable.
Link: Page#:

FDA Comments:
Repotrectinib exhibits the characteristics of a ***BCS IV*** **(low solubility/low permeability)** drug substance.

(b) (4)

b. Dissolution Test

[Applicant to fill]

USP Apparatus	Paddle Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criterion
II *(with capsule sinker)*	75 rpm	900 mL	37°C ± 0.5°C	50mM sodium Phosphate Buffer *(pH 6.8)* with 0.075% sodium lauryl sulfate (SLS)	≥ (b) (4)% (Q) in (b) (4) minutes

Dissolution Test

FDA assessment (FDA to fill):
Acceptable

FDA Comments:
Note that per the Biopharmaceutics Review of IND 130465/SN-146, the proposed dissolution method (as tabulated above) was previously deemed adequate for routine QC testing of the (b) (4) repotrectinib capsules 40 mg at batch release and during shelf-life/stability testing.

[Note also that at the time of the Pre-NDA CMC meeting, based on the Sponsor's plan to revise the formulation composition of the 40 mg capsule, FDA recommended that the Applicant perform additional dissolution method development studies in order to demonstrate suitability of the proposed dissolution method for routine QC testing of the (b) (4) repotrectinib capsules.] Based on the information in 3.2.P.1 of NDA 218213, this Reviewer confirms that the target drug product (i.e., (b) (4) 40 mg capsules) used in dissolution method development studies submitted in IND 130465/SN-

146 has the same formulation composition as that of the current clinical and registration/stability lots and the final proposed to-be-marketed drug product.

HPLC with UV detection at (b) (4) nm is used for the quantification of drug in the dissolution samples. As indicated in Section 7.d.i above, the Drug Product Reviewer considers the analytical method validation for dissolution adequate.

Biopharmaceutics Figure 1: Dissolution Profiles as a function of:

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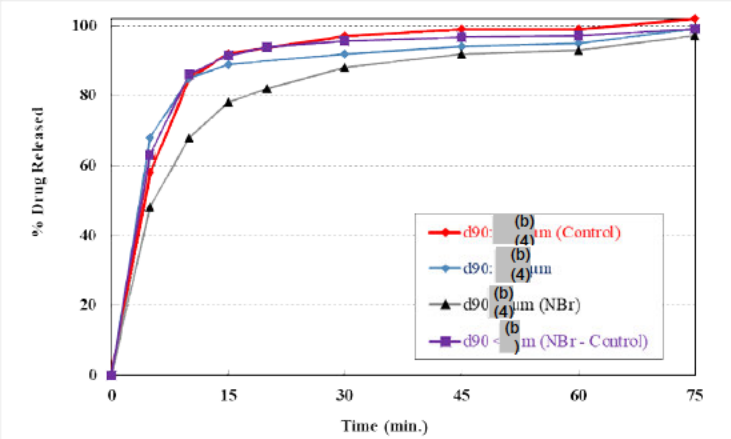


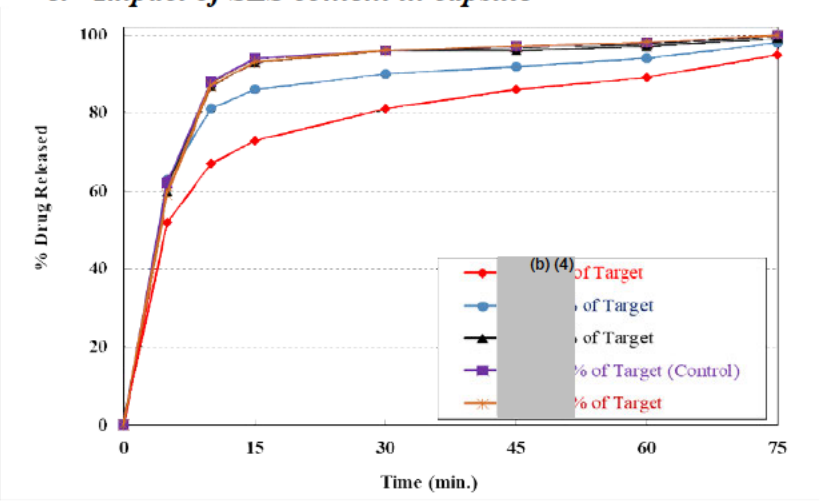
Applicant's comments:
Although similarity factors (F2) cannot be calculated due to the rapid release of the control, the resultant data indicates that the dissolution method can show significant differentiation between the batches manufactured with typical drug substance particle size and one that (b) (4) Prior to performing the testing of the (b) (4) µm particle size batch, Bristol Myers Squibb (at New Brunswick (NBr)) tested a batch manufactured with the typical DS particle size of < (b) (4) µm and compared it to the d90 of (b) (4) µm control batch generated by (b) (4) Resultant data indicates that both batches show no differences in profile.

FDA Comment:

Based on the dissolution profiles generated by BMS New Brunswick (NBr), this Reviewer concludes that the proposed QC dissolution method is capable of showing separation of the profiles of the very rapidly dissolving/*final commercial image* 40 mg capsules (Control Lot CMZVG, manufactured using API particle size, i.e.,d_{90} < (b) (4) µm) and a slow dissolving drug product lot that was intentionally manufactured using (b) (4) larger-than-target API particles (with d_{90} = (b) (4) µm). Figure "d" shows that the dissolution profile of (b) (4) "Control" Capsule Batch CDSNF (with d_{90} = (b) (4) µm) is essentially superimposable with the dissolution profile of NBr's "Control" Capsule Batch CMZVG (with d_{90} < (b) (4) µm). Note that Figure 'd" above no longer includes the dissolution profile of Deviant Batch d_{90} = (b) (4) µm that was previously provided in Figure 5 of the original dissolution method development report submitted in IND 130465/SN-146.

The dissolution profiles in Figure "d" above supports the Applicant's proposed API d_{90} tolerance limit (i.e., NMT (b) (4) µm), by USP<429>. *The evaluation of the adequacy of the proposed (b) (4) PSD specification (b) (4) for drug substance QC testing is deferred to the Drug Substance Reviewer, and/or the Process Reviewer.*

e. Impact of SLS content in capsule



Applicant's comments: Although similarity factors (F2) cannot be calculated due to the rapid release of the Control (SLS/ (b) (4) of Target), a review of the profiles indicate that the method can distinguish SLS level differences of lower than (b) (4) % of the target amount in capsule or was omitted in the formulation.

FDA Comment:

Based on Figure "e" above, the proposed dissolution method is capable of showing separation of the profiles of the very rapidly dissolving Target (Control) drug product and slower dissolving drug product lots intentionally manufactured with substantially-lower-than-target levels of (b) (4)

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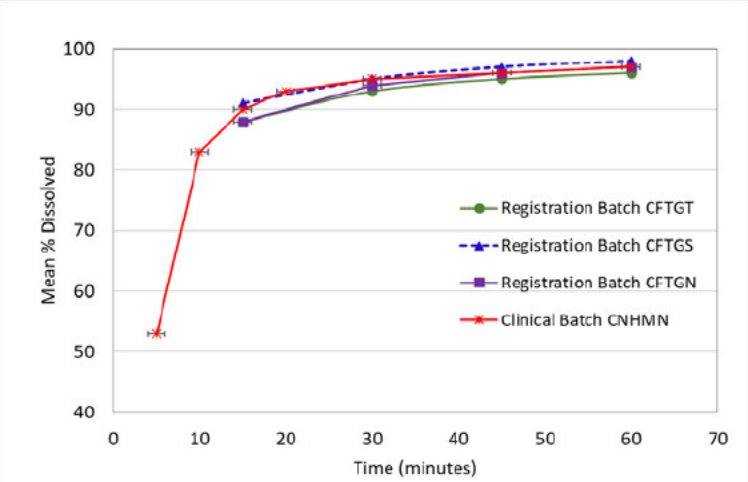
g. Justification for selection of the acceptance criteria (or criterion)



Applicant's comments: Complete dissolution profile data is available up to 24-month stability time point for 3 registration batches. Additionally data from 1 representative clinical batch is also shown in the dissolution profile.

FDA Comments:
Tightening of the dissolution acceptance criterion from "Q = (b)(4)% at (b)(4)min" to "Q = (b)(4)% at (b)(4) min" was initially recommended.

- Per the Applicant, the dissolution profiles in Figure "g" above show that aging has no effect on dissolution of repotrectinib capsules (Module 2.3.P). Based on this figure, the 24-month old registration batches and the reference clinical lot are able to conform to the FDA recommended/tightened dissolution acceptance criterion (Q = (b)(4)% at (b)(4)min). The dissolution data variability at the (b)(4) min sampling time point is low (i.e., NMT (b)(4)%).

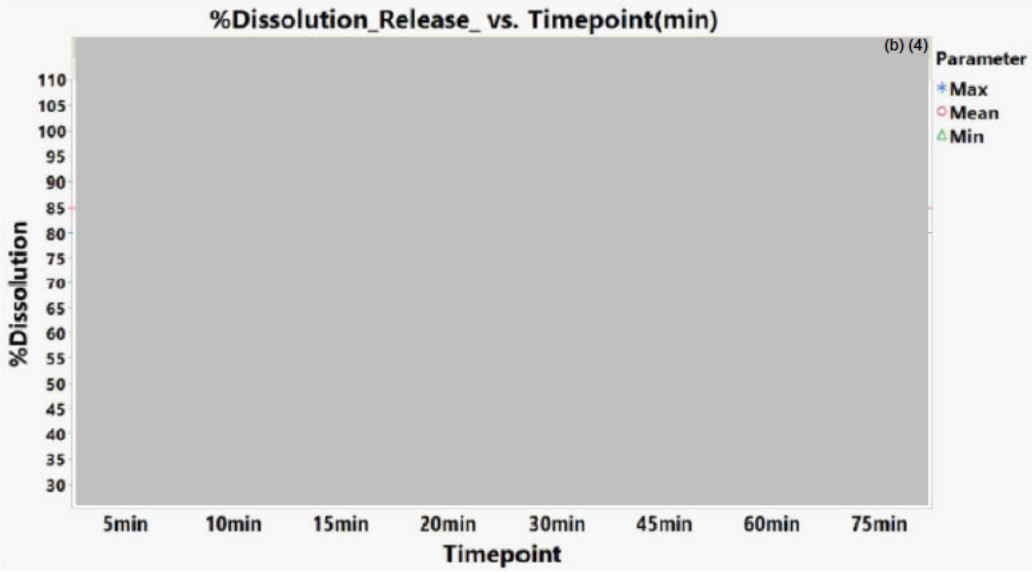
- For a low solubility drug substance, API particle size distribution is considered a critical quality attribute that could potentially impact drug product performance. Based on the mean dissolution profile data in Applicant Figure "d" above, the FDA recommended dissolution acceptance criterion (Q = (b)(4)% at (b)(4) min) but not the proposed dissolution acceptance criterion of "Q = (b)(4)% at (b)(4)min" is anticipated to be able to reject a drug product lot intentionally manufactured with (b) (4) (with d_{90} = (b)(4) µm, which is outside the proposed tolerance limit of NMT (b)(4)µm), i.e., by USP Stage 2 testing.

- Additionally, for a BCS IV drug substance like repotrectinib, the level of added (b) (4) may impact the oral bioavailability of the oral capsules. Based on Applicant Figure "e" above, the FDA recommended dissolution acceptance criterion (Q = (b)(4)% at (b)(4) min) but not the proposed dissolution acceptance criterion of "Q = (b)(4)% at (b)(4) min" will be able to reject a drug product lot intentionally manufactured with no (b) (4) (SLS), i.e., by USP Stage 2 testing.

- Furthermore, based on the mean dissolution profile data of the clinical lots (as shown in excerpted Figure 3.2.P.5.6-1 and Table 3.2.P.5.4-4), a specification time point of (b) (4) minutes for "Q = (b) (4)%" is considered appropriate.

- This Reviewer notes that per the proposed labeling, repotrectinib does not exhibit QT prolongation potential; thus, the safety risk of faster dissolving drug product lots is lower.

Figure 3.2.P.5.6-1: Dissolution Plot of Dissolution Release Data Minimum, Maximum, and Mean Values, % Dissolved



Dissolution on Stability

The proposed expiration dating period of 36 months when stored at USP Controlled Room Temperature conditions is acceptable to the Drug Product Reviewer based on the stability data and per ICH Q1E.

Per the Applicant, there were no trends observed in dissolution at (b) (4) min for the drug product up to 24 months of long-term (25°C/60%RH; as shown in Figure 3.2.P.8.1.4-3 and Figure 3.2.P.8.1.4-4), up to 6 months of accelerated (40°C/75%RH) or under stressed conditions.

Based on the provided dissolution profile on long-term and accelerated stability data, the registration/stability/clinical batches conform to the FDA-recommended/tightened dissolution acceptance criterion (Q = (b) (4)% at (b) (4) min) by USP Stage 1 (n=6) or USP Stage 2 (n=12) testing, with no apparent storage time-dependent trends.

In SN-22, the Applicant agreed to tighten the proposed dissolution acceptance criterion, but counter-proposed "Q = (b) (4)% at (b) (4) min", based on the following justification:

- Dissolution testing is not needed to reject repotrectinib capsule batches intentionally manufactured with larger-than-target API particle size because API particle size distribution is already part of the proposed drug substance QC specifications and there are (b) (4)) that would eliminate the risk of slower dissolving drug products.
- The counter-proposed dissolution acceptance criterion of "Q = (b) (4)% at (b) (4)min" will be capable of rejecting the variant drug product lot intentionally manufactured with (b) (4) SLS (b) (4) by USP Stage 2 testing.
- Based on the Applicant's statistical projections, a large percentage (~(b) (4)%) of the drug product batches will progress to USP Stage 2 testing when the dissolution acceptance criterion is set to "Q = (b) (4)% at (b) (4) min".

The following Biopharmaceutics Information Request was then sent to the Applicant:

Since repotrectinib is a low solubility drug substance , we agree that API particle size distribution is a critical bioavailability attribute of repotrectinib capsules. FDA acknowledges your justification that although your counter-proposed dissolution acceptance criterion of "Q = (b) (4)% at (b) (4) min" will not be able to reject drug product batches intentionally manufactured with larger-than-target API particle size distribution (PSD), there are adequate drug substance PSD and (b) (4) specifications in place to eliminate the risk of releasing a poorly dissolving drug product due to uncontrolled drug substance particle size. Based mainly on the dissolution profile data of the clinical lots (Figure 3.2.P.5.6-1) and considering Figures Q1-2 and Q1-3 of the IR response (in SN-22), it is justified to tighten the dissolution acceptance criterion to "Q = (b) (4)% at 20 min". Revise the finished product QC specifications and other pertinent NDA documents to reflect the final FDA recommended dissolution acceptance criterion.

In SN-26 (dated 7/3/2023), the Applicant agreed to the FDA's recommendation to tighten the dissolution acceptance criterion to "Q = (b) (4)% at 20 min", based mainly on the dissolution profile data of the clinical lots of repotrectinib capsules.

	Applicant to fill:	FDA assessment:
The dissolution method is discriminating for:		
i) Particle size distribution (PSD)	Discriminating	Agree
Link[1]: Section 3.2.P.2.2.3.1, *Dissolution Method Development*		Page#:
ii) Polymorph/solid state form	Not applicable	Agree
Link[1]:		Page#:
iii) Formulation variations	Discriminating	Agree

Link[1]: Section 3.2.P.2.2.3.1, *Dissolution Method Development*		Page#:
iv) Manufacturing process variations	Not applicable	Not applicable
Link[1]:		Page#:
v) Other (specify): Heat Stressed Sample	Discriminating	Not applicable
Link[1]:Section 3.2.P.2.2.3.1, *Dissolution Method Development*		
vi) Other (specify): Gelatin cross-linking	Discriminating	Agree
Link[1]:Section 3.2.P.2.2.3.1, *Dissolution Method Development*		

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

FDA Comments:

- Based on Table 3.2.P.2.2.3.1-12 and Figure 3.2.P.2.2.3.1-9, heat stressing the capsules at (b) (4)°C for (b) (4) days did not result in a change in dissolution profile as compared to unstressed/control capsules. Thus, this Reviewer does not consider the proposed dissolution method discriminating for heat stressed product samples. It is acknowledged that data were provided to demonstrate the ability of the proposed QC dissolution method to detect intentionally crosslinked gelatin capsules.
- The proposed dissolution method was not investigated for the ability to discriminate drug product lots with API polymorphic change. However, it is acknowledged that the only other known API polymorph (b) (4)) was not considered relevant to the Drug Substance and Drug Product manufacturing processes. Furthermore in SN-15, the Applicant provided confirmatory XRD and NIR profile data to demonstrate that API polymorphic change was not observed during drug product manufacture and up to 3 months of accelerated storage of development batches (in HDPE bottles and in open dishes), and thus concluded that there is no risk of API polymorphic change during drug product shelf-life.
- The Applicant indicated that (b) (4) (b) (4) (b) (4)

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

[To the Applicant: Include a schematic representation of the development of your proposed drug product from initial IND-product to the to-be-marketed product. Include all the formulation/manufacturing/process/etc. changes that occurred throughout development, the studies (in vitro or in vivo) bridging those products, and the PK, clinical, stability-registration studies in which those products were used.

Applicant provide supporting data/Figure(s) here:]

Link: Page#:

The proposed commercial repotrectinib capsule, 40 mg has been used in Phase 1, Phase 2, and registrational studies. The composition of the capsule blend used for the repotrectinib capsule, 40 mg is the same for the clinical, registrational, and commercial; only the pre-printed capsule markings are different. The changes in product appearance are for product differentiation only (non-functional) and are not expected to impact drug dissolution and absorption.

(b) (4)

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

All clinical studies (in Table 2 and Table 8 of Module 2.7) {including TPX-0005-01 (TRIDENT-1), TPX-0005-07 (Pediatric Study), Study TPX-0005-08 (Relative Bioavailability/RBA), TPX-0005-09 Part A (Absolute BA), TPX-0005-11 (Food-Effect Study), Study TPX-0005-12 (RBA), TPX-0005-14 (BE and Food Effect)} used one or several lots of the [redacted] (40 mg) Capsule Formulation, which is the proposed to-be-marketed formulation. According to Table 3.2.P.5.4.2-1, the drug product lots produced at commercial scale by the proposed commercial drug product manufacturer [redacted] using the proposed commercial '[redacted] capsules formulation and process and input API [redacted] were used in TRIDENT-1 (the pivotal clinical trial).

According to Table 3.2.P.5.4-3 (for batch analyses data including appearance) and the proposed labeling, as well as Table 3.2.P.5.4-2 (for batch use information), both the unmarked '[redacted]' capsules and the *penultimate market image* '[redacted] capsule were also used in the TRIDENT-1 and other clinical studies.

Based on the batch information in Table 3.2.P.5.4-2, and the TRIDENT-1 clinical study report, all [redacted] manufacturing processes ([redacted] as described by the Applicant above) were used by the R&D and proposed commercial facilities to manufacture lots for the pivotal clinical trial (TRIDENT-1).

Additionally, the *penultimate market image* capsule lots (CFTGT, CFTGS, CFTGN) produced at commercial scale by the proposed commercial drug product manufacturer [redacted] using the proposed commercial '[redacted] capsules formulation and process ([redacted] and input API [redacted] were used in long-term stability studies (LTSS) and clinical studies including TRIDENT-1. As reported in 3.2.P.8.3.2, the LTSS batches were packaged in the proposed commercial container-closure system (60-count and 120-count HDPE bottles) at the time of stability testing.

- All LTSS/Clinical Batches (including lots used in the TRIDENT-1 Clinical Study) that were manufactured by [redacted] in Table 3.2.P.5.4-4 exhibited very rapid dissolution (i.e., with mean dissolution of at least [redacted]% within [redacted] minutes), regardless of [drug substance manufacturer [redacted]) and] batch size ([redacted] capsules), thereby supporting (at least in part) the Applicant's proposed commercial scale range of [redacted] kg. Per the Process Reviewer, the proposed commercial drug product batch size range is acceptable.

Dissolution profile data for future commercial [redacted] (40 mg) capsules representing the "final market image" capsules are not available. As indicated in Table 3.2.P.2.2.1-2, the only difference from the penultimate market image capsules is the pre-printed capsule markings. This Reviewer agrees with the Applicant that this particular difference in capsule shell appearance is not expected to impact drug dissolution and

absorption. Thus, the Applicant's commitment in SN-15 to provide confirmatory dissolution profile data of three process performance qualification (PPQ) batches that possess the final commercial image of the repotrectinib 40 mg capsules (b) (4) when they become available is deemed acceptable.

d. Biowaiver Request

The Applicant's Position:

The NDA does not contain a biowaiver request

[To the Applicant: Explain the reasons why biowaiver is not needed for the proposed drug product. If biowaiver request is made, provide information to support the biowaiver request, if applicable (compositional proportionality, PK linearity, comparative dissolution profiles with f2 analysis)]

Link: Page#:

[To the Applicant: Insert text here]

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

[The proposed (b) (4) repotrectinib 40 mg capsule formulation was used in the pivotal clinical trial and other clinical PK/BA studies (as well as in registration/stability studies). No other strengths are proposed for commercialization at this time.]

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

[To the Applicant: Provide summary of the objective of the model, model development and validation, and outcome. Insert additional text, graphs, and table here to support the information provided above as necessary]

Link: Page#:

[To the Applicant: Insert text here]

The FDA's Assessment: ***Not Applicable***

[Not Applicable. submitted The PBPK Model relates to the assessment of repotrectinib's drug-drug interaction potential. This modeling report and supporting datasets will be assessed by the Clinical Pharmacology Reviewers.]

9. LABELING

[FDA will complete this section.]

USPI
Highlights: ***Adequate***
(Add notes as necessary)

Section 2 (if relevant): ***Adequate***
(Add notes as necessary)

Section 3 Dosage Forms and Strengths: ***Adequate***
(Add notes as necessary)

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.

(Add notes as necessary)

Section 16 How Supplied/Storage and Handling: ***Adequate***
(Add notes as necessary)

Manufacturer Information (Name and Address): ***Provided: Adequate***
The applicant initially did not include the information at end of Patient Labeling. Per FDA's IR, the applicant has included manufacturer information at the end of prescribing information (PI). The PI is deemed acceptable from the CMC perspective.

Carton/Container Label ***Adequate***

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Final Risk Assessments

To the Review Team: *Keep the appropriate Table; delete the rest*

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		Low	
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Medium	(b) (4)	Medium	
Content Uniformity	• Formulation • Container closure • Raw material • Process Parameters • Scale/equipment • Site	Medium		Low	
(b) (4)					
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low		Low	
Dissolution – BCS Class (b) (4) & IV	• Formulation • Container Closure • Raw materials • Process parameters • Scale/equipment • Site	Medium	(b) (4)	Low	

Recommendation Page

[FDA will complete this section.]

Drug Substance: Approval

Primary Reviewer: Kabir Shahjahan Date: October 2, 2023
Secondary Reviewer: Haripada Sarker Date: October 2, 2023

Drug Product: Approval

Primary Reviewer: Xiao Hong Chen Date: October 2, 2023
Secondary Reviewer: Xing Wang Date: October 2, 2023

Manufacturing: Approval

Primary Reviewer: Yifan Wang Date: October 2, 2023
Secondary Reviewer: Zhaoyang Meng Date: October 2, 2023

Biopharmaceutics: Approval

Primary Reviewer: Gerlie Gieser, Ph.D. Date: September 11, 2023
Secondary Reviewer Anitha Govada, Ph.D. Date: October 2, 2023

Application Technical Lead: Approval

Xiao Hong Chen Date: October 2, 2023

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/

XIAOHONG CHEN
10/11/2023 12:48:19 PM

KABIR M SHAHJAHAN
10/11/2023 12:50:53 PM

HARIPADA SARKER
10/11/2023 01:25:37 PM
Adequate from DS.

XING WANG
10/11/2023 01:27:16 PM

YIFAN WANG
10/11/2023 02:01:41 PM

ZHAOYANG MENG
10/11/2023 02:04:27 PM

GERLIE GIESER
10/11/2023 02:06:03 PM

ANITHA P GOVADA
10/11/2023 02:08:51 PM