

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

218213Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: November 13, 2023
Requesting Office or Division: Division of Oncology 2 (DO2)
Application Type and Number: NDA 218213
Product Name, Dosage Form, and Strength: Augtyro (repotrectinib) Capsule, 40 mg
Applicant/Sponsor Name: Bristol Myers Squibb Company (BMS)
TTT ID #: 2023-4198-2
DMEPA 2 Safety Evaluator: Janine Stewart, PharmD
DMEPA 2 Team Leader: Ashleigh Lowery, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on November 2, 2023 for Augtyro. The Division of Oncology 2 (DO2) requested that we review the revised container labels and carton labeling for Augtyro (Appendix A) to determine if it is acceptable from a medication error perspective. The proposed revisions were submitted after our previous label and labeling review^a and reflect a change initiated by BMS to update the container labels and carton labeling by changing the dosage form statement from “Capsules” to “capsules” [lowercase].

2 CONCLUSION

We find the dosage form change from “Capsules” to “capsules” acceptable. We have no additional recommendations at this time.

^a Stewart, J. Label and Labeling Memorandum for Augtyro (NDA 218213). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 NOV 09. TTT ID No.: 2023-4198-1

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON NOVEMBER 2, 2023

Container labels



Carton labeling



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/s/

JANINE A STEWART
11/13/2023 10:59:41 AM

ASHLEIGH V LOWERY
11/13/2023 11:07:11 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: November 9, 2023
Requesting Office or Division: Division of Oncology 2 (DO2)
Application Type and Number: NDA 218213
Product Name, Dosage Form, and Strength: Augtyro (repotrectinib) Capsule, 40 mg
Applicant/Sponsor Name: Bristol Myers Squibb Company
TTT ID #: 2023-4198-1
DMEPA 2 Safety Evaluator: Janine Stewart, PharmD
DMEPA 2 Team Leader: Ashleigh Lowery, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on September 25, 2023 for Augtyro. The Division of Oncology 2 (DO2) requested that we review the revised container labels and carton labeling for Augtyro (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant acknowledged all of our recommendations. We note the Applicant no longer plans to commercialize the 120-count round bottle presentation and thus, the label and labeling were not included in the submission. We also note additional minor updates to the container labels and carton labeling. Further, we find the expiration date format that is used across their manufacturing network (MMM YYYY) acceptable from a medication error perspective. Therefore, we have no additional recommendations at this time.

^a Stewart, J. Label and Labeling Review for Augtyro (NDA 218213). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 AUG 24. TTT ID No.: 2023-4198

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON SEPTEMBER 25, 2023

Container labels



Carton labeling



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JANINE A STEWART
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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: September 13, 2023

To: Idara Ojofeitimi, Regulatory Project Manager
Division of Oncology 2 (DO2)

Barbara Scepura, Associate Director for Labeling, DO2

From: Kelle Caruso, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Rachael Conklin, Team Leader, OPDP

Subject: OPDP Labeling Comments for [PROPRIETARY NAME]TM (repotrectinib) capsules, for oral use

NDA: 218213

Background: In response to DO2's consult request dated April 17, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original NDA submission for [PROPRIETARY NAME]TM (repotrectinib) capsules, for oral use.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on September 1, 2023, and our comments are provided below.

PPI:
A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI, and comments were sent under separate cover.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on September 5, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Kelle Caruso at 301-796-5044 or Kelle.Caruso@fda.hhs.gov.

PI:

<u>Section</u>	<u>Statement from Draft (if applicable)</u>	<u>OPDP Comment</u>
Highlights of Prescribing Information	(b) (4)	For purposes of clarity and also consistency with the PI for the competitor product entrectinib, we recommend revising this statement throughout the HL section to “Withhold or permanently discontinue PROPRIETARY NAME based on severity. If withheld, resume PROPRIETARY NAME at same or reduced dose based on severity.”
Highlights of Prescribing information and 1. Indications and Usage	“PROPRIETARY NAME is indicated for the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC) (b) (4) ”	OPDP notes that other kinase inhibitors that target ROS1 (entrectinib, crizotinib) have FDA-approved companion diagnostics for detecting ROS1 mutations. Does repotrectinib require ROS1 mutations to be detected by an FDA-approved test for approved use? If so, we recommend adding this language to the INDICATION AND USAGE sections in the HL and in Section 1.
2.6 Administration	(b) (4)	OPDP notes that the approved dose is 160mg taken twice daily. If a patient misses their morning dose, are they to skip the evening dose and start again (b) (4)? Or they are still to take their evening dose in the event of a missed morning dose? Please consider revising for clarity given the twice daily dosing schedule. We note that this is reflected in section 17 which includes the recommendation to “to take the next dose at the next scheduled time.” e.g., If a dose is missed (b) (4) . . . skip the dose and (b) (4) at its regularly scheduled time.
5. Warnings and Precautions	Interstitial Lung Disease (ILD)/Pneumonitis	OPDP notes that according to Section 6.1, “Fatal adverse reactions occurred in 4.2% of patients who received PROPRIETARY NAME, including death, pneumonia, pneumonia aspiration, cardiac arrest, sudden

		cardiac death, cardiac failure, sudden death, hypoxia, dyspnea, respiratory failure, tremor, and disseminated intravascular coagulation.” Do any of these fatal adverse reactions coincide with any of the Warnings and Precautions, e.g., fatal case of pneumonia and respiratory failure and W&P for ILD/pneumonitis? If so, we recommend prominently indicating in the Warnings and Precautions section that the warning is for a “serious and sometimes fatal” adverse reaction. For example: “Interstitial Lung Disease /Pneumonitis PROPRIETARY NAME can cause serious and sometimes fatal interstitial lung disease (ILD) / pneumonitis.”
5. Warnings and Precautions	5.1 Central Nervous System (b) (4) 5.2 Interstitial Lung Disease (b) (4) /Pneumonitis 5.3 Hepatotoxicity 5.4 Myalgia with Creatinine Phosphokinase Elevation 5.5 Hyperuricemia 5.6 (b) (4)	OPDP notes that Grade 3 or 4 events occurred in each of these categories. OPDP recommends revising this section to communicate the nature and severity of these risk up front. For example: [PROPRIETARY NAME] can cause “severe” or “severe and life-threatening” [insert name of adverse reaction, e.g. CNS effects]. This can impact shorter promotional materials where the applicant may not present detailed information about the warnings and precautions, including the grades of these adverse events.
(b) (4) (b) (4)	(b) (4) (b) (4)	OPDP notes that throughout the PI, the term (b) (4) is used to describe this warning. We recommend revising this term throughout the PI for consistency (b) (4) (b) (4)

6.1 Clinical Trials Experience

(b) (4)

Once these rates are finalized, we recommend listing the adverse reactions in descending order of frequency.

Highlights of Prescribing Information and 6.1 Clinical Trials Experience

(b) (4)

OPDP notes that the HL and Section 6.1 use the term (b) (4). However, Table 3 in Section 6.1 (b) (4) appears to be using the term "peripheral neuropathy" instead. Once finalized, we recommend using the same terminology for this adverse reaction throughout the PI, including the HL and section 6.1.

	(b) (4)	In addition, we note that according to Table 3, fatigue occurred in 24% of patients. Since this is above the 20% threshold, we recommend keeping fatigue in this list. We also note that Table 3 lists (b) (4) If this is accurate, we recommend adding (b) (4) to this list of adverse reactions $\geq 20\%$. Once this list is finalized, we recommend listing the adverse reactions in descending order of frequency and ensuring consistency between Section 6.1 and the Highlights section.
14.1 (b) (4)	“Eligible patients were required to have <i>ROS1</i>-positive locally advanced or metastatic NSCLC, ECOG performance status ≤ 1, measurable disease per RECIST v 1.1, and <u>≥ 8 months from first dose.</u>” (emphasis added)	It is not clear what ≥ 8 months from first dose is referring to. Can you please clarify what drug is being referred to in terms of the “first dose”?
	“Intracranial response according to modified RECIST v1.1 was assessed by BICR.” (b) (4)	Was this a prespecified subgroup analysis and/or is this analysis considered exploratory? We acknowledge that similar information is in the competitor label; however, if this was not a prespecified analysis, is there consideration for including a statement that this was an exploratory analysis, or conducted post-hoc, in order to provide adequate context for interpreting this data in the event it is used in promotion? In considering how this information may be used in promotion, are there any limitations associated with this data/analysis that should be taken into account? If so, OPDP recommends this information be included in the PI. Otherwise, we would not be able to

	(b) (4)	ask for additional context for this data in promotion.

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/s/

KELLE E CARUSO
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: September 11, 2023

To: Idara Ojofeitimi, M.S.
Chief, Project Management Staff
Division of Oncology 2 (DO2)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Ruth Mayrosh, PharmD
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Kelle Caruso, PharmD, BCPS
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): TRADENAME (repotrectinib)

Dosage Form and Route: capsules, for oral use

Application Type/Number: NDA 218213

Applicant: Bristol-Myers Squibb Company

1 INTRODUCTION

On March 27, 2023, Bristol-Myers Squibb Company submitted for the Agency's review an original New Drug Application (NDA) 218213 for TRADENAME (repotrectinib) with proposed indication for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology 2 (DO2) on April 17, 2023, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TRADENAME (repotrectinib) capsules.

2 MATERIAL REVIEWED

- Draft TRADENAME (repotrectinib) capsules PPI received on March 27, 2023, and received by DMPP and OPDP on September 5, 2023.
- Draft TRADENAME (repotrectinib) capsules Prescribing Information (PI) received on March 27, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 5, 2023.
- Approved ROZLYTREK (entrectinib) capsules comparator labeling dated June 16, 2023.
- Approved LORBRENA (lorlatinib) tablets comparator labeling dated March 3, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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KELLE E CARUSO
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LASHAWN M GRIFFITHS
09/11/2023 04:13:10 PM

Clinical Inspection Summary

Date	September 6, 2023
From	Lee Pai-Scherf, MD Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) DCCE, OSI
To	Michael Barbato, MD, Medical Officer Diana Bradford, MD, Team Leader (CDTL) Division of Oncology 2 (DO2), Office of Oncology Products
NDA #	NDA 218213
Applicant	Bristol Myers Squibb Co. (BMS)
Drug	Repotrectinib (TPX-0005)
NME (Yes/No)	Yes
Therapeutic Classification	Tyrosine Kinase Inhibitor
Proposed Indication(s)	Treatment of adult patients with locally advanced or metastatic ROS1-positive Non-Small Cell Lung Cancer
Consultation Request Date	May 15, 2023
Summary Goal Date	September 27, 2023
Action Goal Date	October 27, 2023
PDUFA Date	November 27, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study TPX-0005-1 (TRIDENT-1) were submitted to the Agency in support of New Drug Application (NDA 218213) for repotrectinib (TPX-0005) for the treatment of adults with locally advanced or metastatic ROS1-positive Non-Small Cell Lung Cancer (NSCLC). Two clinical investigators, Drs. Misako Nagasaka (Site # 1001/2101), and Alexander Drilon (Site # 1002/2102), as well as the imaging Contract Research Organization (CRO) (b) (4) and the study sponsor, Turning Point Therapeutics Inc. (Turning Point), a wholly owned subsidiary of BMS, were inspected.

Inspections of the CIs, Drs. Nagasaka, and Drilon, the sponsor, Turning Point, and the imaging CRO, (b) (4) revealed no discrepancies or regulatory violations. Based on these inspections, Study TPX-0005-1 appears to have been conducted adequately by the study sponsor and the data generated by the inspected clinical investigators and the imaging CRO and submitted by the applicant, Bristol Meyers Squibb (BMS) appear acceptable in support of the proposed indication.

Of note, the inspection results of Dr. Nagasaka are based on a summary provided by the FDA field investigator and are therefore preliminary. If significantly new or different information is

contained in the final FDA Establishment Inspection Report, an addendum to this clinical inspection summary will be filed.

II. BACKGROUND

Bristol Myers Squibb submitted NDA 218213 seeking approval for repotrectinib for the treatment of patients with advanced or metastatic ROS-1 positive non-small cell lung cancer based on the pre-specified analysis of pooled efficacy from the Phase 1 and Phase 2 portion of the pivotal Study TPX-0005-01 (TRIDENT-1).

TPX-0005-01 is an ongoing Phase 1/2, first-in-human, open-label, multicenter study evaluating the safety, pharmacokinetics, and anti-tumor activity of repotrectinib in subjects with advanced solid tumors harboring ROS1, ALK, or NTRK rearrangements.

Efficacy data from 71 ROS1 TKI-naïve patients and 56 patients who received 1 prior ROS1 TKI with no prior platinum-based chemotherapy, and safety data from 444 subjects enrolled in TRIDENT-1 were submitted to support the current NDA. The key efficacy endpoint is overall response rate (ORR) and duration of response (DOR) according to RECIST v 1.1 as assessed by blinded independent central review (BICR).

Subjects were to sign the informed consent form before any study-specific procedures were to be performed. Imaging assessments were to be performed at baseline, Cycle 3 Day, every 2 cycles up to Cycle 19, every 3 cycles up to Cycle 37, and then every 4 cycles thereafter until documented progression of disease regardless of treatment delays resulting from toxicity. All scans were to be submitted ^{(b) (4)} for blinded central imaging assessment.

Study TRIDENT-1 was ongoing at the time of NDA submission. The first subject was enrolled on February 27, 2017. The data cut-off date for the NDA was June 20, 2022. Subjects were enrolled across 152 clinical sites across 19 countries globally, including 33 sites in the United States.

Drs. Misako Nagasaka (Site # 1001/2101), and Alexander Drilon (Site # 1002/2102), as well as the imaging CRO, ^{(b) (4)}, and the Sponsor, Turning Point Therapeutics Inc., were inspected.

III. RESULTS (by site):

- 1. Dr. Misako Nagasaka (Site # 1001/2101)**
101 The City Dr. S Bild. 56, Rm. 240
Orange, CA 92868

Inspection dates: July 5-11, 13-14, 2023

The official establishment inspection report (EIR) is pending. The review below is

from the summary close out email and communications with the inspector during the inspection. This report will be updated after review of the official EIR, if relevant additional information is included.

Dr. Nagasaka was inspected as a routine PDUFA inspection for Study TRIDENT-1. This was the first FDA inspection for this investigator.

The site had 4 PIs before Dr. Nagasaka: the initial CI of the site was Dr. Ignatious Ou, who was replaced in December 2019 by the Sponsor due to site performance issues and GCP non-compliance. Three subsequent investigators left due to various reasons: Dr. Samuel Ejadi due to excessive patient load, Dr. Viola Zhu, left the site, and Dr. Fa-Chyi Lee due to other research interests. Dr. Misako Nagasaka assumed CI responsibilities for TRIDENT-1 in February 2022.

At the time of the inspection, the site had screened 19 subjects and had enrolled 16 subjects in the study. At the time of the data cutoff date of June 20, 2022, 3 out of 3 subjects enrolled in the Phase 2 portion remained on study.

Source records for 8 subjects (5 enrolled in the Phase 1 and 3 in the Phase 2) were reviewed. Records reviewed included: informed consent forms, medical records, inclusion and exclusion criteria, investigational drug administration, adverse events reporting, protocol deviations, and subject dispositions. Records were compared with data listing tables submitted to the NDA and no discrepancies were noted.

All subjects had imaging scans performed at protocol specified timepoints and scans were submitted to imaging CRO for central assessment of disease response and progression for determination of the primary and secondary efficacy endpoints.

Based on the results of the inspection, data generated at Nagasaka's site appear acceptable in support of the proposed indication in the NDA.

2. Dr. Alexander Drilon (Site # 1002/2102)

1275 York Ave
New York, NY 10065

Inspection dates: June 12 – June 16, 2023

Dr. Drilon was inspected as a routine PDUFA inspection for Study TRIDENT-1. Dr. Drilon was previously inspected in April 2019.

At the time of the inspection, the site had screened 54 and enrolled 47 subjects in the study, of which 40 have completed study treatment, 4 subjects remain on treatment, 3 subjects are in follow-up. Of the 40 subjects who completed study treatment, 34 subjects have expired.

Source records for 11 subjects were reviewed in full and compared with line listings

submitted to the NDA. Records reviewed included informed consent documents, eligibility criteria, protocol adherence, adverse events reporting, investigational product administration, protocol deviations, laboratory reports, and concomitant medications. Record review did not identify any discrepancies.

Imaging scans for tumor assessment were performed according to the protocol specified timepoints and were submitted to the imaging CRO for central assessment of disease response and progression for determination of the efficacy endpoints.

Additional records reviewed during the inspection included, but not limited to, IRB documents and communication, monitoring logs, electronic medical records, financial disclosure forms, staff training records, and drug accountability.

Based on the results of the inspection, the TRIDENT-1 study data generated at Dr. Drilon's site appear acceptable in support of the proposed indication in the NDA.

3. Turning Point Therapeutics Inc. (a wholly owned subsidiary of BMS)

3491 Princeton Pike
Lawrence Township, NJ 08648

Inspection dates: June 20 – June 28, 2023

This inspection assessed Turning Point's oversight responsibilities for TRIDENT-1 study. Turning Point was acquired by BMS Company in August 2022, becoming a wholly owned subsidiary of BMS Company. This was the first FDA inspection for Turning Point.

Documents reviewed during the inspection included, but not limited to TRIDENT-1 study documents, data management plans, DMC charters, data collection and handling procedures, safety reporting and handling, selection of clinical site investigators and monitors, form FDA 1572s, financial disclosures, data monitoring committee activities, investigational product disposition, and vendor, contract, and service agreements.

The inspection reviewed site records of the 2 sites selected for inspection (Training and monitoring files from 2 clinical sites, Site # 1001/2101, current CI Misako Nagasaka (Site # 1001/2101), and Dr. Alexander Drilon (Site # 1002/2102). Records reviewed included training lots, monitoring visit logs and reports, Form 1572, financial disclosure forms, and IRB correspondence.

At Site # 1001/2101, the initial PI, Dr. Ignatious Ou was replaced by the Sponsor in December 2019 due to GCP non-compliance, The sponsor generated a CAPA for the GCP noncompliance and replaced Dr. Ou as PI. Site # 1001/2101 had 3 subsequent investigators who left due to various reasons: Dr. Samuel Ejadi due to excessive patient load (PI from 08/2018 – 12/2019), Dr. Viola Zhu, left the site (PI from 12/2019 – 06/2021), and Dr. Fa-Chyi Lee to pursue other research interests (06/2021 – 02/2022).

Dr. Misako Nagasaka assumed CI responsibilities for TRIDENT-1 in February 2022.

Overall, Turning Point's oversight of the investigators and the study appeared adequate, as appropriate actions were taken with all issues identified during oversight activities. There were no issues with the staff qualifications, training, experience, or compliance with the investigational plan. The inspection did not observe issues related to safety/adverse event reporting for Study TRIDENT-1.

Based on the results of the inspection, Turing Point's oversight and monitoring of Study TRIDENT-1 appeared adequate.

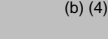
4.  (b) (4)

 (b) (4) was inspected as a routine PDUFA inspection for Study TRIDENT-1. The firm was previously inspected  (b) (4)

This inspection reviewed  (b) (4) responsibilities to perform an independent central imaging review for Study TRIDENT-1. Records reviewed included imaging source data, overview of electronic systems, written agreements, meeting minutes, standard operating procedures (SOPs), manuals, and reviewer's selection and training records.

Tumor measurement data from 20 subjects enrolled in Cohort 1 and 4 of Study TRIDENT-1, who were reported as have achieved a complete (CR) or partial tumor response (PR) per RECIST 1.1, were reviewed. Target, and non-target lesion response, reported new and new unequivocal lesions, overall tumor response, and percentage (%) change from baseline were reviewed and compared with the data submitted to the FDA for all imaging time points for the selected subjects. In addition, intracranial tumor response from six subjects with measurable brain metastasis, as determined by BICR using modified RECIST 1.1 was also reviewed and compared with the data submitted to the NDA. No discrepancies were identified.

 (b) (4) assessment, procedures in performing image analysis, compliance with the Imaging Review Charter, clinical protocol, and appropriate regulations were reviewed and appeared adequate.

Based on the results of the inspection, the imaging review data generated by  (b) (4) appear acceptable in support of the proposed indication in the NDA.

{See appended electronic signature page}

Lee Pai-Scherf, MD
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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CONCURRENCE:

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Jenn Sellers, M.D., Ph.D.
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Office of Scientific Investigations

CC:

DARRTS: NDA 218213
Review Division /Project Manager/Opeyemi Udoka
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

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/s/

LEE HONG PAI SCHERF
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MICHELE B FEDOWITZ
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JENN W SELLERS
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 24, 2023
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 218213
Product Name, Dosage Form, and Strength:	Repotrectinib ^a Capsule, 40 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Bristol Myers Squibb Company
FDA Received Date:	March 27, 2023
TTT ID #:	2023-4198
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

^a Labels and labeling submitted by the Applicant for NDA 218213 include the previously proposed proprietary name, Augtyro, which was found unacceptable by DMEPA on June 22, 2023. Therefore, the established name, repotrectinib, is used throughout this review.

1 REASON FOR REVIEW

As part of the approval process for Repotrectinib Capsule, the Division of Oncology 2 (DO2) requested that we review the proposed Repotrectinib prescribing information (PI), container labels, and carton labeling, and patient information for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the repotrectinib PI, patient information, container labels, and carton labeling to identify areas of vulnerability that may lead to medication errors and other areas of improvement. We note instances of lack of continuity of product information between the labeling components, ambiguous administration instructions, and incomplete information for how to manage missed doses. Thus the labeling components can be revised to support the safe and effective use of the product.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed repotrectinib PI, patient information, container labels, and carton labeling can be improved to promote the safe and effective use of the product. We provide recommendations for DO2 in Section 4.1 and recommendations for Bristol Myers Squibb Company in Section 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 2 (DO2)

A. Prescribing Information

1. Dosage and Administration Section

- a. Consider revising the information proposed in Section (b) (4) informing users of how to manage a missed dose similar to the missed dose information that is provided in the proposed Patient Information. Include the acceptable interval for taking a missed dose before the next scheduled dose before having to wait to resume dosing the next day and in order to avoid risks associated with taking 2 doses too close together similar to the following:

(b) (4)

- b. Consider revising Section (b) (4) Recommended Dosage and Section (b) (4) Administration and combining the product information to appear in Section (b) (4) as proposed below. We recommend dosage and administration information in the same section to support the safe and effective use of the drug product.

The recommended dosage of PROPRIETARY NAME is 160 mg orally once daily for 14 days, then increase to 160 mg twice daily until disease progression or unacceptable toxicity.

Take PROPRIETARY NAME at approximately the same time each day with or without food.

Swallow PROPRIETARY NAME capsules whole. Do not open, chew, crush, or dissolve the capsule prior to swallowing. Do not take any PROPRIETARY NAME capsules that are broken, cracked, or (b) (4) damaged.

If a dose is missed (b) (4) or if vomiting occurs at any time after taking a dose, skip the dose and (b) (4) at its regularly scheduled time.

2. Dosage Forms and Strengths Section

- a. Consider revising Section 3 for brevity and clarity to read as follows:

Capsules: 40 mg, white, opaque, immediate release, Size 0 hard (b) (4) capsule, filled with white to off-white powder which may appear as a plug, imprinted with "REP 40" in blue text on the cap.

3. How Supplied/Storage and Handling Section

- a. Consider revising Section 16 for clarity and brevity to read as follows:

PROPRIETARY NAME (repotrectinib) 40 mg, Size 0, white opaque cap, white opaque body, hard shell capsules, filled with a white to off-white powder which may appear as a plug, imprinted with "REP 40" in blue text on the cap are supplied as follows:

- Bottles of 60 capsules (NDC 0003-4040-60)
- Bottles of 120 capsules (NDC 0003-4040-12)

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*].

4. Patient Information

- a. Include the acceptable interval for taking a missed dose before the next scheduled dose in order to avoid risks associated with taking 2 doses too close together similar to the following:

If you miss a dose (b) (4) or vomit at any time after taking PROPRIETARY NAME, (b) (4) Do not take 2 doses at the same time to make up for a missed dose.

- b. Revise the storage temperature statement for consistency across all labeling components as follows:

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*].

4.2 RECOMMENDATIONS FOR BRISTOL MYERS SQUIBB COMPANY

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD

format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a forward slash or a hyphen be used to separate the portions of the expiration date.

2. To ensure consistency with the language used in the Prescribing Information, revise the statement, (b) (4) to read "Recommended Dosage: See prescribing information."

B. Container Labels

1. The linear barcode is missing on the 60-count and the 120-count (round) container labels. The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label and is a requirement per 21 CFR 201.25(c)(2). Add the product's linear barcode in a vertical position to each individual container label in accordance with 21CFR 201.25(c)(2).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Repotrectinib received on March 27, 2023 from Bristol Myers Squibb Company.

Table 2. Relevant Product Information for Repotrectinib	
Initial Approval Date	N/A
Active Ingredient	repotrectinib
Indication	For the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC)
Route of Administration	Oral
Dosage Form	Capsule
Strength	40 mg
Dose and Frequency	160 mg (four 40 mg capsules) daily for the first 14 days, then increase to 160 mg twice daily, with or without food, until disease progression or unacceptable toxicity.
How Supplied	60-count bottles or 120-count bottles
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].
Container Closure	(b) (4) high density polyethylene (HDPE) bottles with (b) (4) closures. Both closures have an aluminum-foil induction seal (inner seal).

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Repotrectinib labels and labeling submitted by Bristol Myers Squibb Company.

- Container label received on March 27, 2023
- Carton labeling received on March 27, 2023
- Prescribing Information with Patient Information (Image not shown) received on March 27, 2023, available from <\\CDSESUB1\EVSPROD\nda218213\0002\m1\us\initial-nda-repo-pro.pdf>

F.2 Label and Labeling Images

Container Labels

60-count container label

(b) (4)

^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

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/

JANINE A STEWART
08/24/2023 01:25:48 PM

ASHLEIGH V LOWERY
08/24/2023 04:39:28 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 218213
Submission Number	0003
Submission Date	3/27/2023
Date Consult Received	4/17/2023
Drug Name	Repotrectinib
Indication	ROS-1 Positive Non-Small Cell Lung Cancer
Therapeutic Dose	160 mg QD for 14 days followed by 160 mg BID, with or without food.
Clinical Division	DO2
Protocol Review	11/06/2018 and 12/06/2021

Note: Any text in the review with a light background should be considered to be copied from the sponsor's document.

This review responds to your consult dated 4/17/2023 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review under IND 130465 dated [11/06/2018](#) in DARRTS;
- Previous IRT review under IND (b) (4) dated [12/06/2021](#) in DARRTS;
- Cardiac Safety Report for TRIDENT-1 (TPX-0005-01 or 00515) (NDA 218213 / SDN 003; [link](#));
- QT Evaluation Report checklist (NDA 218213 / SDN 008; [link](#));
- Highlights of clinical pharmacology and cardiac safety (NDA 218213 / SDN 008; [link](#));
- Study Report 00514 (NDA 218213 / SDN 003; [link](#));
- Summary of Clinical Pharmacology Studies (NDA 218213 / SDN 003; [link](#));
- Annotated draft label (NDA 218213 / SDN 003; [link](#)); and
- Investigator's brochure version 13.0 (NDA 218213 / SDN 008; [link](#)).

1 SUMMARY

Repotrectinib does not cause large mean increases (i.e., 20 msec) in the QTc interval at therapeutic exposures with 160 mg QD followed by 160 mg BID – see Table 1 for overall results. Without a positive control or large exposure margin, we are reluctant to conclude that repotrectinib has no effect on the QTc interval (E14 Q&A 6.1).

The clinical study TPX-0005-01 (TRIDENT-1) was a phase 1/2, open-label, multiple-center, first-in-human study which evaluated the safety, tolerability, pharmacokinetics and anti-tumor activity of repotrectinib in subjects with advanced solid tumors harboring ALK, ROS1 or NTRK1-3 rearrangements. Study TPX-0005-01 has four parts, phase 1a, 1b, 1c and phase 2, see Table 11 for detail. The highest dose provided 0.59-fold high

clinical exposure. Data were analyzed using by-time analysis as the primary analysis, which did not suggest that repotrectinib is associated with large mean increases in the QTcF interval (refer to section 4.3). The findings of the primary analysis are further supported by the categorical analysis (section 4.4).

Table 1: Summary of findings

QT assessment pathway	☐ <i>Thorough QT study</i> ☐ <i>Substitute for thorough QT study (5.1)</i> ☒ <i>Alternative QT study when a thorough QT study is not feasible (6.1)</i>				
Clinical QT study findings	- The high clinical exposure scenario is 1.7-fold increase in Cmax with CYP3A4 inhibition (section 3.1) - The highest exposure in TPX-0005-01 is 713 ng/mL which is 0.59-fold of the identified high clinical exposure, 1212 ng/mL.				
	ECG parameter	Treatment	Visit	ΔQTcF (msec)	90% CI (msec)
	ΔQTcF	Repotrectinib 160 mg QD/BID	1	6.2	(4.8 to 7.7)
	ΔQTcF	Repotrectinib 160 mg QD/BID	2	8.3	(6.6 to 9.9)
	ΔQTcF	Repotrectinib 160 mg QD/BID	3	7.9	(6.2 to 9.6)
ΔQTcF	Repotrectinib 160 mg QD/BID	4	8.3	(6.6 to 10.0)	
In vitro findings	Integrated nonclinical risk assessment was not performed.				
In vivo findings					

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to eCTD 0002 ([link](#)).

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

PROPRIETARY NAME does not cause a mean increase in the QTc interval > 20 milliseconds (ms) at 160 mg QD followed by 160 mg BID, the approved recommended dose.

Reviewer's comment: We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

Repotrectinib, a tyrosine kinase inhibitor, is proposed for the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer. The proposed therapeutic dose is 160 mg QD for 14 days followed by 160 mg BID, with or without food.

We previously agreed to using the Phase 1 part of the TRIDENT-1 study for QTc characterization and recommended following the ECG monitoring plan for Phase 2 before considering the QT assessment complete (DARRTS [11/06/2018](#)). We also recommended that the sponsor considers concentration-QTc analysis.

The sponsor subsequently noted that Phase 1 included intensive ECG/PK collection and was anticipated to cover up to 2x the clinical exposure and therefore proposed to use a combined concentration-QTc analysis based on pooled data across healthy volunteers, in addition to by-time and categorical analysis to support the QT assessment. It was also noted that if significant changes in HR were observed that individual QT correction would be explored. We responded that we agreed to using data from Phase 1 and 2 of TRIDENT-1 using by-time and concentration-QTc analysis to assess the effects on the QTc interval and if a 20 msec mean increase could be excluded (DARRTS [12/06/2021](#)).

The sponsor has now submitted a QT assessment based on TRIDENT-1, which includes an evaluation by phase (i.e., Phase 1a [dose escalation with modified fasting conditions]; Phase 1c [dose escalation with food]; and Phase 2 [dose expansion with labeled dose]). Data from Phase 1b, food effect and midazolam DDI-substudy were not included as the exposures were not exceeding the exposures in other parts and the results could be

confounded by food and drug-drug interactions. Notably, the cohort sample sizes were small in Phase 1a and 1c and only 2 subjects received doses greater than the therapeutic dose (i.e., 200 mg BID). In contrast, Phase 2 included the therapeutic exposure, a larger sample size (n = 334) and sufficient ECG/PK collection to support QT assessment, i.e., C1D1 (pre-dose and 4 h post-dose); C1D14 (time not specified, no PK sample); C1D15 (pre-dose and 4 h post-dose); Cycles 2-4 (pre-dose and 4 h post-dose). Baseline was pre-dose on cycle 1 day 1 except for subjects in the Phase 2 lead-in who would have day -3 as the baseline.

The sponsor has also submitted study report 00514, an integrated concentration QTcF analysis of repotrectinib including data from healthy volunteers participating in Phase 1 studies TPX-0005-08, TPX-0005-09, TPX-0005-010, TPX-0005-011, TPX-0005-012, and TPX-0005-014 and subjects enrolled in Phase 1/2 Study TPX-0005-01 (TRIDENT-1) receiving repotrectinib from the safety population. However, TRIDENT-1 data alone as described above are best for QTc characterization because only three of the healthy volunteer studies achieved therapeutic concentrations: TPX-0005-011 and TPX-0005-014 when given with food, and TPX-0005-010 when coadministered with itraconazole (see Summary of Clinical Pharmacology Studies Tables 31 and 32) and these healthy volunteer studies collected single non-digital ECGs (Table 11).

In our analysis, we will use TRIDENT-1 data from phase 2 for the by-time analysis and include data from all TRIDENT-1 phases in categorical analysis. Concentration-QTc analysis was not performed with the data as there is a limited exposure range within each subject due to the ECG/PK sampling and goodness of fit plots in the cardiac safety report 00515 Phase 1/2 data show a large intercept and do not support linear concentration-QTc model.

3.1.1 Clinical pharmacology

See highlights of clinical pharmacology and cardiac safety.

Table 2: Summary of dose and exposure assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	160 mg QD for 14 days followed by 160 mg BID with food	713 ng/mL (C _{max,ss})
Sponsor's High clinical exposure scenario	1.7-fold increase with CYP3A4 inhibition ^a	1212 ng/mL
Highest dose in QT assessment	160 mg QD for 14 days followed by 160 mg BID	713 ng/mL
C_{max} Ratio	0.59 (713 / 1212)	

a: The hepatic impairment study is still pending.

3.1.2 Nonclinical Safety Pharmacology Assessments

Refer to the Highlights of Clinical Pharmacology and Cardiac Safety Table.

Electrocardiographic examinations were performed on cynomolgus monkeys in the 28-day and 91-day toxicology studies with repotrectinib (TPX-0005). Measurements were taken on all animals at pretest, predose, and 2 to 3 hours postdose on Day 1, predose and

2 to 3 hours postdose on all surviving animals during the last week of dosing (Day 28 or Day 90), and during the last week of the recovery period of the 91-day study (Day 118). RR, PR, and QT intervals and QRS duration were measured, and heart rate was determined. There was no effect of TPX-0005 on qualitative and quantitative ECG parameters.

Inhibition of the hERG potassium channel by TPX-0005 (1, 3, 10, 30 μM) was investigated using a stably transfected Chinese hamster ovary [CHO] cell line expressing the hERG mRNA. The positive control was cisapride (1 μM). The inhibition of human Nav1.5 sodium channel by TPX-0005 (10, 30 μM) was investigated using human embryonic kidney (HEK) 293 cells transfected with human Nav1.5 sodium ion channel (alpha subunit). Tetracaine (30 μM) was used as the positive control. The inhibition of human L-type Cav1.2 calcium channel by TPX-0005 (10, 30 μM) was investigated using HEK293 cells transduced with human $\alpha 1$ and β Cav1.2 subunits. Nifedipne (30 μM) was the positive control.

TPX-0005 had minimal effects on human ion channels, including hERG (IC₅₀ = 18 μM , CHO cells), hNav1.5 (IC₅₀ > 30 μM , HEK293 cells), and human L-type Cav1.2 (IC₅₀ > 30 μM , HEK293 cells).

Reviewer's assessment: *The sponsor evaluated the effects of repotrectinib (TPX-0005) on hERG, Cav1.2 and Nav1.5 currents in recombinant cells (BMS-986472-00204;link). The hERG current was assessed at room temperature, at every 12 s, using a step-step voltage protocol (from a holding potential of -80 mV to a depolarizing pulse of 20 mV for 5 seconds, followed by a repolarizing pulse to -50 mV for 5 seconds) that is different from the recommended hERG current protocol by the FDA (link). The positive control (cisapride at 1 μM) was added to the end of the experiment and inhibited hERG potassium >95%. Drug concentration verifications were not performed in this study.*

Repotrectinib concentration-dependently inhibited the hERG current. The IC₅₀ is 18 μM . In addition, TPX-0005 inhibited hCaV1.2 current and Nav1.5 current by approximately 35% and 15% at 30 μM , respectively.

The hERG safety margins of repotrectinib on hERG current are summarized below:

Table 3 Safety Margin of repotrectinib on hERG Current

	C _{max} (ng/mL)	Protein Binding	Free C _{max} (ng/mL)	hERG IC ₅₀ (μM)	Mol Weight (g/mol)	Safety Margin (Ratio)
Repotrectinib	1212.1	95.4%	55.75	18	355.4	114x

High clinical C_{max}: 1212.1 ng/mL.

The in vivo monkey study (BMS-986472-00357) assessed the potential effects of repotrectinib on ECG parameters when administered orally, once daily, for up to 91 consecutive days. The dose levels were 0, 5, 15 and 50 mg/kg/day. Electrocardiographic examinations were performed on all animal's pretest, predose and 2 to 3 hours postdose on Day 1, predose and 2 to 3 hours postdose on all surviving animals during the last week of dosing (Day 90), and during the last week of the recovery period. Blood (plasma) collection on Days 1 and 91 from all surviving animals predose (Day 91 only) and at approximately 1, 2, 4, 8, 12, and 24 hours postdose. The mean plasma concentration of

repotrectinib was 280 ng/mL at 50 mg/kg/day. The exposure didn't exceed the anticipated high clinical exposure in humans (1221 ng/mL). There were no repotrectinib-related QTc changes at dose up to 50 mg/kg/day. No positive drugs were used in the study.

In summary, the hERG assay showed deviations (e.g., room temperature; a slow stimulating rate; no drug concentration verification; positive control was tested at one concentration) from best practice recommendations for an in vitro assay according to the new draft ICH S7B Q&A 2.1. The limitations of the hERG assay may overestimate the hERG IC50 and safety margin. The estimated hERG safety margin was 114x, suggesting the direct inhibition of the hERG current at high therapeutic exposure by repotrectinib cannot be ruled out without demonstrating that the hERG safety margin is higher than safety margins computed under the same experimental protocol for a series of reference drugs known to cause TdP.

No QTc prolongation was observed at exposure lower than (~0.3-fold) the anticipated high clinical exposure in a GLP in vivo study in monkey.

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

In the sponsor's by-time analysis, there was no clear evidence that repotrectinib 160 mg QD/BID had any clinically significant effect on QTc based on time points with ≥ 200 or more observations in Phase 2. The largest mean Δ QTcF was on Cycle 2 Day 1 at the pre-dose time point, reaching 8.6 ms (90% upper bound of CI is 10.1 ms).

Reviewer's comment: Reviewer evaluated the Δ QTcF effect using descriptive statistics, which is based on time points with ≥ 200 or more observations from Phase 2 excluding Japanese and Chinese lead-in cohorts except Cycle 1 Day 1 -1 hour. The maximum mean Δ QTcF is 8.3 msec with upper confidence limit of Δ QTcF 10 msec on Cycle 4 Day 1 at the pre-dose time point from the reviewer's analysis. The trend shown in by-time analysis from reviewer's analysis is similar to the trend shown in sponsor's by-time analysis. Please see section 4.3 for details.

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

In the overall safety population of TRIDENT-1 (N=444), 33 (7.4%) subjects were reported with a worst postbaseline QT interval corrected for heart rate using Fridericia formula (QTcF) ≥ 450 to ≤ 480 msec, with 3 (0.7%) ≥ 481 to ≤ 500 msec, and 1 (0.2) subject reported with a worst postbaseline > 500 msec. In total, 82 (18.5%) subjects were reported with a maximum worst postbaseline increase in QTcF ≥ 30 to ≤ 60 msec, and 5 (1.1%) > 60 msec.

In addition, per sponsor's analysis, there were 22 outliers for HR (>100 beats/min and 25% over baseline), three outliers for PR (>200 msec and 25% over baseline), and six outliers for QRS (>100 msec and 25% over baseline).

Reviewer's comment: Reviewer's categorical analyses included all subjects from Phase 1a, Phase 1c, and Phase 2. Reviewer's analysis results are similar with sponsor's analysis results. Please see Section 4.4 for details.

3.2.3 Exposure-Response Analysis

The sponsor conducted C-QTc analyses for Phase 1a dose escalation phase, Phase 1c dose escalation phase, and Phase 2 dose expansion phase, separately. The sponsor's analysis included subjects with at least 1 pair of post-dose PK and Δ QTcF data. A pooled analysis was also conducted. The sponsor used the model recommended (b) (4)

Results from all 4 C-QTc analyses indicated statistically significant negative C-QTc relationships. Based on phase 1c data, the estimated C-QTc slope and intercept were -0.0037 ms per ng/mL (-0.00702 to -0.00032) and 4.85 (1.435 to 8.272) respectively. The estimated C-QTc slope and intercept based on phase 1c data were -0.0044 ms per ng/mL (-0.00847 to -0.00041) and 9.48 ms (90% CI: 6.514 - 12.455) respectively. For the phase 2 data, the estimated slope and intercept were -0.0069 ms per ng/mL (-0.00799 to -0.00581) and 7.85 (6.650 to 9.041), respectively, while for the pooled analysis, the estimated slope and intercept were -0.0064 ms per ng/mL (-0.00740 to -0.00535) and 7.54 ms (90%CI: 6.452 - 8.619).

In general, the results of the sponsor's analyses show an absence of concentration dependent QTc prolongation.

Reviewer's comment: IRT-QT team did not perform C-QT analysis due to large intercepts in the sponsor's analyses indicating possible nonlinear relationship or delayed QT prolongation which cannot be described by linear mixed effects modeling. See section 4.5 for details. Reviewers consider by-time and categorical analyses to be appropriate for these data.

3.2.4 Safety Analysis

There were 15 treatment-emergent AEs included in the MedDRA SMQ for Torsade de pointes/QT prolongation (plus seizure) that were associated with death, SAE, non-SAE with QTc prolongation > 500 msec, or discontinuation from the study.

Reviewer's comment: Other than the event associated with QTc prolongation, there was no increase in QTc above 450 msec except for a single time-point for one of the events and no patient experienced other AEs related to torsade de pointes or QT prolongation.

There were also two deaths ((b) (6)) that are included in the customized query used by the IRT but not in the MedDRA query. Neither patient had QTc

measurements > 450 msec, received concomitant medication associated with QTc or had other AEs related to QT or torsade de pointes.

There were 20 additional treatment-emergent adverse events included in the IRT's customized query not captured above: 9 syncope; 5 presyncope; 4 seizures; and 4 Electrocardiogram QT prolonged. None of these were serious and the majority were of mild-to-moderate severity (13/20).

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| <10 beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Both digital ECG waveforms and non-digital ECG waveforms (scanned and digitized ECGs) were submitted for review. Digital and digitized ECG waveforms were semi-automatically read. The ECG reader were blinded to subject, treatment, and visit. However, the automatic measurements were not available. Since the submission includes digitized ECG waveforms, sensitivity analysis was performed excluding the digitized ones, which resulted in similar QTc changes to the primary analysis.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG from TRIDENT-1 Phase 2 excluding Japanese and Chinese lead-in cohorts. The time points with more than 200 observations are included, which are Day 1 and Day 15 in Cycle 1, Day 1 in Cycle 2, 3, and 4 except Cycle 1 Day 1 -1 hour.

The statistical reviewer evaluated the Δ QTcF effect using parametric descriptive statistics.

4.3.1 QTc

Figure 1 displays the time profile of Δ QTcF for repotrectinib 160 mg QD/BID treatment group. The maximum Δ QTcF values by cycle and day are shown in Table 4. The excluding digitized data are used for sensitivity analysis. Figure 3: Mean and 90% CI of Δ HR Time-course displays the time profile of Δ QTcF for repotrectinib 160 mg QD/BID treatment group excluding digitized data. The maximum Δ QTcF values by cycle and day in sensitivity analysis are shown in Table 5.

Figure 1: Mean and 90% CI of Δ QTcF Time-course (unadjusted CIs).

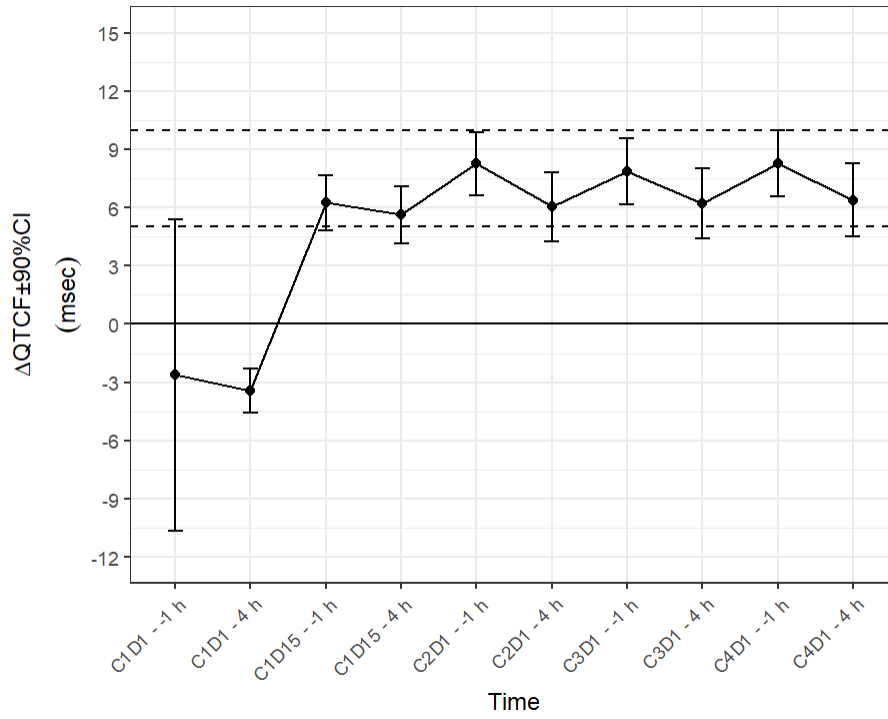


Table 4: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Δ QTcF

Actual Treatment	Period (C)	Analysis Nominal Period Day (C)	N	Time (Hours)	Δ QTcF (msec)	90.0% CI (msec)
Repotrectinib 160 mg QD/BID	1	1	16	-1.0	-2.6	(-10.6 to 5.4)
Repotrectinib 160 mg QD/BID	1	15	295	-1.0	6.2	(4.8 to 7.7)
Repotrectinib 160 mg QD/BID	2	1	282	-1.0	8.3	(6.6 to 9.9)
Repotrectinib 160 mg QD/BID	3	1	234	-1.0	7.9	(6.2 to 9.6)
Repotrectinib 160 mg QD/BID	4	1	204	-1.0	8.3	(6.6 to 10.0)

Figure 2: Mean and 90% CI of Δ QTcF Time-course (unadjusted CIs) Excluding Digitized Data.

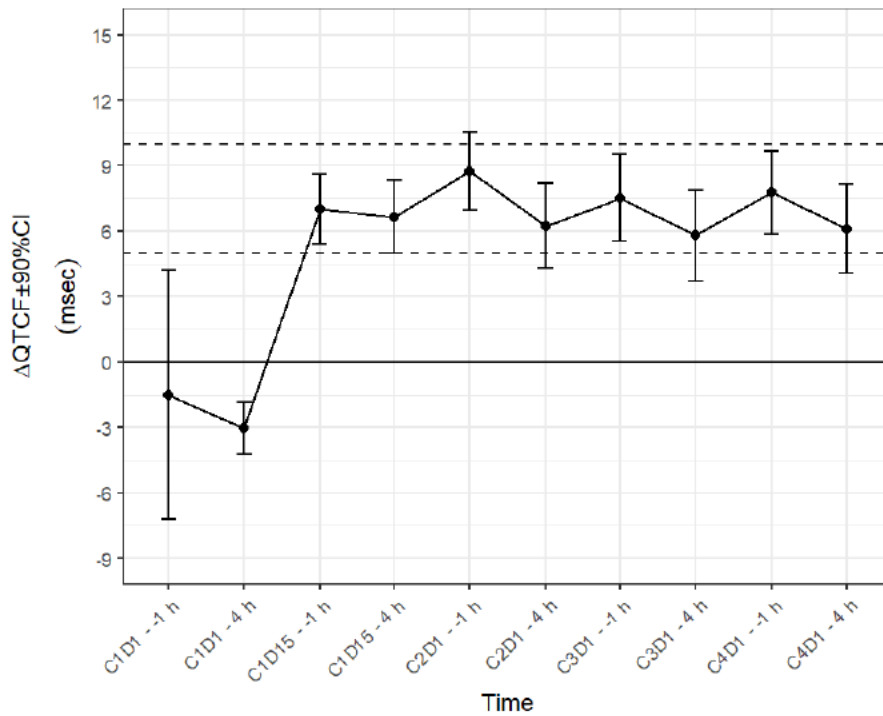


Table 5: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Δ QTcF Excluding Digitized Data

Actual Treatment	Period (C)	Analysis Nominal Period Day (C)	N	Time (Hours)	Δ QTcF (msec)	90.0% CI (msec)
Repotrectinib 160 mg QD/BID	1	1	11	-1.0	-1.5	(-7.2 to 4.2)
Repotrectinib 160 mg QD/BID	1	15	231	-1.0	7.0	(5.4 to 8.6)
Repotrectinib 160 mg QD/BID	2	1	213	-1.0	8.7	(7.0 to 10.5)
Repotrectinib 160 mg QD/BID	3	1	184	-1.0	7.5	(5.5 to 9.5)
Repotrectinib 160 mg QD/BID	4	1	163	-1.0	7.8	(5.8 to 9.7)

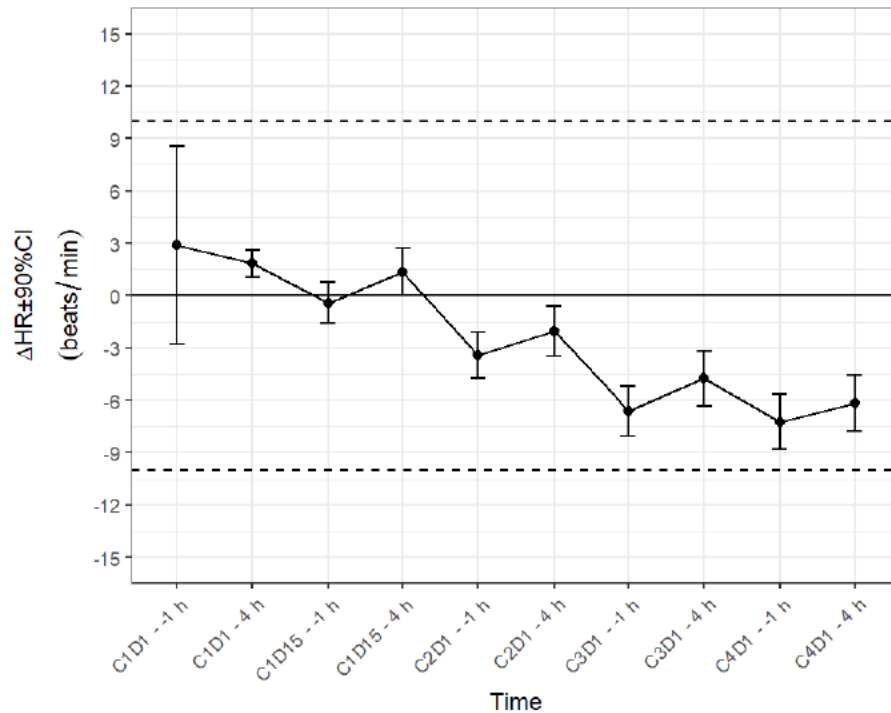
4.3.1.1 Assay Sensitivity

Not applicable.

4.3.2 HR

Figure 3 displays the time profile of Δ HR for repotrectinib 160 mg QD/BID treatment group.

Figure 3: Mean and 90% CI of Δ HR Time-course

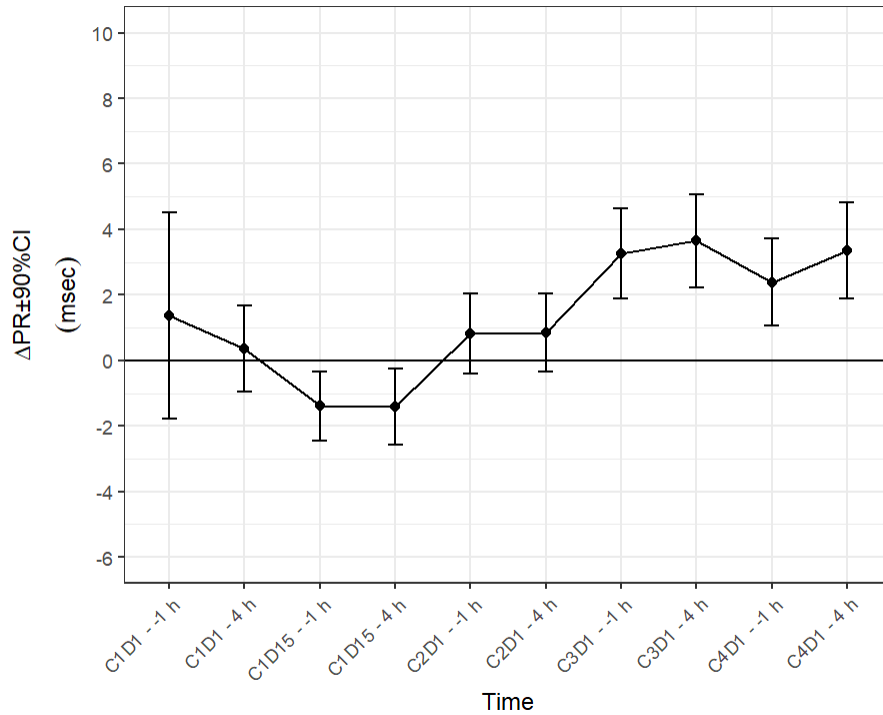


r

4.3.3 PR

Figure 4 displays the time profile of Δ PR for repotrectinib 160 mg QD/BID treatment group.

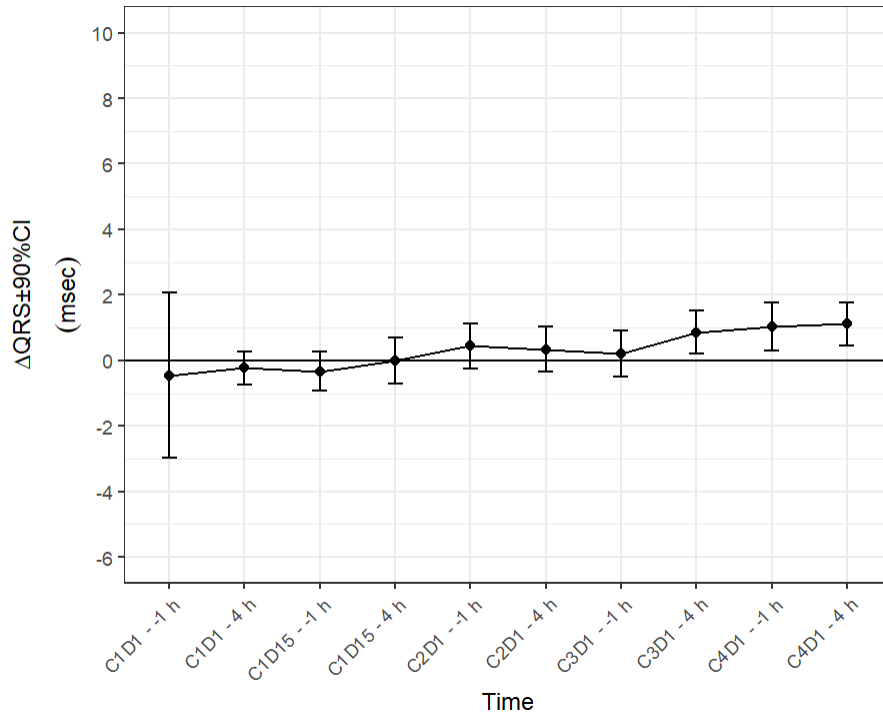
Figure 4: Mean and 90% CI of Δ PR Time-course



4.3.4 QRS

Figure 5 displays the time profile of Δ QRS for repotrectinib 160 mg QD/BID treatment group.

Figure 5: Mean and 90% CI of Δ QRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs from TRIDENT-1 Phase 1a, Phase 1c, and Phase 2. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

Table 6 lists the number of subjects, as well as the number of observations with QTcF values of ≤ 450 msec, >450 and ≤ 480 msec, >480 and ≤ 500 msec, and >500 msec with or without a change from baseline >60 msec. There was one subject having observed maximum QTcF above 500 msec with a change from baseline >60 msec in the Repotrectinib 160 mg QD/BID treatment group.

Table 6: Categorical Analysis for QTcF (maximum)

Actual Treatment	Total (N)		Value <=450 msec		450 msec < Value <=480 msec		480 msec < Value <=500 msec		Value >500 msec & >60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Repotrectinib 40 mg QD	13	287	11 (84.6%)	279 (97.2%)	2 (15.4%)	8 (2.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Repotrectinib 80 mg QD	12	283	10 (83.3%)	279 (98.6%)	2 (16.7%)	4 (1.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Repotrectinib 120 mg QD with Food	3	54	3 (100.0%)	54 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Repotrectinib 160 mg QD	23	500	21 (91.3%)	497 (99.4%)	2 (8.7%)	3 (0.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Repotrectinib 160 mg QD/BID with Food	12	217	11 (91.7%)	215 (99.1%)	1 (8.3%)	2 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Repotrectinib 160 mg BID	11	221	10 (90.9%)	219 (99.1%)	1 (9.1%)	2 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Repotrectinib 160 mg QD with Food	6	115	6 (100.0%)	115 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Repotrectinib 160 mg QD/BID	344	2713	320 (93.0%)	2651 (97.7%)	20 (5.8%)	54 (2.0%)	3 (0.9%)	7 (0.3%)	1 (0.3%)	1 (0.0%)
Repotrectinib 200 mg BID	2	40	1 (50.0%)	39 (97.5%)	1 (50.0%)	1 (2.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Repotrectinib 240 mg QD	10	179	9 (90.0%)	166 (92.7%)	1 (10.0%)	13 (7.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 7 lists the categorical analysis results for Δ QTcF (<30 msec, >30 and <60, and >60 msec). There were five subjects having observed maximum Δ QTcF above 60 msec in the Repotrectinib 160 mg QD/BID treatment group and Repotrectinib 160 mg BID treatment group.

Table 7: Categorical Analysis for Δ QTcF (maximum)

Actual Treatment	Total (N)		Value $\leq$ 30 msec		30 msec < Value $\leq$ 60 msec		Value >60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Repotrectinib 40 mg QD	13	287	11 (84.6%)	282 (98.3%)	2 (15.4%)	5 (1.7%)	0 (0%)	0 (0%)
Repotrectinib 80 mg QD	12	283	11 (91.7%)	281 (99.3%)	1 (8.3%)	2 (0.7%)	0 (0%)	0 (0%)
Repotrectinib 120 mg QD with Food	3	54	3 (100.0%)	54 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Repotrectinib 160 mg QD	23	500	21 (91.3%)	496 (99.2%)	2 (8.7%)	4 (0.8%)	0 (0%)	0 (0%)
Repotrectinib 160 mg QD/BID with Food	12	217	9 (75.0%)	209 (96.3%)	3 (25.0%)	8 (3.7%)	0 (0%)	0 (0%)
Repotrectinib 160 mg BID	11	221	6 (54.5%)	199 (90.0%)	4 (36.4%)	16 (7.2%)	1 (9.1%)	6 (2.7%)
Repotrectinib 160 mg QD with Food	6	115	3 (50.0%)	104 (90.4%)	3 (50.0%)	11 (9.6%)	0 (0%)	0 (0%)
Repotrectinib 160 mg QD/BID	344	2713	282 (82.0%)	2556 (94.2%)	58 (16.9%)	152 (5.6%)	4 (1.2%)	5 (0.2%)
Repotrectinib 200 mg BID	2	40	2 (100.0%)	40 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Repotrectinib 240 mg QD	10	179	8 (80.0%)	162 (90.5%)	2 (20.0%)	17 (9.5%)	0 (0%)	0 (0%)

4.4.2 HR

Table 8 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). There were 92 subjects having observed Δ QTcF above 100 beats/min in all Repotrectinib treatment groups except the Repotrectinib 120 mg QD with Food treatment group.

Table 8: Categorical Analysis for HR (maximum)

Actual Treatment	Total (N)		Value ≤100 beats/min		Value >100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Repotrectinib 40 mg QD	13	287	7 (53.8%)	244 (85.0%)	6 (46.2%)	43 (15.0%)
Repotrectinib 80 mg QD	12	283	8 (66.7%)	268 (94.7%)	4 (33.3%)	15 (5.3%)
Repotrectinib 120 mg QD with Food	3	54	3 (100.0%)	54 (100.0%)	0 (0%)	0 (0%)
Repotrectinib 160 mg QD	23	500	17 (73.9%)	441 (88.2%)	6 (26.1%)	59 (11.8%)
Repotrectinib 160 mg QD/BID with Food	12	217	7 (58.3%)	189 (87.1%)	5 (41.7%)	28 (12.9%)
Repotrectinib 160 mg BID	11	221	7 (63.6%)	196 (88.7%)	4 (36.4%)	25 (11.3%)
Repotrectinib 160 mg QD with Food	6	115	5 (83.3%)	109 (94.8%)	1 (16.7%)	6 (5.2%)
Repotrectinib 160 mg QD/BID	346	2715	285 (82.4%)	2574 (94.8%)	61 (17.6%)	141 (5.2%)
Repotrectinib 200 mg BID	2	40	1 (50.0%)	39 (97.5%)	1 (50.0%)	1 (2.5%)
Repotrectinib 240 mg QD	10	180	6 (60.0%)	171 (95.0%)	4 (40.0%)	9 (5.0%)

4.4.3 PR

Table 9 lists the categorical analysis results for PR (<200 msec, >200 and ≤220 msec, and >220 msec; with and without 25% increase over baseline). There were two subjects having observed PR above 220 msec with 25% increase over baseline in the Repotrectinib 160 mg QD/BID treatment group and Repotrectinib 160 mg QD with Food treatment group.

Table 9: Categorical Analysis for PR

Actual Treatment	Total (N)		Value ≤220 msec		Value >220 msec & <25%		Value >220 msec & ≥25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Repotrectinib 40 mg QD	13	287	12 (92.3%)	285 (99.3%)	1 (7.7%)	2 (0.7%)	0 (0%)	0 (0%)
Repotrectinib 80 mg QD	12	283	11 (91.7%)	260 (91.9%)	1 (8.3%)	23 (8.1%)	0 (0%)	0 (0%)
Repotrectinib 120 mg QD with Food	3	54	3 (100.0%)	54 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Repotrectinib 160 mg QD	23	500	23 (100.0%)	500 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Repotrectinib 160 mg QD/BID with Food	12	217	11 (91.7%)	216 (99.5%)	1 (8.3%)	1 (0.5%)	0 (0%)	0 (0%)
Repotrectinib 160 mg BID	11	221	11 (100.0%)	221 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Repotrectinib 160 mg QD with Food	6	115	4 (66.7%)	111 (96.5%)	1 (16.7%)	2 (1.7%)	1 (16.7%)	2 (1.7%)
Repotrectinib 160 mg QD/BID	342	2700	332 (97.1%)	2673 (99.0%)	9 (2.6%)	26 (1.0%)	1 (0.3%)	1 (0.0%)
Repotrectinib 200 mg BID	2	40	2 (100.0%)	40 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Repotrectinib 240 mg QD	9	148	9 (100.0%)	148 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

4.4.4 QRS

Table 10 lists the categorical analysis results for QRS (≤ 120 msec, and > 120 msec; with and without 25% increase over baseline). There were four subjects having observed QRS above 120 msec with 25% increase over baseline in the Repotrectinib 160 mg QD/BID treatment group.

Table 10: Categorical Analysis for QRS

Actual Treatment	Total (N)		Value <=120 msec		Value >120 msec & <25%		Value >120 msec & >=25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Repotrectinib 40 mg QD	13	287	13 (100.0%)	287 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Repotrectinib 80 mg QD	12	283	12 (100.0%)	283 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Repotrectinib 120 mg QD with Food	3	54	3 (100.0%)	54 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Repotrectinib 160 mg QD	23	500	23 (100.0%)	500 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Repotrectinib 160 mg QD/BID with Food	12	217	12 (100.0%)	217 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Repotrectinib 160 mg BID	11	221	10 (90.9%)	197 (89.1%)	1 (9.1%)	24 (10.9%)	0 (0%)	0 (0%)
Repotrectinib 160 mg QD with Food	6	115	6 (100.0%)	115 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Repotrectinib 160 mg QD/BID	344	2713	333 (96.8%)	2670 (98.4%)	7 (2.0%)	35 (1.3%)	4 (1.2%)	8 (0.3%)
Repotrectinib 200 mg BID	2	40	2 (100.0%)	40 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Repotrectinib 240 mg QD	10	180	9 (90.0%)	166 (92.2%)	1 (10.0%)	14 (7.8%)	0 (0%)	0 (0%)

4.5 EXPOSURE-RESPONSE ANALYSIS

Concentration-QTc analysis was not performed because we noted from the sponsor's C-QT analyses of Phase 1/2 data that the intercepts of the C-QT models were large, and the slopes were negative. It is not clear if the sponsor models are adequate characterization of repotrectinib QT effects. Large statistically significant intercept for linear C-QT relationship is usually an indication that a linear model is not an adequate description of the data. Large intercept may occur due to plateau of C-QT relationship at high concentrations or due to delayed QT effects. In fact, the sponsor's assessment of hysteresis indicated some delayed increase in $\Delta QTcF$ over treatment cycle 1 in Phase 1a, Phase 1c and Phase 2. Therefore, due to possible nonlinear relationship or delayed QT prolongation, the reviewers find linear mixed effect modelling to be inappropriate for data from the TRIDENT-1 study.

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

5 APPENDIX

5.1 EVALUATION OF CLINICAL QT ASSESSMENT PLAN

We previously reviewed the sponsor's QT assessment plan (DARRTS [11/06/2018](#) and [12/06/2021](#)).

5.2 SUMMARY OF STUDIES

Table 11: Summary of Studies

Study	Design	Dose: geomCmax	Digital ECGs	ECG/PK
TRIDENT-1 Phase 1a	Dose escalation (3+3) under modified fasted conditions	Day 1: 160 mg (n=18): 714 ng/mL 240 mg (n=10): 1190 ng/mL Day 15: 240 mg QD (n=6): 720 ng/mL	Yes TriPLICATE Central semiauto	Dense on Day -3 (predose, 1, 2, 4, 6, 8, 24, 48 and 72 hours postdose) and C1D15 (predose, 1, 2, 4, 6, 8, 24 hours post dose) Predose and 4 hr postdose on Day 1 of Cycles 1-4
TRIDENT-1 Phase 1b	Fed (high-fat)	Day 1: 160 mg fed (n=13): 932 ng/mL	Yes TriPLICATE Central semiauto	Dense (predose, 1, 2, 4, 6, 8, 24, 48, 72 hours postdose) on Day -7 and C1D1 Predose and 4 hr postdose on C1D15 and Day 1 of Cycles 2-4
TRIDENT-1 Phase 1c	Dose escalation (3+3) study	Day 1: 120 mg (n=3): 922 ng/mL 160 mg (n=18): 851 ng/mL Day 15: 120 mg QD (n=3): 715 ng/mL 160 mg QD (n=8): 747 ng/mL 160 mg BID (n=7): 713 ng/mL	Yes TriPLICATE Central semiauto	Dense (predose, 1, 2, 4, 6, 8 and 24 hours postdose) on C1D1 and C1D15 Predose and 4 hr postdose on Day 1 of Cycles 2-4

Study	Design	Dose: geomCmax	Digital ECGs	ECG/PK
TRIDENT-1 Phase 2	open-label, multi-center at RP2D	All cohorts 160 mg (n=334) Japanese lead-in Day -3: 160 mg (n=6): 1350 ng/mL Day 14: 160 mg QD (n=6): 816 ng/mL Chinese lead-in C1D1: 160 mg (n=14): 1260 ng/mL C1D14: 160 mg QD (n=14): 1140 ng/mL	Yes TriPLICATE Central semiauto	Predose and 4 hr postdose Day 1 cycles 1-4 and C1D15 (all) Dense (Japanese lead-in cohort) on Day -3 (predose, 1, 2, 4, 6, 8, 24, 48, 72 hours postdose) and C1D14 (predose, 1, 2, 4, 6, 8, 24 hours postdose) Dense (Chinese lead-in cohort) on C1D1 (predose, 1, 2, 4, 6, 8, 24 hours postdose) and C1D14 (predose, 1, 2, 4, 6, 8, 24 hours postdose).
TPX-0005-10	open-label, ascending dose + 200 mg itraconazole	80 mg + itraconazole fasted (n=16): 726 ng/mL	No Single PI or designee	Predose, 1, 2, 4, 12, 24, 48, 96, 168 hours postdose.
TPX-0005-11	Open label food study	160 mg fed (n=14): 1240 ng/mL	No Single PI or designee	Predose, 1, 2, 4, 12, 24, 48, 96, 168 hours postdose.
TPX-0005-14	BE & food effect study	160 mg high-fat (n=16): 999 ng/mL 16 mg low-fat (n=16): 1050 ng/mL	No Single PI or designee	Predose, 1, 2, 4, 12, 24, 48, 96, 168 hours postdose.

TRIDENT-1: Phase 1/2 open-label study in patients with no placebo. Listing only cohorts achieving concentrations around or above therapeutic Cmax (i.e., Cmax > 700 ng/mL).

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